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19th March 2004

Dear Professor Hytten

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

encs.

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27. 3. 04

Dear Dr Christie

Witness Seminar on Prenatal Corticosteroids
Tuesday 15th June.

I am most grateful to have had an invitation to take part in this seminar; it sounds excellent.

Unfortunately I shall not be able to attend.

Yours sincerely

Frank Hytten

# The Wellcome Trust Centre for the History of Medicine at University College London

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UCL

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16 June 2004

Dear Ian

**The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth**

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

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# The Wellcome Trust Centre for the History of Medicine at University College London

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14 June, 2005

Dear Ian,

**Witness Seminar: Prenatal Corticosteroids, 15 June 2004**

I hope you have received the draft copy of the transcript on *'Prenatal Corticosteroids for reducing Morbidity and Mortality'*, to which you contributed.

We have yet to receive any comments or corrections, so we are enclosing a copy of the original letter of 7 December 2004, the pages with your contribution and a second copyright assignment form (plus one for your records).

Your corrections along with any correspondence will be deposited in Archives and Manuscripts, Wellcome Library, along with the tapes from the meeting.

I would be grateful if you could return your corrections by **27 June 2005**.

Any further delay could compromise the planned publication date of November 2005. Earlier volumes are freely available at: www.ucl.ac.uk/histmed/witnesses.html

If you think I could answer any questions, please contact me by telephone on 020 7679 8123, by fax on 020 7679 8193 or by e-mail at *l.reynolds@ucl.ac.uk*

Yours sincerely,

Lois

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
enc: Jones page, 2 x copyright assignment form, original letter 7/12/04

signed 6/7/05


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were interacting, and how it was you came to be discussing, and it seems to me that what you have said, and I just wondered if this was an accurate impression, is that he actively sought out your data, he came to hear your talk, came to talk to you because it was of particular interest to him, and that we have not so much the coincidence that Richard intimated earlier with his question, but a deliberate conversation between people with a common interest.

**Avery**: We didn't know we had a common interest until we were drinking tea of all things.

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

**Avery**: Oh they had invited me over as a visiting speaker. They had heard of this, no not of this, I was fooling around with surfactants.

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

**Harding**: The short answer is no, I cannot, and I could go back and ask him. He commented about who gave him the money and I think probably he simply asked for research funding, looking at preterm labour. I cannot tell you more details about how much it was, not his personal salary, it must have been working expenses. It was for some considerable period of time, because he worked on this for several years.

### Professor Jane Harding

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

### Dr John Hayward

xxxx (b. 19xx) was in general practice for 16 years before re-training in public health. From 1994/6 he led the Effective Care Project in maternity services for the Camden and Islington Health Authority. He has been the Director of Public Health in Newham, London, since xxxx. See Hayward (2001).

### Dr Edmund Hey

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

### Professor Ross Howie

MR

### Dr Ian Jones

(b. 1965) is Publisher at the Wellcome Trust

has been

### Professor Richard Lilford

converted 26/7/05

### Professor Sir William Liley

KCMG FRS(NZ) (1929–83) was trained at Otago University, New Zealand, did research under Professor John Eccles on neuromuscular transmission, switching to obstetrics at the Women's National Hospital, Auckland, from 1959 as a New Zealand Medical Research Council Senior Research Fellow, then at the Auckland University Medical School as Research Professor in Perinatal Physiology from 1969 until his sudden[?premature?unfortunate?] death in 1983. His diagnostic procedure for rhesus haemolytic disease of the newborn was perfected so that he could predict which could remain in the uterus and which could not; led the team that performed the first successful intrauterine transfusion, and believed in the rights of the unborn child. See Hawgood (2005).

### Professor Sir Graham (Mont) Liggins

FRCOG FRCS (Edin) PhD (b. 19xx)

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WITNESS SEMINARS

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************

1. NAME Mr Ian Jones

2. ADDRESS
Publishing Manager, Wellcome Trust, 215 Euston Road, London NW1

3. WITNESS SEMINAR: Prenatal Corticosteroids for Reducing Morbidity and Mortality
15 June 2004

4. ASSIGNMENT

I confirm that I am the author and legal owner of my contribution to the proceedings of the Witness Seminar and of any comments I may have made on any draft transcript ("my Contribution"), and I assign to the Trustee of the Wellcome Trust ("the Trust") the copyright in my Contribution.

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Signed..... Date 6/7/05

Ind: 14/6/05

Please sign and return

**Lois Reynolds**

**From:** Jones ,Mr Ian [i.jones@wellcome.ac.uk]
**Sent:** 09 November 2005 21:24
**To:** ucgarey@ucl.ac.uk
**Subject:** RE: Witness Seminar: prenatal corticosteroids : last query

hi Lois, Publisher since 2003, at the Wellcome Trust since 1992.

incidentally i was born in 1965 not 1945 - i must be ageing particularly badly...

ian

✓ corrected 10/11/05.

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: Tue 10/25/2005 10:28 AM
To: Jones ,Mr Ian
Cc:
Subject: Witness Seminar: prenatal corticosteroids : last query

Hi Ian,
Could you let me have the missing date in your biographical note below?
Best wishes from Lois

0-0-0-0
Mr Ian Jones
(b. 1945) has been Publisher at the Wellcome Trust since 19xx.

0-0-0-0

Mrs Lois Reynolds
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11 March 2004

Fax: 0061 8 8204 5454

Dear Professor Keirse

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2pm-6pm**

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Continued/... Page 2

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Sir Iain Chalmers tells me that he has already spoken to you about this meeting and your important role as one of the key witnesses. Unfortunately, as he may have mentioned, we do not have the funds to assist with travel from overseas. However, we are able to fund your travel within the UK to and from the meeting and to offer you accommodation for the night of the meeting at the Ibis Hotel London Euston.

It really would be a great opportunity to document this obstetric success story. I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Daphne Christie

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

atts.

********************
*** TX REPORT ***
********************

NO See Chalmers e-mail 31/3/04

TRANSMISSION OK

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# Full Details

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Source: Who's Who About this publication
Publisher: A. & C Black
Category: Biography
Date of publication: 2004



LIGGINS, Sir Graham (Collingwood)

**Details:** Kt 1991; CBE 1983; FRCSE, FRACS, FRCOG; FRS 1980; FRSNZ 1976; Professor of Obstetrics and Gynaecological Endocrinology, University of Auckland, New Zealand, 1968-87, now Professor Emeritus (formerly Senior Lecturer); Consultant to National Women's Hospital, Auckland

**Education:** Univ. of NZ. MB, ChB, Univ. NZ, 1949; PhD, Univ. of Auckland, 1969

**Career:** MRCOG 1956; FRCSE 1958; FRACS 1960; FRCOG 1970. Is distinguished for his work on the role of foetal hormones in the control of parturition. Hon. FAGS, 1976; Hon. FACOG, 1978. Hon. MD Lund, 1983; Hon. DSc Edinburgh, 1996. Hector Medal, RSNZ, 1980

**Publications:** approx. 200 published papers

**Recreations:** forestry, sailing, fishing

**Address(es):** Postgraduate School of Obstetrics and Gynaecology, National Women's Hospital, Claude Road, Auckland 3, New Zealand, *Telephone:* (9) 3775127. 3/38 Awatea Road, Parnell, Auckland 1, New Zealand

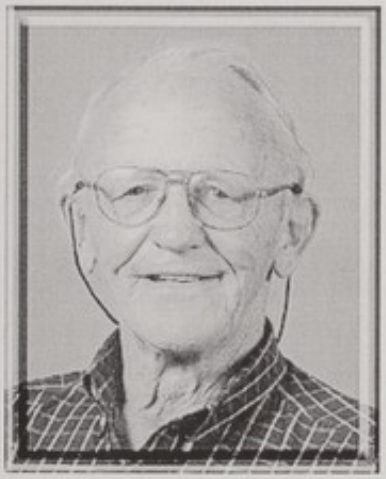
# Sir Graham Collingwood Liggins

**CBE, KB, MBChB (Otago), PhD, FRCS(Edin.), FRACS, FRCOG, FRNZCOG, FRS, FRSNZ**

**Emeritus Professor of Obstetrics and Gyneacology**

**Links**

The Liggins Institute



Soon after Professor Liggins joined the Department in 1959, Sir William Liley startled the world by performing a successful fetal transfusion. The international pre-eminence in the field of fetal medicine of the School at National Women's Hospital was consolidated subsequently by the work of Professor Liggins who pioneered chronic experiments fetal sheep. He solved the question that had perplexed philosophers and scientists from the time of Hippocrates as to how the time of birth was determined. He showed by ablating the fetal pituitary gland or adrenal glands in sheep that it was the fetus, not the mother as generally believed, who controlled birth. In subsequent work he found that the same mechanism controlling parturition also accelerated maturation of fetal organs to prepare for birth. The organs so affected included the lungs, immaturity of which is the major cause of mortality and morbidity in prematurely born infants. He showed that by stimulating the adrenal glands or infusing the adrenal steroid hormone, cortisol, lung development proceeded very rapidly to a mature state. With his paediatric colleague, Dr R.N. Howie, he organised a large randomised, placebo-controlled clinical trial of antepartum glucocorticoid treatment of women who were likely to deliver preterm to prevent respiratory distress syndrome (RDS) in the newborn. The success of the trial established the treatment worldwide and has been responsible for the prevention of death and intellectual handicap in tens of thousands of infants born preterm. Subsequently, with Dr J-C Schellenberg he continued his work in fetal sheep exploring the mechanism of corticosteroid action on the lung and the factors controlling growth of the lung. With the first surgical treatment of the human fetus (transfusion) and the first medical treatment (antepartum steroids), National Women's Hospital can claim to be the birthplace of Fetal Medicine.

Return to top

Professor Sir Graham Liggins
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16 February 2004

Fax: 00649 630 9858

Dear Sir Graham

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**2pm-6pm**

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These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I attach a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and lists our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

Sir Iain has suggested we invite you to this meeting and I am writing to enquire whether, in principle, you would be able to travel to England to participate as a main witness on Tuesday 15th June 2004. We are hoping to be able to raise the funds to assist with the cost of your travel.

It really would be a great opportunity to document this obstetric success story. I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

atts.

**********
*** TX REPORT ***
**********

TRANSMISSION OK

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|---|---|
| TX/RX NO | 2000 |
| CONNECTION TEL | 9006496309858 |
| SUBADDRESS | |
| CONNECTION ID | |
| ST. TIME | 17/02 12:11 |
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| PGS. | 8 |
| RESULT | OK |


# The Wellcome Trust Centre for the History of Medicine at University College London

24 Eversholt Street • London • NW1 1AD
www.ucl.ac.uk/histmed • +44 (0) 20 7679 8100

UCL


Professor Sir Graham Liggins
Department of Obstetrics & Gynaecology
University of Auckland
National Women's Hospital
Claude Road
Epsom
Auckland 3
NEW ZEALAND


Dr Daphne Christie
d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193


16 February 2004

Fax: 00649 630 9858

Dear Sir Graham

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2pm-6pm**

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## Wendy Kutner

**To:** g.liggins@auckland.ac.nz
**Subject:** Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesdsay 15th June 2004


WHATIS--sept2003 rev3ttdcwhk.DO...


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Dear Sir Graham, Please find attached a letter from Dr Daphne Christie inviting you to participate at a forthcoming Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth'. A paper outlining 'What is a Witness Seminar' is also attached. We have faxed a copy of the letter to you at the Department of Obstetrics & Gynaecology, The National Women's Hospital, and have sent you a hard copy, together with a copy of the Witness Seminar transcript on Maternal Care, which we hope you will find interesting. We very much hope you will be able to participate at the meeting. Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
24 Eversholt Street
LONDON NW1 1AD

Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

## Wendy Kutner

**From:** Graham Liggins [g.liggins@auckland.ac.nz]
**Sent:** 17 February 2004 23:50
**To:** w.kutner
**Subject:** RE: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesdsay 15th June 2004

Dear Ms Kutner,

I regret that my health rules out travel to the UK to join the Witness Seminar much as I would like to. Please thank Ian Chalmers for rmembering me and give him my best wishes.

Graham Liggins

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: Wednesday, 18 February 2004 2:36 AM
To: g.liggins@auckland.ac.nz
Cc: ucgachr@ucl.ac.uk
Subject: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesdsay 15th June 2004

Dear Sir Graham, Please find attached a letter from Dr Daphne Christie inviting you to participate at a forthcoming Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth'. A paper outlining 'What is a Witness Seminar' is also attached. We have faxed a copy of the letter to you at the Department of Obstetrics & Gynaecology, The National Women's Hospital, and have sent you a hard copy, together with a copy of the Witness Seminar transcript on Maternal Care, which we hope you will find interesting. We very much hope you will be able to participate at the meeting. Yours sincerely, Wendy Kutner

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## Wendy Kutner

**To:** g.liggins
**Cc:** Ichalmers; ucgachr@ucl.ac.uk
**Subject:** RE: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesdsay 15th June 2004

Dear Sir Graham, Thank you for your e-mail. We are obviously very disappointed that you are unable to travel to London for the meeting, but understand the difficulties involved. We are proceeding with plans for the Witness Seminar and will be in contact again in the near future. Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
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for the History of Medicine at UCL
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Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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## Wendy Kutner

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 18 February 2004 14:41
**To:** Alan (E-mail)
**Cc:** Wendy
**Subject:** FW: witness seminar query

Dear Alan
We have just heard that Sir Graham is unable to travel to the UK for the meeting. We are exploring the possibility of using either a video, or written statement, to document his work. Either way, a lot less expense involved.
I'll keep you informed of progress.
Daphne

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 17 February 2004 10:04
To: Alan Shiel
Cc: Wendy
Subject: RE: witness seminar query

Dear Alan
Thanks for this. At the moment we don't even know if he is willing (or able) to travel to the meeting, but at least I can say in my letter that we can offer assistance to bring him over. I'll ask the Royal College of Obstetricians and Gynaecologists if they might share the expense of bringing him across.
I'll let you know.
Many thanks,
Daphne

-----Original Message-----
From: Alan Shiel [mailto:a.shiel@ucl.ac.uk]
Sent: 16 February 2004 09:43
To: d.christie
Subject: RE: witness seminar query

well if its M Walport's idea..whom am I to say no???? Will he be doing anything else while he is here? ie..is it reasonable to try to spread the cost amongst other organisations ..I guess we would have to give him at least 3 nights hotel accom..maybe 4...
any idea what we are talking about for air fare...£800??
A

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 13 February 2004 14:08
To: Alan Shiel
Cc: Wendy
Subject: RE: witness seminar query

no - we would offer the cheapest option, or up to a certain amount, if you agree. Thanks, Daphne

-----Original Message-----
From: Alan Shiel [mailto:a.shiel@ucl.ac.uk]
Sent: 13 February 2004 13:35
To: d.christie
Cc: Wendy
Subject: RE: witness seminar query

goodness.how old is he? is tranporting him across the globe even a fair thing to do?? would he need business class travel? that would be a real problem..
A

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 13 February 2004 13:02
To: Alan (E-mail)
Cc: Wendy
Subject: witness seminar query

Dear Alan

Sir Iain Chalmers has recently passed on the suggestion (from Mark Walport) of 'Prenatal corticosteroids for reducing morbidity and mortality' as a suitable topic for a witness seminar. We are all very enthusiastic about developing a witness
seminar on this subject and are looking into holding a meeting in June, subject to room availability.

There are two witnesses from overseas whom Iain regards as essential to this story. Sir Graham Liggins, who made the initial discovery in the late 1960s
and early 1970s in New Zealand, and had been in receipt of Trust support for his animal work, and Professor Patricia Crowley (who lives in Dublin). Dublin is not such a problem but New Zealand sounds a difficult one - please can you tell me what funds might be available to bring Sir Graham over, that is of course if he was able to participate? According to Iain he hasn't travelled in a while. Iain also suggests that I could ask the Royal College of Obstetricians and Gynaecologists if they might share the expense of bringing him across, as a great opportunity to document an obstetric success story, etc. What are your views?

As you know Tilli is away and so I may be contacting you more frequently than usual over the next three weeks!

Best wishes, Daphne

Dr Daphne Christie
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine at UCL
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London NW1 1AD

Tel 020 7679 8125
Fax 020 7679 8193
Mobile 07810 541812
E-mail d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed

## Wendy Kutner

**To:** c.farquhar@auckland.ac.nz
**Cc:** ichalmers@jameslindlibrary.org
**Subject:** RE: Professor Sir Graham Liggins

Thank you very much for your help. Sir Graham has replied that he is unable to travel to England for the meeting. Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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for the History of Medicine at UCL
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LONDON NW1 1AD

Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

-----Original Message-----
From: c.farquhar@auckland.ac.nz [mailto:c.farquhar@auckland.ac.nz]
Sent: 18 February 2004 08:42
To: w.kutner@ucl.ac.uk
Cc: c.farquhar@auckland.ac.nz; ucgachr@ucl.ac.uk
Subject: Re: Professor Sir Graham Liggins

Thank you- I have asked the departmental secretary to get onto it as I am out of the department at present.

I am not sure if Iain relises that Cecelia Liggins died last year and Mont may not be well enough to travel that far but you never know.

All the best to Iain.

Cindy Farquhar

Quoting Wendy Kutner <w.kutner@ucl.ac.uk>:

> Dear Professor Farquhar, Sir Iain Chalmers has suggested I e-mail you to
> ask
> whether you would be kind enough to contact Sir Graham at his home and let
> him know that we have today sent him a fax to the Department of Obstetrics
> &
> Gynaecology at The National Women's Hospital (fax number 00649 630 9858)
> and
> an e-mail (g.liggins@auckland.ac.nz) inviting him to participate in a
> Witness Seminar on 15th June 2004 in London, England on 'Prenatal
> corticosteroids for reducing morbidity and mortality associated with
> preterm
> birth'. I do hope you are able to assist us in contacting Professor
> Liggins. Yours sincerely, Wendy Kutner
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www.ucl.ac.uk/histmed

**Wendy Kutner**

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 02 March 2004 09:10
**To:** g.liggins
**Cc:** Iain Chalmers; Wendy
**Subject:** RE: Witness Seminar

Dear Sir Graham
I have copied your message to Sir Iain as you requested. For your information his e-mail address is ichalmers@jameslindlibrary.org
WIth best wishes
Daphne Christie

-----Original Message-----
**From:** Graham Liggins [mailto:g.liggins@auckland.ac.nz]
**Sent:** 29 February 2004 21:58
**To:** d.christie
**Subject:** re: Witness Seminar

Dear Dr. Christie,
I don't have Iain Chalmmer's email address but would be grateful if you could send on a message to him. I will be happy to send him some information about 'What it was like at the time' and 'Why did things happen the way they did' for him to use any way he likes.

Regards, Mont Liggins

June 28, 2002, 4:23 pm
Search for grown up 'babies' follows ground-breaking 1970's prem baby study

Almost 1000 people who took part in the ground breaking medical discovery of a leading New Zealand scientist are being searched for 30 years later by researchers from The University of Auckland.

At the moment, the researchers don't even know their names.

The people were born to mothers who took part in the 1972 landmark study by Auckland doctors Professors Mont Liggins and Ross Howie. It made medical history by showing that giving steroids to mothers in premature labour speeds up the development of their babies' lungs.

"We only have their mother's name at the time of the birth, their sex, and their date of birth. We hope that anyone who was part of the original trial will get in touch with us," says Professor Jane Harding of the University's Liggins Institute.

Along with Dr Natalie Walker, Dr Stuart Dalziel and Dr Anthony Rodgers, she will compare the health of people whose mothers received an injection of steroids during the study with those who were in the placebo group.

"We are interested in whether receiving steroids before birth has any long-term effects on health once those babies reach adulthood," says Dr Walker of the University's Clinical Trials Research Unit.

The treatment was so effective that deaths from lung problems were halved in these tiny babies. As a result, steroid treatment is now routinely given to women at risk of premature delivery all around the world and has saved tens of thousands of lives.

The 'babies' are now aged between 28 and 33.

"Their mothers should remember that they were part of the trial," says Dr Dalziel of the Liggins Institute and Clinical Trials Research Unit. "Any woman who was likely to deliver a premature baby – between one to four months early – at National Women's Hospital between 1969 and 1974 was invited to participate in it.

"We have tracked down 80 people but have over 900 to go," he says.

"The original study was the first and largest trial of steroid treatment ever done, so this group of people is the only one of its kind in the world. The new study is an opportunity for them to once again enhance international medical knowledge," says Professor Harding.

People who think they were part of the trial either as mothers or babies can contact the study manager, Mary Wills on 0800 783 764 or via www.ctru.auckland.ac.nz.

Professor Sir Graham Liggins CBE FRCSE FRACS FRCOG FRS FRSNZ
Department of Obstetrics & Gynaecology
University of Auckland
National Women's Hospital, Claude Road, Epsom
Auckland 3, NEW ZEALAND

Dr Daphne Christie
d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

7 December 2004

Dear Professor Liggins

**Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality**

I enclose a draft transcript of the Witness Seminar on '**Prenatal Corticosteroids for reducing Morbidity and Mortality**' for your information. We intend to publish a version of the transcript in November 2005 under the auspices of the Wellcome Trust Centre for the History of Medicine at UCL.

If you would like to comment on any part of the transcript please feel free to do so. We do not encourage extensive alterations, as the purpose of these publications is to retain the freshness and informality of the meeting. However, any additional information can be added as a footnote and you may like to suggest such material. Please mark all corrections clearly on this copy and return it to me by **Monday 10 January.** Earlier published volumes in the series can be viewed on our website, www.ucl.ac.uk/histmed/witnesses.html

We would be grateful if you would provide a 2–3 sentence biographical piece for inclusion in the notes at the end of the volume including year of birth and dates of major appointments. We would also like to include illustrations of early work in the volume. If you have any suitable images or figures, please include these with the pages. They will be carefully scanned and returned in protective packaging.

The tapes, earlier versions of the transcript, and any additional correspondence generated by the editorial process, will be deposited in Wellcome Library. A version of the transcript will also be mounted on the Wellcome Trust Centre's website shortly after publication.

I look forward to hearing from you.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

LIGGINS
edited 2/6/05

3/38 Awatea Rd.
Parnell
Auckland

January 8, 200

Dear Dr. Chris

Here is the edited version of my tape recording contribution to the Witness Seminar. Also included is a reprint which contains Fig 1 which carries the history back a little since it summarises my work in sheep from which the serendipitous discovery of the effect of cortisol in accelerating fetal lung maturation was made. Do not use it if you do not feel that it is appropriate.Had I been present at the Seminar, I would have used it to introduce my comments. I thoroughly enjoyed reading the transcript and will look forward to reading the final version.I wish that I could have been present to enjoy it Live

omitted (e)

With kindest regards,

Mark

Graham C. Liggins

P.S. Please return this reprint which is my only one

Ret'd 21.1.05 DC

[Reprint enclosed was
Liggins GC, Fairclough RJ, Grieves SA, Kendall JZ, Knox BS. (1973) The mechanism of initiation of Parturition in the ewe. Recent Progress in Hormone Research 29: 111–58.

3/38 Awatea Rd.
Parnell
Auckland

January 8, 2005

Dear Dr. Christie,

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# FINAL REPORT TO THE WELLCOME TRUST, 1976

G.C. Liggins

Postgraduate School of Obstetrics and Gynaecology
University of Auckland
Auckland, New Zealand

December 31, 1976 marks the end of 8 years continuous support by the Trust. My research group remains intact with the continued support of the New Zealand Medical Council. The results of our research during this period of 8 years can be summarised as the discoveries of a new physiological system, a new disease and a new treatment.

1. A new physiological system

In the course of 8 years, knowledge of the physiology of the fetal control of parturition has progressed from an embryonic hypothesis to a well-substantiated and detailed understanding of the system in a number of species. My laboratory has maintained a leading place in the field.

2. A new disease

Our discovery of placental sulphatase deficiency, a rare disease of no great clinical importance, advanced the understanding of placental metabolism of oestrogen in a way analagous to the contribution of the discovery of steroid deficiencies to adrenal physiology.

3. A new treatment

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

The scientific community has recognized the contributions of my laboratory by various personal Awards and Distinctions. I wish to place on record my appreciation of the fact that these

modest achievements have resulted as much from the efforts of my colleagues and the support of the Wellcome Trust as from my own work. The support of the Trust not only has been generous but also understanding of the problems of budgeting during a period of development and of the need for flexibility. I have the satisfaction of feeling that the Trust's investment in my laboratory has yielded worthwhile dividends and I hope the Trust can share this sentiment.

## APPENDIX B

### Summary of progress during the current tenure of a Wellcome Trust Grant

A

1. Assays of plasma oestradiol-17β, plasma and tissue progesterone, 17α-hydroxyprogesterone and 20α-hydroxyprogesterone, and plasma and tissue prostaglandins have been developed and have been applied to animal and human materials.

2. The fetal role in the control of parturition has been extended in the sheep and has been demonstrated for the first time in a polytocous species (the rabbit).

3. The first direct evidence has been found for the involvement of a prostaglandin in the physiological control of parturition in any species. Dr Karim has described circumstantial evidence of this in humans but cannot exclude the possibility that release of prostaglandins is a consequence of labour. Our observations in sheep strengthen his case for a causal relationship between prostaglandins and labour in humans.

4. Withdrawal of a 'progesterone block' has been shown to be a minor component of the mechanism controlling labour in sheep.

5. We independently recognised the preparturient oestrogen surge in sheep described by Challis at Cambridge and demonstrated for the first time its relationship to fetal adrenal activity and to $PGF_{2\alpha}$.

6. We made the first serial measurements of the production rates and metabolic clearance rates of cortisol in fetal animals. We demonstrated that the preparturient rise in the concentration of cortisol in fetal lamb blood is a consequence of increased adrenal secretion.

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

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

/B

Investigations in Pregnant Women

1. Application of our assay of prostaglandins to the study of the physiological role of $PGF_{2\alpha}$ in human parturition.

2. A substantial quantity of $PGF_{2\alpha}$ for clinical use has been made available to me by the Upjohn Company. This material will be used for physiological rather than pharmacological investigations of the control of parturition.

3. Grossly deformed fetuses incapable of extra-uterine survival (e.g. anencephaly, severe hydrocephalus and spina bifida) will continue to provide suitable material for experimental investigations of the roles of fetal corticosteroids and oestrogens in human parturition. Experimental procedures are incorporated into the usual clinical management and the willing co-operation of such patients is usually readily obtained.

ack (e)
26.1.05

Dear Daphne,

Re: Mel Avery's comment on p.48. This is news to me and I cannot imagine where she got this idea from. I had no reason to make such a statement. I think it should be deleted unless it can be validated.

Best regards, Mont

**Hey:** I don't think we will take questions at this stage, because Mel has just set the scene. She's been very modest, she's our main American witness and she will be able to tell us later a lot more about the way in which things rolled out. We shall want to hear from her about when the collaborative trial was done and how it was done, and why it was done the way it was. But that's a long way down the line this afternoon. What we should do now, before we have our first break for discussion and questions is to hear from Jane Harding, who sits in the room Ross once worked in. I get the impression she almost had to sit on the papers that he had left behind, because he had left rather a lot, and it's surprising how much more is still coming out of those papers. So we haven't got Ross here in person, but you might just hear his voice.

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

> When I returned to a position as a Senior Lecturer in O and G, at the National Women's Hospital in 1959 I asked my friend Bill Limie, of fetal transfusion fame, how to choose a topic. He said to look for a major problem that

> was potentially solvable. The major problem was easy. Prematurity stood out above everything else. I naively thought that all I had to do was solve the ancient question of what controlled the onset of labour at term and the reason for premature onset would become apparent.

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

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

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

> From a tape recording, Mont Liggins: ~~I returned to fetal lungs, where~~ I had always been meticulous in doing a complete autopsy of all the lambs that I delivered, weighed

organs, helped I must say by my secretary. And I remember one morning, there was a lamb lying in a cage with its mother. A lamb that had been infused as a fetus with cortisol. And to my surprise this lamb was still breathing, not very healthy breathing, but it was alive and breathing. It had no right to be, it was so premature that its lungs should have been just like liver, and quite uninflatable. And this struck me as surprising. When we came to do the autopsy the lungs were partly inflated and this was absolutely surprising. So ~~rather than decide by~~ I speculated ~~that~~ ..... ~~that~~ the cortisol had accelerated the maturation of enzymes in the lung that caused accelerated maturation. Now at that time ...my...facilities were ~~kind of~~ fully occupied in studying the ~~serious~~ question of parturition and I didn't have time to pursue this problem. But it so happened that Mary Ellen Avery who was working on respiratory distress syndrome, and lung problems, and ~~one of~~ the discoverer that surfactant was necessary for the maintenance of lung expansion. ~~So~~ we were both going to ~~New Zealand and I was~~ where I was visiting New Zealand at a meeting in Christchurch and described my findings in ~~this, well it was~~ a series of lambs ~~actually,~~ with expanded lungs. She went home and ~~couldn't~~ ..... Set up experiments in rabbits, giving fetal rabbits cortisol, and produced the definitive paper on the effects of corticosteroids on lung maturation. So, as far as I was concerned, I left it at that point and thought, 'Well if it works in animals why shouldn't it work in human babies?' As far as we knew lungs in human babies had the same enzymes as animal lungs. Should we do a clinical trial

> in premature babies
> ~~on these~~ and put it to test? ~~So~~ I was working with Ross Howie, our paediatric colleague, and Ross is a very meticulous guy and Ross and I, with most input from Ross, ~~broke~~ wrote the protocol for ~~doing~~ a controlled clinical trial of corticosteroids in preterm infants. That protocol I might say has been cited as one of the earliest and best designed controlled trial protocols'.

**Harding:** One of the things that I noted in this recording and in my many discussions with the principal players was how they always give the credit to everybody else. You heard on the tape that Mont gives all the credit for surfactant work to Mary Ellen Avery, and for the clinical trials to Ross Howie. Ross, on the other hand, assures me that it's all Mont's idea. In fact it's my view that it was a quite remarkable partnership. Ross at the time was an MRC research fellow, he was the only paediatrician at the National Women's Hospital and indeed in New Zealand who was able to ventilate babies. I would like to quote now from his words describing these events, although I have abbreviated them somewhat:

> At the outset it might be worth reminding others that the project was only a sideline of the major work of both Mont Liggins and myself. Mont had his much more widely ranging research into reproductive endocrinology. My own main interest was in health rather than science, especially developing newborn services and I just happened to be around at the time. But I helped to design the trial,

Emeritus Professor Sir Graham ( Mont ) Liggins
FRCOG FRCS ( Edin ) PhD
Graduated in medicine at University of Otago in 1949. Appointed to a personal chair at the Postgraduate School of Obstetrics and Gynaecology, University of Auckland, specialising in Endocrinology and Fetal Physiology. His most important discovery was that the time of birth was controlled by the fetus, not the mother.

3/38 Awatea Rd.
Parnell
Auckland

June 15,2005

Dear Mrs. Reynolds,

I enclose a slide of partly aerated lungs of a newborn lamb treated with ACTH for 4 days at 118 days of gestation.
Please copy it and return it by return as I need to use it in the near future.

Best wishes,
Yours sincerely,
Mont

Mont Liggins

Returned by airmail 21/6/05. Received back by email 21/6/05.

Professor Sir Graham Liggins CBE FRCSE FRACS FRCOG FRS FRSNZ,
3/38 Awatea Road,
Parnell,
AUCKLAND,
New Zealand.

Lois Reynolds
*l.reynolds@ucl.ac.uk*
*www.ucl.ac.uk/histmed*
Tel: *020 7679 8123*
Fax: *020 7679 8192*

21 June, 2005

Dear Sir Graham,

**Witness Seminar: Prenatal Corticosteroids, 15 June 2004**

Thank you very much for the loan of the slide of the foetal sheep heart and lungs at 118 days after 4 days of ACTH, 1970, which is enclosed, looking as crisp and fresh as it did then.

Is there a similar slide – in your published work, and therefore accessible? – of a foetal sheep heart and lung at 118 days with no ACTH, for comparison?

Yours sincerely,

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey

**Lois Reynolds**

**From:** Lois Reynolds [ucgarey@ucl.ac.uk]
**Sent:** 10 August 2005 16:39
**To:** g.liggins@auckland.ac.nz
**Subject:** Witness Seminar: Prenatal Corticosteroids : final proof for authors

cortico6-1008
05-xpix.txt

Dear Sir Graham,

Attached is an electronic version of the Witness Seminar transcript without the illustrations (234KB), as sent to Ross Howie and Jane Harding for final comments and corrections. We would be grateful for your corrections by 7 September 2005

A hard copy will also be sent by post tomorrow, which includes permission to reproduce your letter to Iain Chalmers, dated 6 April 2004, as an appendix along with Ross's memoir as distributed at the meeting. Tilli will provide a second appendix on the funding from the Wellcome Trust.

I would like to draw your attention again to the matter of Mel Avery's comments on page 48 in footnote 75 (copied below). Your response in January 2005 was to suggest that the comments should be deleted, because you considered them to be inaccurate. We have not removed Mel's comment, for a number of reasons.

A Witness Seminar brings together people whose memories of the same event may differ. This was certainly the case, for example, at the meeting on the Committee of Safety of Drugs (Volume 1, 1997, freely available at www.ucl.ac.uk/histmed following 'Publications' link). Three different versions of the origin of the yellow cards for adverse reactions (see pages 111, 124 and 127) were revealed.

Sometimes, participants disagree with each other during or after the meeting. For example, a remark by Sir Christopher Booth during 'The origins of neonatal intensive care in the UK' (Vol. 9, 2001) concerning the appointment of Sir Peter Tizard's successor as Professor of Paediatrics at the Royal Postgraduate Medical School at the Hammersmith in 1972 irritated several contributors sufficiently for them to send us their objections, and to ask that these be made clear in the publication. This we were happy to do (please see note 183, page 44 of the transcript of the meeting). All the original letters are also deposited along with the tapes and the other records of the meeting in the Wellcome Library, London, and are available to researchers.

The published transcript of the meeting offers everyone the opportunity to comment on others' views, which we then include in an appropriate footnote. (viz. the objections about Chris Booth's comments above). In this particular instance, both you and Mel could be right. Mel may be completely correct in saying she was told what she reports she was told about you. You may be completely correct in saying that you said no such thing. As historians and editors, we cannot judge what might have happened, nor censor what participants say. What we can do is to offer transparency and invite further participation by witnesses.

I've asked Ross if he would like to reply on the subject of the relative efficacy of betamethasone and dexamethasone, as you suggested.

Best wishes from Lois Reynolds

0-0-0-0-0-0 (page 48)0-0-0-0-0-0

AVERY: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically told Dawes that he would not allow anyone to do any work, even discuss, surfactants for the whole time that Mont was there. (FN)

The footnote at present reads:
Professor Mont Liggins wrote to Dr Ross Howie: 'I spent a sabbatical with Geoffrey in 1970 but I certainly made no such statement about surfactant. I can't imagine where Mel got that idea. It should be deleted unless it can be validated. I was aware of the suggestion about the relative efficacy of batamethasone and dexamethasone [see note 163]. I think the evidence deserves your critical comment. I recall that Peter Nathanielsz reported that betamethasone was more active than dexamethasone in an effect on a kidney function (I think) in fetal sheep. I don't have the reference but I could get it from Peter if you would like me to.' E-mail to Professor Ross Howie, 11 January 2005. Professor Liggins also wrote to Dr Daphne Christie: 'Mel Avery's comment …is news to me and I cannot imagine where she got this idea from. I had no reason to make such a statement. I think it should be deleted unless it can be validated.' E-mail to Dr Daphne Christie, 8 January 2005.

Note 163: Dr Clive Dash wrote: 'Various preparations of betamethasone are available in different countries. The preparations are all designed to release the active sterol, betamethasone, but at different rates. The soluble phosphate preparation is suitable for intravenous administration, like hydrocortisone, as well as intramuscular injection. The acetate preparation is not suitable for intravenous (IV) use. Some products are a mixture of the acetate and phosphate derivatives (e.g. Celestone®, Schering). In some countries dexamethasone is more readily available than betamethasone and this is why it has featured in some studies. These two steroids are isomers in which the methyl group differs in its orientation (dexamethasone is 9-a-fluoro 16-a methyl prednisolone; betamethasone is 9-a-fluoro 16-b methyl prednisolone) [Sweetman (2002): 1063 and 1067]. In the usual pharmacological tests of corticosteroid potency, they are equivalent. In general, the mode of action (pharmacodynamics) seem similar, so they should be therapeutically equivalent.' E-mail to Dr Daphne Christie, 10 January 2005.

0-0-0-0-0

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine
at UCL
210 Euston Road,
LONDON
NW1 BE

Tel: 020 7679 8123
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Fax: 020 7679 8192
www.ucl.ac.uk/histmed

The Wellcome Trust Centre is supported by the Wellcome Trust, a registered charity, no. 210183.

To: The History of Twentieth Century Medicine Group

I agree to the above request to reproduce the complete letter from me to Sir Iain Chalmers, dated 6 April 2004, a selection of which was read at the Witness Seminar on Prenatal Corticosteroids on 15 June 2004, along with the three slides, to be described as:

> Liggins to Chalmers, 6 April 2004.
>
> The slides will be credited to you as: Reproduced by permission of Professor Sir Graham Liggins.

as an appendix in the edited and annotated transcript, 'Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth', Volume 25, in the series, *Wellcome Witnesses to Twentieth Century Medicine* edited by L A Reynolds and E M Tansey to be published by the Wellcome Trust Centre for the History of Medicine at UCL in November 2005.

Signed ..... Dated 19/8/05

Professor Sir Graham Liggins CBE FRCSE FRACS FRCOG FRS FRSNZ,
3/38 Awatea Road,
Parnell,
AUCKLAND,
New Zealand

Appendix 1 · permission from Chalmers + Liggins.

Dear Mrs. Reynolds,
I think the Seminar has done a great job of recording the history of Antenatal Steroids and putting the story into perspective.

P.12 the tape is held by The Director, Liggins Institute, University of Auckland, P.O. Box 92 019 Auckland.
P. 14 Second to last line. 'Progesterone' should be ' Oestrogen '
P. 15 Footnote. Third to last line. ' Clear ' should be ' Opaque '.
P. 17 San Francisco Group is as listed in the Authors.
P 25 Harding. " He did all that before he left New Zealand for California and when etc".
P 115 Please add FRS to my qualifications. Born 1926 Chair 1971

Re my letter to Iain Chalmers. Slides 2 and 3 were originals and I do not have copies .But I think only Slide 1 needs publishing.

I am sure that the Editor, Australian and New Zealand Journal of Obstetrics and Gyaecology will be pleased to arrange and publish a review

Kindest regards,

Mont

G.C. Liggins

permission filed with copyright form 1/9/05.
rec'd 05/8/05 ack by email 1/9/05

## Lois Reynolds

**From:** Lois Reynolds [ucgarey@ucl.ac.uk]
**Sent:** 01 September 2005 15:14
**To:** g.liggins@auckland.ac.nz
**Subject:** Witness Seminar: prenatal corticosteroids

Thanks, Prof Liggins, for your corrections and permission to reproduce your letter to Sir Iain Chalmers of 6 April 2004 and the slide.
(1) Do you have a photograph of a premature lamb's lung that cannot be inflated, for comparison?
(2) Dr Howie asks whether it was Nature or Lancet that refused your first joint paper, which eventually appeared in Pediatrics? There is no me ntion of this journal in your reports to the Welcome Trust. Can you remember which it is?
Ross wrote:
'It would be rather fun to send it to the last-mentioned [Lancet]: it rejected our original paper. See letter from Mont Liggins to Iain Chalmers (your proposed appendix). In the letter Mont said it was Nature but he queried this with me after he had written it. My firm memory is that it was The Lancet and not Nature. The latter journal in my time was not I think interested in clinical papers, but could well have been offered some of Mont's other work. The rejection letter was as I remember very prompt, courteous and brief: there would have been very little time to send it to referees.

I was, ironically, reminded of The Lancet by a circular email that I received only this morning which included this paragraph:
"Medical professionals like you subscribe to The Lancet because of our practice-changing content. They know that they can rely on The Lancet to publish the cream of the world's medical research - and to provide the news and analysis that puts that research into a clinical context."
I was pleased to read it. The Lancet must have changed its policies in the last 33 years! It has of course recently published the 30-year followup by Stuart Dalziel et al, the reference to which you have cited somewhere in the transcript.'

(3) Your email to Dr Howie said: 'I recall that Peter Nathanielsz reported that beta was more active than dex in an effect on a kidney function (I think) in fetal sheep. I don't have the reference but I could get it from Peter if you would like me to.' E-mail to Professor Ross Howie, 11 January 2005. Could you suggest the appropriate paper that should appear here?

Hope all is well with you.

Best wishes from Lois

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The Wellcome Trust Centre is supported by the Wellcome Trust, a registered charity, no. 210183.

## Lois Reynolds

**From:** Graham Liggins [g.liggins@auckland.ac.nz]
**Sent:** 02 September 2005 02:03
**To:** ucgarey@ucl.ac.uk
**Subject:** RE: Witness Seminar: prenatal corticosteroids

Dear Lois,

Yes, Lancet, not Nature. ✓ on transcript
No, I don't have a photo of uninflated lamb lungs but everyone (except you, perhaps ) knows what they look like. ✓ asked again 2/9/05
If you have Peter Nathanielsz address which I don't have please ask him about beta v. dex.
I have lost Ross's e-mail of January 11 so I am unclear as to as to the comment requiring a reference. Please enlighten me. (sent

also emailed list of Binns publications to Mont 2/9/05

Best wishes, Mont
-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: Friday, 2 September 2005 2:14 AM
To: g.liggins@auckland.ac.nz
Subject: Witness Seminar: prenatal corticosteroids

Thanks, Prof Liggins, for your corrections and permission to reproduce your
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1: J Nat Toxins. 1999 Feb;8(1):63-80. 

# Teratological research at the USDA-ARS poisonous plant research laboratory.

James LF.

USDA-ARS Poisonous Plant Research Laboratory, Logan, UT 84341, USA.

Research on teratogenic plants started at the USDA-Agricultural Research Service-Poisonous Plant Research Laboratory in the mid 1950s when Dr. Wayne Binns, Director of the laboratory, was asked to investigate the cause of a cyclopian facial/skeletal birth defect in lambs. Dr. Lynn F. James joined the staff shortly after. These two people worked as a team wherein most planning was done jointly with Binns supervising most of the laboratory work and James the field studies. It was determined that when pregnant ewes grazed Veratrum californicum on day 14 of gestation a significant number of lambs had the cyclopic defect. Skeletal and cleft palate birth defects in calves was associated with pregnant cows grazing certain lupine species during 40-70 days of gestation. Shortly thereafter research work was initiated on locoweed which caused abortions, wasting, right heart failure, skeletal birth defects, and fetal right heart failure. Dr. Richard F. Keeler, a chemist who joined the staff in the early 1960s, isolated and characterized the teratogens in V. californicum as the steroidal alkaloids cyclopamine, jervine, and cycloposine. He also described the teratogen in lupines as the quinolizidine alkaloid anagyrine and the piperidine alkaloid ammodendrine. Drs. Russell Molyneux and James identified the toxin in locoweed as the indolizidine alkaloid swainsonine. In 1974 the editor of Nutrition Today (Vols. 9 and 4) wrote "The idea that birth defects occurring in humans may be in some way related to diet is not widely held ..." Dr. Lynn James pointed out in this issue that such defects in animals can be produced with absolute predictability and regularity by foods ordinarily beneficial to livestock. Management strategies have been developed to prevent or minimize the economic impact of the cyclopian lamb and the crooked calf condition on livestock producers and well on the way to doing the same with locoweed. It is of interest to note that livestock research on Veratrum, lupines and locoweed and toxins therefrom are now significant research tools for specific human health problems.

Publication Types:
- Historical Article

PMID: 10091129 [PubMed - indexed for MEDLINE]

## Lois Reynolds

**From:** Lois Reynolds [ucgarey@ucl.ac.uk]
**Sent:** 02 September 2005 10:04
**To:** g.liggins@auckland.ac.nz
**Subject:** RE: Witness Seminar: prenatal corticosteroids

Liggins-1970fe
lamblungs-21€

Thank you for your email , Prof Liggins.

Many readers of this volume will be historians of medicine and are not familiar with animal work. The spectacular contrast that you describe (see quote following) would be more accessible with an image of an untreated premature lung alongside the image attached.

'A lamb that had been infused as a fetus with cortisol. And to my surprise this lamb was still breathing, not very healthy breathing, but it was alive and breathing. It had no right to be. It was so premature that its lungs should have been just like liver, and quite uninflatable.'

Your email of 11 January 2005 follows. Best wishes from Lois

---

From: Graham Liggins
To: 'Howie'
Sent: Tuesday, January 11, 2005 3:55 PM
Subject: RE: Wellcome seminar June 2004

Dear Ross,
I spent a sabbatical with Geoffrey in 1970 but I certainly made no such statement about surfactant. I can't imagine where Mel got that idea. It should be deleted unless it can be validated.
I was aware of the suggestion about the relative efficacy of betamethasone and dexamethasone. I think the evidence deserves your critical comment. I recall that Peter Nathanielz reported that beta was more active than dex in an effect on a kidney funtion ( I think ) in fetal sheep. I don't have the refernce but I could get it from Peter if you would like me to.

Regards, Mont

---

-----Original Message-----
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Sent: 02 September 2005 02:03
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: prenatal corticosteroids

Dear Lois,

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about beta v. dex.
I have lost Ross's e-mail of January 11 so I am unclear as to as to the comment requiring a reference. Please enlighten me.

Best wishes, Mont
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## Lois Reynolds

**From:** Lois Reynolds [ucgarey@ucl.ac.uk]
**Sent:** 05 September 2005 10:57
**To:** g.liggins@auckland.ac.nz
**Subject:** RE: Witness Seminar: prenatal corticosteroids

Thank you, Prof Liggins. We would need the photo by early October. Is there an alternative approach that I could pursue? Would there be a photo included in any of the early papers?

Best wishes from Lois

-----Original Message-----
From: Graham Liggins [mailto:g.liggins@auckland.ac.nz]
Sent: 03 September 2005 07:19
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: prenatal corticosteroids

Dear Lois,
I will find out whether someone in Peter Gluckman's lab could get a photo of premature uninflated lamb lungs but it will not be easy at this time of the year.

Regards, Mont

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: Friday, 2 September 2005 9:04 PM
To: g.liggins@auckland.ac.nz
Subject: RE: Witness Seminar: prenatal corticosteroids

Thank you for your email , Prof Liggins.

Many readers of this volume will be historians of medicine and are not familiar with animal work. The spectacular contrast that you describe (see quote following) would be more accessible with an image of an untreated premature lung alongside the image attached.

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charity, no. 210183.

**Lois Reynolds**

**From:** Lois Reynolds [ucgarey@ucl.ac.uk]
**Sent:** 09 September 2005 10:46
**To:** g.liggins@auckland.ac.nz
**Subject:** RE: lungs

Many thanks, Mont. That is a great help, which might do the trick. Hope all is well with you. Best wishes from Lois

PS Jane has just sent a photo of you, Ross, Jane and Stuart taken in July, which we hope to use.

-----Original Message-----
**From:** Graham Liggins [mailto:g.liggins@auckland.ac.nz]
**Sent:** 09 September 2005 00:28
**To:** ucgarey@ucl.ac.uk
**Subject:** lungs

Dear Lois,

I am afraid I cannot locate a photo of uninflated lungs but will keep trying. I suggest that your historians will be satisfied if you add to the Figure Legend as follows: " The pale areas are tissue inflated with air. The dark areas are uninflated lung " Modify this as you wish.
Regards, Mont

**Lois Reynolds**

**From:** Lois Reynolds [ucgarey@ucl.ac.uk]
**Sent:** 25 October 2005 12:43
**To:** g.liggins@auckland.ac.nz
**Subject:** WitSem: prenatal corticosteroids : queries : urgent

cortico-app1-gins-251005.d

Hi Prof Liggins,

Attached are images of your letter to Iain Chalmers, with footnotes attached. I haven't located slides two or three and reference to them will be deleted in the final layout. There are a couple of queries:

1. Caption to the partially inflated lamb lungs: Is this suitable? I guessed at the date of birth:
Figure 7. Partially inflated lamb lungs infused with cortisol at 118 days, born at 120 days, photographed after autopsy, 1968? 69?.

2. Binns et al: I could find no reference to the work you suggested. Could you let me have the full reference? The appreciation used is: James L F. (1999) Teratological research at the USDA–ARS poisonous plant research laboratory. Journal of Natural Toxins 8: 63–80. If there is a more appropriate one, we would be glad to substitute it.

Hope all is well with you.

I would be glad of the information by 7 November.

Best wishes from Lois

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine
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210 Euston Road,
LONDON
NW1 BE

Tel: 020 7679 8123
email: l.reynolds@ucl.ac.uk
Fax: 020 7679 8192
www.ucl.ac.uk/histmed

## Lois Reynolds

**From:** Tilli UUnet [almo45@uk.uumail.com]
**Sent:** 01 November 2005 12:08
**To:** ucgarey@ucl.ac.uk
**Subject:** RE: Avery/Liggins FN : which combination required??

You are very confused( and confusing)- this needs attention.
What is in the text should be what has been agreed with Avery - I thought this had been changed to be quite precise - Avery's recollections are that she was told that Liggins had told Dawes there should be no work on surfactant.
There should then be afootnote to the effect that we have been in contact with both Liggins & Avery about the sentence. Liggins requested removal, but we have asked for it to be retained - this is what Avery remembers - and it's interesting that thtat is what she recalls - the details of the 'Editors note' are superfluous - that is a lazy paste job from th eletter we wrote to Liggins - please re-draft and sent it to me for approval.
Tilli

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 01 November 2005 11:43
To: Tilli UUnet
Subject: RE: Avery/Liggins FN : which combination required??

Hi Tilli,

Which variables would you prefer in the footnote?

The more options I looked at the more complicated it got. As you say, the dates raise questions that look like hostages to fortune.

Logically the paragraph in the text should be as delivered -- Mel Avery implying that Liggins told Dawes not to talk about sufactant, with Liggins' reply in the footnote.

I lose my logic at this point -- as we asked both Avery and Liggins not to withdraw their statement (10 August), to which they both tacitly agree.

You urge clarification from Avery (it is now October) -- who was the mover and her reply is that Dawes told Liggins not to talk about sufactant during his visit.

The final requirement is the Editors' Note on differing points of view of people involved in the same story (which is the same argument we used in the 10 August email to Avery and Liggins).

You have clearer sight than I do. Perhaps I need to distance myself from the Editors' note.

All advice welcome.

Keep warm.

Best wishes from Lois

-----Original Message-----
From: Tilli UUnet [mailto:almo45@uk.uumail.com]
Sent: 01 November 2005 11:22
To: ucgarey@ucl.ac.uk
Subject: RE: Avery/Liggins FN : which combination required??

lois - I don't understand this - please be clear as to what you wish me to do. Tilli

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 01 November 2005 10:20
To: Tilli UUnet
Subject: Avery/Liggins FN : which combination required??

Hi Tilli,

Just to recap:

(i) original statement about Dawes and Liggins by Mel Avery as delivered in the text
(ii) Liggins complaint, Jan 05 in footnote
(iii) Avery changing who said what Oct 05
(iv) Editors' note: cut by one third

OR:

(i) Avery's changed statement, Oct 05, in the text.
(ii) Liggins complaint, Jan 05 about Avery's statement delivered in June 04, Jan 05
(iii) editor's note, again shortened

OR

(i) Avery's changed statement, Oct 05, in the text
(ii) editor's note, incorporating the original Avery-Liggins wish to withdraw described, but the rest cut.

Many thanks from Lois

PS Sorry to hear you are feeling poorly still -- bed is best and there is a nip in the air -- damp and cold. Take care.

-----Original Message-----
From: Tilli UUnet [mailto:almo45@uk.uumail.com]
Sent: 01 November 2005 08:02
To: ucgarey@ucl.ac.uk
Subject: RE: Wellcome Trust not to respond to Chalmers & Avery/Liggins FN

I still don't understand why Mel Avery's comments are in the text AND in the footnote.This needs further atention. The rest of the footnote iws also too verbose - all this detail is not necessary.
Tilli

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 31 October 2005 20:12
To: Tilli UUnet
Subject: RE: Wellcome Trust not to respond to Chalmers & Avery/Liggins FN

Thanks, Tilli. Revised (2). Best wishes from Lois

0-0-0-0
Avery: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically told Dawes that he would not allow anyone to do any work on, even discuss, surfactants for the whole time that Mont was there. (FN)

(FN) Professor Sir Graham (Mont) Liggins wrote: 'I spent a sabbatical with Geoffrey in
1970 but I certainly made no such statement about surfactant. Mel Avery's comment is news to me and I cannot imagine where she got this idea from. I had no reason to make such a statement. I think it should be deleted unless it can be validated.' E-mail to Dr Daphne Christie, 8 January 2005. See also note 185. Professor Mel Avery wrote: 'My statement
should say: "Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically was told by Dawes that he would not allow anyone to do any work on, even discuss, surfactants for the whole time that Mont was there."'E-mail to Mrs Lois Reynolds, 26 October 2005. Editors note: We have not removed Avery's comment nor the reply from Liggins, as they
both requested, for a number of reasons. A Witness Seminar brings together people whose memories of the same event may differ. This was certainly the case, for example, at the meeting on the Committee of Safety of Drugs (Volume 1, 1997, freely available at www.ucl.ac.uk/histmed following the links to Publications/Wellcome Witnesses). Three different versions of the origin of the yellow cards for adverse reactions were revealed (see pages 111, 124 and 127). Sometimes, participants disagree with each other during or after the meeting. For example, a remark by Sir Christopher Booth during 'The origins of neonatal intensive care in the UK' (Vol. 9, 2001) concerning the appointment of Sir Peter Tizard's successor as Professor of Paediatrics at the Royal Postgraduate Medical School at the Hammersmith in 1972 irritated several contributors sufficiently for them to send us their objections, and to ask that these be made clear in the publication. This we were happy to do (please see note 183, page 44 of the transcript of the meeting). All the original letters from each meeting are also deposited along with the tapes and the other records in the Wellcome Library, London, and are available to researchers. The published transcript of the meeting offers everyone the opportunity to comment on others' views, which we then include in an appropriate footnote (viz. the objections about Chris Booth's comments above). In this particular instance, both Avery and Liggins could be right. Avery may be completely correct in saying that she was told what is reported above. Liggins may be completely correct in saying that he said no such thing. As historians and editors, we cannot judge what might have happened, nor censor what participants say. What we can do is to offer transparency and invite further participation by witnesses. 1 November 2005.

0-0--0

-----Original Message-----
From: Tilli UUnet [mailto:almo45@uk.uumail.com]
Sent: 31 October 2005 19:45
To: ucgarey@ucl.ac.uk
Cc: t.tansey@ucl.ac.uk
Subject: RE: Wellcome Trust not to respond to Chalmers & Avery/Liggins FN

dera Lois,

irritated several contributors sufficiently for them to send us their objections, and to ask that these be made clear in the publication. This we were happy to do (please see note 183, page 44 of the transcript of the meeting). All the original letters from each meeting are also deposited along with the tapes and the other records in the Wellcome Library, London, and are available to researchers. The published transcript of the meeting offers everyone the opportunity to comment on others' views, which we then include in an appropriate footnote (viz. the objections about Chris Booth's comments above). In this particular instance, both Avery and Liggins could be right. Avery may be completely correct in saying that she was told what is reported above. Liggins may be completely correct in saying that he said no such thing. As historians and editors, we cannot judge what might have happened, nor censor what participants say. What we can do is to offer transparency and invite further participation by witnesses. 1 November 2005.

0-0-0-0-0

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www.ucl.ac.uk/histmed

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## Lois Reynolds

**From:** Graham Liggins [g.liggins@auckland.ac.nz]
**Sent:** 15 November 2005 00:37
**To:** l.reynolds@ucl.ac.uk
**Subject:** response to queries

Dear Mrs. Reynolds,

Query 1. In letter. Binns, W. Anderson, W.A. and Sullivan, D. J. ( 1960 ) Further observations on a congenital cyclopian-type malformation in lambs. J. Amer. Vet. Assn. 137, 515
Query 2. I am happy with Mel Avery's comment as it now stands although I was unaware of it.

Query 1. In e-mail. Caption is O.K.

Query 2. See above

Incidentally, there is a sentence I don't understand .The first sentence on page 7 beginning "The story'. I am sorry I didn't pick it up earlier

Best regards, Mont

**Lois Reynolds** copy in Avery file. 20/3/07

**From:** Lois Reynolds [ucgarey@ucl.ac.uk]
**Sent:** 15 November 2005 10:28
**To:** Avery, Mary
**Subject:** RE: Prenatal Corticosteroid Transcript : Final query 15 Nov 2005, urgent

**Importance:** High

Thank you, Prof Avery.

To confirm, (1) below is the Dawes statement as it will appear in the published volume.

May I also raise a final query conerning the sentence below (2). Would it be more accurate with one phrase removed?

Best wishes from Lois

FN 86: Avery-Liggins.

0-0-0-0

1) Avery: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically was told by Dawes that he [Dawes] would not allow anyone to do any work on, even discuss, surfactants for the whole time that Mont was there.FN86

FN86 There was some discussion between Avery, Liggins and the editors on this point. This correspondence, along with tapes and other records of the meeting, will be deposited in CG/253, Archives and Manuscripts, Wellcome Library, London.

(2) Query on following sentence:

The story of the glucocorticoids moved ahead when Liggins and Howie proposed a randomized control trial [of glucocortico-steroids], I think 100 days before the birth of the lamb, and it was obvious that the effect was reproducible.

Would it be more accurate as follows??

The story of the glucocorticoids moved ahead when Liggins and Howie proposed a randomized control trial and it was obvious that the effect was reproducible.

0-0-0-0--0

-----Original Message-----
From: Avery, Mary [mailto:Mary.Avery@childrens.harvard.edu]
Sent: 14 November 2005 20:05
To: l.reynolds@ucl.ac.uk
Subject: Prenatal Corticosteroid Transcript

Good afternoon Lois,

In regards to the letter you sent the 1st of November, I see no need for further elaboration.

Thank you for all your efforts to clarify a complicated situation.

Cheers, Mel

**Lois Reynolds** copy in Avery file. 20/3/07

**From:** Lois Reynolds [ucgarey@ucl.ac.uk]
**Sent:** 15 November 2005 10:28
**To:** Avery, Mary
**Subject:** RE: Prenatal Corticosteroid Transcript : Final query 15 Nov 2005, urgent

**Importance:** High

Thank you, Prof Avery.

To confirm, (1) below is the Dawes statement as it will appear in the published volume.

May I also raise a final query conerning the sentence below (2). Would it be more accurate with one phrase removed?

Best wishes from Lois

0-0-0-0

1) Avery: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically was told by Dawes that he [Dawes] would not allow anyone to do any work on, even discuss, surfactants for the whole time that Mont was there.FN86

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Would it be more accurate as follows??

The story of the glucocorticoids moved ahead when Liggins and Howie proposed a randomized control trial and it was obvious that the effect was reproducible.

0-0-0-0--0

-----Original Message-----
From: Avery, Mary [mailto:Mary.Avery@childrens.harvard.edu]
Sent: 14 November 2005 20:05
To: l.reynolds@ucl.ac.uk
Subject: Prenatal Corticosteroid Transcript

Good afternoon Lois,

In regards to the letter you sent the 1st of November, I see no need for further elaboration.

Thank you for all your efforts to clarify a complicated situation.

Cheers, Mel

# The Wellcome Trust Centre for the History of Medicine at University College London

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Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

11 March 2004

Professor Lilford

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

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We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion. We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Daphne Christie

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

encs.

## Wendy Kutner

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 16 April 2004 10:33
**To:** Wendy
**Subject:** FW: Invitation to Prof Lilford for 15 June

Wendy
I'm a bit confused ... have you spoken to Annette? Did Prof Lilford receive the original invitation? If not please send another. Thanks Daphne
-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 07 April 2004 10:49
To: Daphne Christie (E-mail)
Cc: Richard Lilford (E-mail)
Subject: Invitation to Prof Lilford for 15 June

Dear Daphne

Annette (0121 414 2226), Prof Lilford's PA, called because I asked her to ensure that Prof Lilford sends an acceptance of his attendance at The Wellcome Trust event on the 15th June (Richard told me in conversation that he would attend). Annette cannot find any evidence of an invitation. Please would you contact her to clarify the situation.

Best wishes, Iain

# The Wellcome Trust Centre for the History of Medicine at University College London

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26 April 2004

Dear Professor Lilford

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004, 2pm–6pm**

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

pp **Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

enc.

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

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C MacArthur
**Professor of Clinical Epidemiology**
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Our Ref: 714RJL/ace

29 April 2004

Mrs W Kutner
The Wellcome Trust Centre
For the History of Medicine
University College London
24 Eversholt Street
London
NW1 1AD

Dear Mrs Kutner

**The Wellcome Trust's History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday, 15 June 14:00-18:00hrs**

Would you kindly distribute the attached paper at the above meeting.

Many thanks.

Yours sincerely

Evans

Richard J Lilford, PhD., FRCOG., FRCP., FFPH
Professor of Clinical Epidemiology
Email: r.j.lilford@bham.ac.uk
Tel: 0121 414 2226
Fax: 0121 414 2752

Att

International Journal for Quality in Health Care 2002; Volume 14, Number 3: 175–181

# The Leeds University maternity audit project

B. WILSON[1], J. G. THORNTON, J. HEWISON[2], R. J. LILFORD[3], I. WATT[4], D. BRAUNHOLTZ[3] AND M. ROBINSON[5]

[1]Centre for Reproduction Growth and Development, [2]Department of Psychology and [5]Nuffield Institute, Leeds University, Leeds, [3]Department of Public Health, Birmingham University, Birmingham and [4]Department of Health Studies, York University, York, UK

## 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

Address reprint requests to J. G. Thornton, Department of Paediatrics, Obstetrics and Gynaecology, 34 Hyde Terrace, Leeds LS2 9LN, UK. E-mail: j.g.thornton@leeds.ac.uk

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

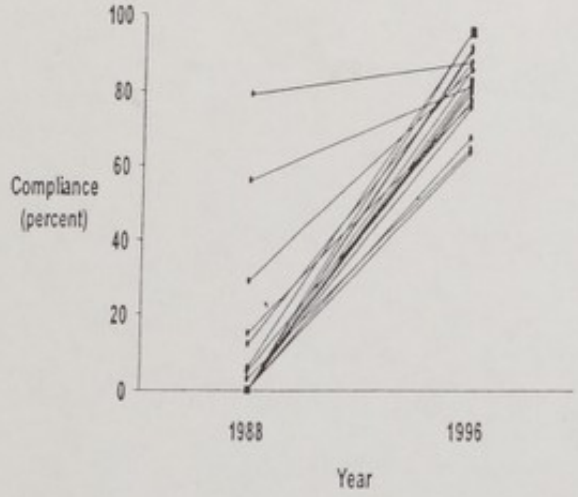


Figure 1 The rate of compliance with the steroid use standard in each unit for each time period.

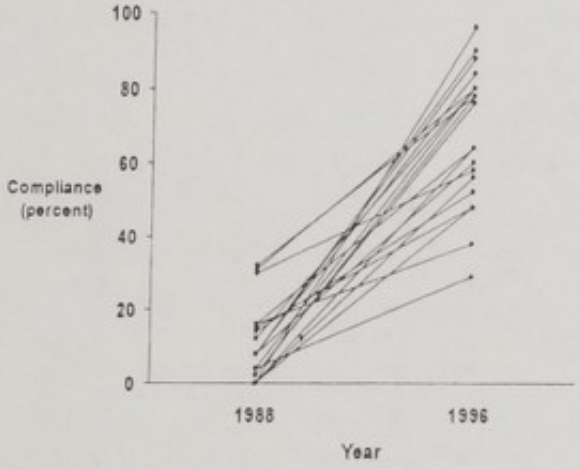


Figure 2 The rate of compliance with the instrumental delivery standard in each unit for each time period.

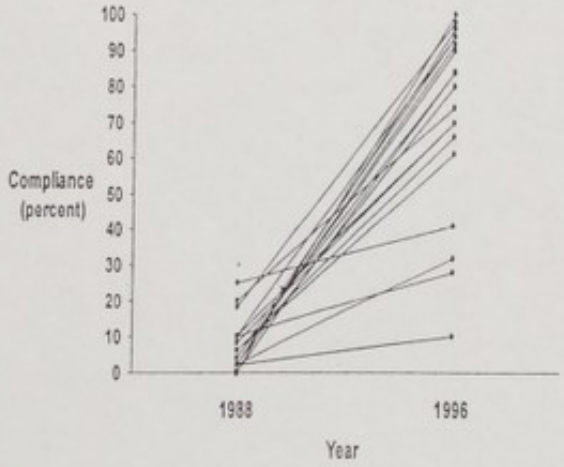


Figure 3 The rate of compliance with the antibiotic standard in each unit for each time period.

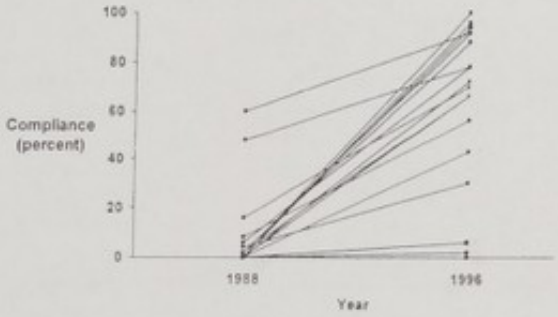


Figure 4 The rate of compliance with the suture material standard in each unit for each time period.

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

after those with clinical contraindications, uncertain diagnosis, and uncertain event timing have been excluded, the shortfall in prescribing falls from 64 to 20% [13].

Nevertheless, if we assume that shortfalls in compliance in the units we studied are similar to those in other units, we can estimate the avoidable morbidity caused by failing to follow the evidence. For example, in 1996 only 72% of women were benefiting from the 60% reduction in wound infection from prophylactic antibiotics, which would imply about 2000 avoidable infections per year (assuming a 15% CS rate and 6% infection rate [14]). Similarly, we estimate that only 81% of babies who could benefit from steroids were receiving them, and can assume that 3% births occur at less than 35 weeks, of which 77% would be eligible for steroids, with a 44% rate of RDS, and 18% mortality, reducible by 50% and 40%, respectively [15]. This would imply approximately 500 avoidable cases of RDS and 200 avoidable deaths from prematurity each year in the UK. About 350 000 women require perineal repair each year, of which 25% experience short-term pain when sutured with catgut [16]. Since this can be reduced by 30% if PGA sutures are used [17] and only 61% of perineal repairs use this, we estimate that over 10 000 women experience avoidable perineal pain every year. There are about 50 000 instrumental deliveries per year in the UK, which if the forceps were used for all would be associated with 10 000 unnecessary cases of severe pain and 5000 of severe perineal trauma [18]. Since even in 1996 the ventouse was used only 67% of the time, this implies 3000 unnecessary cases of severe pain and 1500 cases of severe trauma. These estimates are similar to the rates of forceps (5.8%) and ventouse delivery (4.8%) recorded in national statistics for 1994–1995, although those figures refer to instrument used to achieve delivery rather than of first choice [19]. Nevertheless, this is a considerable burden of avoidable suffering.

The varying response to different evidence-based recommendations may reflect different levels of belief in the evidence from the randomized controlled trials. This has been documented to vary widely [7]. In general, respondents to our survey were in agreement with the recommendations. What our results appear to show is that, contrary to much prevailing opinion, doing good research and disseminating it does result in a change of practice, provided that one is prepared to wait for the necessary consensus. It remains to be seen whether national organizations (such as the National Institute for Clinical Excellence in the UK) will carry greater authority than professional organizations, although they should continue to work with them. The evidence would suggest that a systematic and managed approach to the uptake of research findings was rudimentary over the time period of the study. The Department of Health has placed a duty on all managers to implement such as strategy forthwith. If this is effective we would predict that future research will show strong correlation between adherence to one standard and another, and interviews with staff should unmask such a systematic approach. In the meantime, it is worth reflecting that uptake of evidence now appears to be a far more rapid than in 1992 when Antman published his famous article on the inordinate delay in responding to clear-cut research results [20]. Our study shows that clinicians do respond to the evidence, albeit imperfectly, and in the case of magnesium treatment for eclampsia did so within a year [7]. Furthermore, they know the evidence, and by and large accept the results of well-conducted research. Clearly the culture, at least within the UK, has changed radically. Whether there has been a similar response to the evidence in other countries must await similar local audits.

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5 May 2004

reference: 714RJL/ace

Dear Professor Lilford

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

Thank you for your letter of 29th April, with attached paper..

I confirm receipt and will arrange for a copy to be distributed to everyone at the meeting.

Yours sincerely

**Mrs Wendy Kutner**
**Secretary to Dr Tilli Tansey**

# The Wellcome Trust Centre for the History of Medicine at University College London

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12 May 2004

Dear Professor Lilford

**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Venue: Franks II, Mezzanine Floor, The Wellcome Building, 183 Euston Road, London NW1**
**Tuesday 15th June 2004: 2.00 pm – 6pm**

We are delighted that you are able to attend the above meeting and are happy to tell you that plans for the meeting are proceeding well. A copy of our publicity material has been sent to you under separate cover and I am now enclosing a draft programme. A full attendance list will be available at the meeting.

We would be very grateful if you would be prepared for the Chairman to call upon you to say a few words, for about 5 minutes, on 'Getting research into practice'. We like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

The Wellcome Trust Centre for the History of Medicine at UCL will reimburse your travel costs of a second class, preferably an Apex or Saver rail fare and/or underground fare supported by suitable receipts. Please note that University College London will reimburse your travel costs for a second class, preferably Apex or Saver rail fare, underground ticket or taxi only if supported by suitable receipts. They are inflexible in this matter.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

Please note that informal drinks will be served immediately after the meeting. We look forward to seeing you on the 15th June.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

enc.

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

## Wendy Kutner

**To:** Lilford, Richard
**Subject:** RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Professor Lilford, Thank you for your reply. We look forward to seeing you at the meeting and supper. Yours sincerely, Wendy Kutner

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-----Original Message-----
From: Lilford, Richard [mailto:R.J.Lilford@Bham.ac.uk]
Sent: 03 June 2004 15:59
To: 'w.kutner'; Lilford, Richard
Cc: Daphne Christie; Evans, Annette
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Thank you; I do dinner, so that would be very nice, please thank the doctors Christie and Tansey.

Richard Lilford

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 03 June 2004 12:32
To: r.j.lilford
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Professor Lilford, further to our recent correspondence about the above meeting, Dr Tilli Tansey and Dr Daphne Christie would like to invite you to join them for an early supper at a local restaurant after the meeting. Supper should be finished by 9pm to give you ample time to return home. Please let me know on 020 7679 8106 or by e-mail w.kutner@ucl.ac.uk whether you are able to attend the supper. Yours sincerely, Wendy Kutner

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16 June 2004

Dear Professor Lilford

**The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth**

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne Christie

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

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7 December 2004

Dear Professor Lilford

**Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality**

I enclose a draft transcript of the Witness Seminar on '**Prenatal Corticosteroids for reducing Morbidity and Mortality**' to which you contributed. We intend to publish a version of the transcript in November 2005 under the auspices of the Wellcome Trust Centre for the History of Medicine at UCL.

I would be most grateful if you could check your own contributions for general sense, accuracy and typographical mistakes. We do not encourage extensive alterations, as the purpose of these publications is to retain the freshness and informality of the meeting. However, any additional information can be added as a footnote and you may like to suggest such material Please mark all corrections clearly on this copy and return it to me by **Monday 10 January** Earlier published volumes in the series can be viewed on our website, www.ucl.ac.uk/histmed/witnesses.html

If you would like to comment on any other part of the transcript, other than the corrections to your own contribution, please feel free to do so.

- Please provide a 2–3 sentence biographical piece for inclusion in the notes at the end of the volume including year of birth and dates of major appointments.
- Please sign and return the standard form assigning copyright to the Wellcome Trust.
- Please let us know if you do not want your name included in our twice-yearly marketing mailings.
- We would like to include illustrations of early work in the volume. If you have any suitable images or figures, please include these with the pages. They will be carefully scanned and returned in protective packaging.
- A final proof version, incorporating the changes made by all the participants, added footnotes, and any queries will be sent to you in **September 2005** for return within a week**. At this stage only minor corrections, such as those of a typographical nature, will be possible**.

The tapes, earlier versions of the transcript, and any additional correspondence generated by the editorial process, will be deposited in Wellcome Library. A version of the transcript will also be mounted on the Wellcome Trust Centre's website shortly after publication.

I look forward to hearing from you.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

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DEBRETT'S

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## LILFORD, Prof, Richard James

**Details:** LILFORD, Prof, Richard James; s of Maj Victor Lilford, and Eileen, *née* Gifford; *born* 22 April 1950; *marr* 23 May 1981, Victoria Alice Lilford; 1 s (Peter), 2 da (Nicola, Philippa).

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**Publications:** Basic Science for Obstetrics and Gynaecology (1984, 3 edn 1989), Prenatal Diagnosis and Prognosis (1990), Computing and Decision Suport in Obstetrics and Gynaecology (1991).

**Recreations:** flying, tennis.

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**Professor Richard J Lilford, PhD., FRCOG., FRCP., FFPH**

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27 June 2005

Mrs L Reynolds
The Wellcome Trust Centre for the History
of Medicine at University College London
210 Euston Road
London
NW1 2BE

Dear Mrs Reynolds

**Witness Seminar: Prenatal Corticosteroids, 15 June**

Please find enclosed documents from Professor Richard Lilford as requested.

Yours sincerely

AEvans

Annette Evans
Email: A.Evans@bham.ac.uk
Tel: 0121 414 2226

Enc

Need back by email 28/6/05

Lilford
14 June 2005



committee at that time, and the hospital medical committee approved it without further discussion. Mont was very keen to get started, because the head of department was actually planning a different trial that would have precluded this one and Mont was going to get in first, which he did.

**Professor Richard Lilford:** I wonder what would have happened if Professor Avery hadn't transclaimed that conservation. It sounds from the way you speak, as though Mont regarded this as a sideline and there wasn't a need to pursue it himself.

? Anne ?

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

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

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



Please correct and return by 27 June 2005.

beware, and I cannot counter that, I'm glad he's looking at it, and I just think we have to be vigilant and those of us who spend more time with babies than I am, have to keep track of the babies. Hard as it is to control, because so many interterm events take place over 30 years, but I hope we learn some more at this meeting.

**Lilford**: Since this is a history meeting, and while you have been talking about the early 1970s, I have been thinking back into the recesses of my own mind. I was a young doctor in Cape Town and news about this crossed the Indian Ocean and people were interested there. There seemed to be, as I can recall it, a notion that many babies would in retrospect be found not to have needed to have had antenatal steroids because their lungs were very mature. And so the idea that was being put around then was that one should test first to see if the lungs were already mature. And the person who did that testing was me. So if somebody needed early delivery, then I would do an amniocentesis upon her and then we had a thing called a bubble test and I would take this off to a side room and I would mix it with something else I have completely forgotten what now, but you would know the chemistry of this. But anyway I would shake it and then there was this little thing on the wall, what's the number of bubbles, and if there was more than a certain

number of bubbles, then we could safely proceed with the delivery the next day. If there weren't, then we gave steroids. And then we would re-test two days later and if there were now bubbles we knew we could go ahead with delivery. So there must have been running at that time, another scientific climate, which said that discriminate more before we shove these steroids in. But as far as I know, that line of thought ran ~~a~~ into the ..... sands, it didn't progress in any way. And I just mention that for your edification.

**Mrs Brenda Mullinger**: At the time of the UK multicentre trial, I was working for Glaxo and I coordinated the trial in the UK.[26] What I wanted to say relates to what Professor Crowley said about uptake. Although we originally coordinated the study after different clinicians had approached Glaxo, we found that we needed more centres to join the study, and so we did actually try approaching other centres in the UK and, looking at the paper [now?] because I cannot [could not] remember, we got underway in mid-1975, but I was told by Dr Clive Dash, the medic at Glaxo who unfortunately cannot be here, that many of the UK centres who were approached wouldn't join the study because they were already using betamethasone and they felt that it wasn't ethical to have control groups. So that although your uptake maybe was only 10 per cent,

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

group, and that will make the interpretation of the results interesting.

**Lilford:** I was looking at the debate of my 14-year-old daughter about whether history is just an interesting thing to read, or whether it helps us to design our own futures, and listening to Jane speak makes me think that there really are occasions when history really does have a lesson for the future. Listening to you speak about finding these records was very interesting, but people were amazed in this room that you really could find those source materials after 30 years, and that you could find the trial documents and so on. When Harold Gamsu moves the documents in his office, goodness knows where they might go. So the lesson that we might want to learn from this is the importance of some sort of systematic paid-for archive for trial information and I don't know if you might want to comment. I know that the ESRC on their precious data sources do archive them and build into the grant the cost of so doing and the more I listen the more I think this might be something we ought to try to take forward as a matter of some urgency.

**Chalmers:** The MRC has got a working party under the chairmanship of Peter Dukes, which is creating circumstances through which it would be possible for

**Hey**: The problem with your logo, of course, is as my maths teacher would have told me, is that it doesn't have a scale on it.

**Chalmers**: Is there no artist in you?

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

**Lilford**: Thank you very much, it's a great honour to be here today to say a few words about moving knowledge into clinical practice. I was plucked from obscurity in 1991 I think it was by the then President of the Royal College of ~~Physicians, a gynaecologist~~, Stan Simmons, ~~who~~ He called me into his office and said he wanted me to take over the audit committee. ~~I thought for a moment, and I thought well I certainly could do this as he had asked me~~. I went down to the first meeting as their Chair, I had never been on ~~it~~ the before, and it was a very boring meeting, It didn't seem to go anywhere, ~~I cannot remember what its contents were, but I do remember I was very unimpressed with the meeting as a whole, and my application of my chairmanship of it. So on the train I went back I thought I had better do something a bit better than that with this position, and so the idea came into my head, I suppose because~~

The guidelines were just coming into existence in people's consciousness then. The idea came into my head that what I should do with the committee was actually [?] guidelines. So I told the council how I was going to do this, and they must have had something else in their mind that day, because they sort of bundled it through, and went on to the next thing. So I don't think they quite worked out what they had signed themselves up to, but you know a mandate to go into these guidelines, which would then be disseminated. The next thing was what to do the guidelines on. Now Iain Chalmers had recently published with his colleagues his book, I think it was *Effective Care in Pregnancy and Childbirth*, and so I thought well okay, that's what we will do, we will go through all these trials, and we will come out with lots of guidelines. So I called a small group together, Marc Keirse, who was an obstetrician, I think he now works in Australia, but he was then an associate of Iain's, and a chap called Jim Thornton who was my clinical partner, and we sat down and we went through this whole data... in a day, came up early in the morning, whipped round [From the floor: 'In a day!']. Yes, in a day, a long day I can tell you, but it was a day. I remember it went on into the evening and Iain came round to our house for supper after, and we went through the whole thing in a day, and I thought we would have say 100 guidelines, and the book

was very thick, but when we went through it, we cut off at 21, only 21. That really surprised me, I had no idea it would be as little as that. How many trials were there in those days, there would have been about 20 000 trials [Chalmers: Three and a half thousand]. From these 3500 trials, so what do you get? Twenty-one guidelines, which you can say, this is what people should do. Even some of those were quite close to the edge. The one that worried me most, was the Ventouse, but I think subsequent events have vindicated us from that, or just, or not, as the case may be. We'll leave that one open shall we. But the Ventouse was on the extreme right of the distribution, you know just got in. But one of the ones that made it through, very comfortably, I think second only to antibioties, ……caesarean section or something like that, was the one that we have been hearing about today, which is giving steroids antenatally. Anyway this was our yield, 21, and we went and showed it to a bemused council who made a few derogatory, not derogatory, but a few non-committal remarks, and off it went. So it was then distributed with the President's signature, to all the people practising obstetrics and gynaecology in the country. Of course, as so often happens in life, in our modern complex society, and I wasn't alone, Edmund Hey wrote me a letter, and told me all the other things that were going on at the time, there was a publication,

~~a commentary by~~ Liam Donaldson, who was then just a regional director of public health, in the *British Medical Journal* ~~which~~ ~~...had touched on the issue in passing, and I will say is a problem with the methodology of his study. I am not criticising the chief medical officer you understand, that wouldn't do me any good at all. I am just saying that there was a problem with the methodology for that.~~ Then there was a publication from the *BAPM, British Association of Perinatal Medicine*, and there were letters in the *Lancet* in 1993. An NHS Management Executive letter, EL93 1115 in 1993. There was NIH consensus development conference. So there was quite a lot of buzz going on, and I didn't realize that my idea was so unoriginal, but there again that's life. So anyway we ~~did~~, and I rested myself content, ~~and~~ in fact we ~~went on and did some~~ other guidelines about communication in maternity services and organizational standards ~~that~~ were studiously ignored. I then applied with Lesley Page, a Professor of Midwifery... for a prize from BUPA. They gave a prize for he or she who communicated best that year, and we didn't get it. The reason we didn't get it, again it was quite proper, all we had done was propagate these guidelines, and we hadn't investigated what effect they had. So I then ~~discerned that we should~~ apply for a grant ~~so~~ that Jenny Hewison, ~~the same~~ Jim Thornton, a GP called Ian Watt

FN. Liam Donaldson's BMJ commentary

FN. 1993 letters

FN. NHS letter EL/93/1115? date, from? to?

Dan Bramholtz + Michael Robinson.

Edward Hey



and many other people I cannot remember all their names. We applied for a grant and got it to do a study of the uptake of guidance. Now Ed also sent me a paper by a very nice man called John Sinclair, and in it he says and I quote from it, "Despite the evidence of efficacy, effectiveness, I guess, in reducing as well as RDS and death rates, the use by obstetricians of antenatal corticosteroids has remained low by many accounts. For example, in the Canadian multicentre trial and it goes on to explain. I look at the reference and it's also early 1990s. So the question really was had something suddenly changed between before the systematic review, the guidelines that followed the systematic review. Has something changed following that, because a lot of these publications that people complained about, preceded first of all the collection of evidence and what's now the Cochrane database, the systematic review as Pritchard (?) did and the emanating of guidelines to give them some sort of societal authority. Or a lot of the complaints about ..... [?] were before all that endorsement took place. After all, if it wasn't necessary to have systematic reviews, if it wasn't necessary to put them into databases, and if it wasn't necessary to show that they had societal endorsement, why then would we have needed all that thing? So the question seems to me, the interesting question isn't that people didn't take them up

was around the

where is the quote? and the page no?

what happened after that — did the [illegible] more following dissemination of the guidelines + the other activities in the early 1990s.

why embark on all these activities.

The 76 Lancet in the

of neonatal surfactant, it was found that many of the mothers had NOT had steroids.

before, what would you have expected? The interesting question would be, 'Well, then what happened after that?'. That was what our study was designed to find out. So we took four guidelines which were the Ventouse, the stitching up of the perineum by different materials, it having been discovered that whatever you do you should not use cat gut to do this, antenatal steroids, antibiotics in preterm labour. Then we added one on the hoof, because during the course of the study, [Lelia Duley] and her colleagues published a spectacular trial, it must be *the* trial of the 1990s I think, which was about magnesium for the treatment of a horrible condition of labour called eclampsia, when magnesium was better for the woman treated than the treatment such as currently being promulgated on this side of the Atlantic. So we quickly took the opportunity of seeing what effect that had. Anyway the results were published and I did try to circulate a copy of the paper, and so you can see the results there. There is one thing to say about these results with particular reference to corticosteroids and that is this. We have said right from the start, that simply looking at who had given preterm birth, and seeing whether or not they had had corticosteroids, was not going to tell you the right information. It would be like be like the ecological fallacy experiment. Because what you really need to know is, when there was a woman who



FN. Duley * Which of the attached would be useful? The original and a review? the attached.

* Wilson et al. (2002) The Leeds University maternity audit project, IJQHC 14: 175-81

because not all
women who give
birth prematurely would
have had indications
for steroids.

1: Duley L.
Evidence and practice: the magnesium sulphate story.
Best Pract Res Clin Obstet Gynaecol. 2005 Feb;19(1):57-74.
PMID: 15749066 [PubMed - in process]

2: Duley L.
Pre-eclampsia and hypertension.
Clin Evid. 2004 Jun;(11):1886-902. Review. No abstract available.
PMID: 15652087 [PubMed - indexed for MEDLINE]

3: Gulmezoglu AM, Duley L.
Use of anticonvulsants in eclampsia and pre-eclampsia: survey of obstetricians in the United Kingdom and Republic of Ireland.
BMJ. 1998 Mar 28;316(7136):975-6. No abstract available.
PMID: 9550956 [PubMed - indexed for MEDLINE]

4: Duley L, Johanson R.
Magnesium sulphate for pre-eclampsia and eclampsia: the evidence so far.
Br J Obstet Gynaecol. 1994 Jul;101(7):565-7. No abstract available.
PMID: 8043532 [PubMed - indexed for MEDLINE]

NCBI PubMed National Library of Medicine NLM [Sign In] [R

All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals

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Related Resources
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NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

All: 1 Review: 0

1: Broughton Pipkin F, Crowther C, de Swiet M, Duley L, Judd A, Lilford RJ, Onwude J, Prentice C, Redman CW, Roberts J, Thornton J, Walker J. Related Articles, Links

Where next for prophylaxis against pre-eclampsia?
Br J Obstet Gynaecol. 1996 Jul;103(7):603-7. No abstract available.
PMID: 8688382 [PubMed - indexed for MEDLINE]

through the eyes of the person caring for her, should have prompted the use of antenatal steroids, didn't or did get it. That's what you really want to find out, not that she had it. In fact the same situation arises in audit of the treatment of people with a heart attack. Some audits have been done on treatment of heart attacks, you know that is one of the tenets of good care for if you are having a heart attack is a clot busting drug ought to be given to you, and some people have done studies which have shown only 50 per cent of people who had a heart attack had had the clot busting drug, and that gives you a huge underestimate, because when you arrive in casualty, the clot busting drug can only be given for a short period of time after you have started the onset of pain, a day or so. If you come into casualty and they don't think you have had a heart attack, you haven't got raised ST segments on your ECG and that is what it comes down to, if you haven't got that, then they quite properly don't give you the clot busting drug, because it can have some nasty side-effects, and cause a brain haemorrhage itself. When you go to leave hospital many of those people will have been found out to have had a heart attack. So you need to look at people who have presented with clear features of heart attack, not those coded as having a heart attack. So we took a lot of trouble and your money really to make sure that the people who were judged not to have got

antenatal steroids and they deserved it or should have had it, really had been a condition where they could have it, whereas it was clear that they were in preterm labour, and preterm labour wasn't so advanced, but there wouldn't have been time for it to have worked. So that's what we did, and what we showed in all of these respects is that there was massive change in the uptake and if you have got a copy of the paper you can see it in the graphs in the paper, massive change in practice in line with the evidence over that period of time. So the notion that the doctors aren't using the evidence, the obstetricians anyway, that notion is no longer true, there is massive change. Now is it perfect? No. With effective steroids, for example, it's only 80 per cent of people who the audit was judged should have got it, only 80 per cent got it, so there was a 20 per cent shortfall. On some of the other stands, it's more like 70 per cent, so there is still work to be done, I am not saying everything is perfect. And indeed, when this result was published it was carried in a newspaper, the *Observer* I think, as shame on us, as great as it all was, still lots of people weren't getting the treatment that they deserved. They can always put two spins on anything if they really want to. But one thing that it did show was the amount of change in the evidence.

* date? maternity audit published 2002 – any suggestions?

Just since I have titivated you all, I will just mention magnesium as well. Within a year of Lelia Duley published her study, she and her colleagues, within a year of that 80 per cent, from zero 80 per cent of women in this country with eclampsia were getting magnesium. So that was without any guidelines and analysis. But that was a particularly powerful study and very useful.

I have got one last thought to leave you with and the thought is this. You know that the whole notion of diffusion of information into a community of experts is one that has been studied for a long time, and I understand that it started with a man called Rogers, who was looking at the uptake of effective agriculture practice, in farmers, back in the 1930s. And he wrote, described the original diffusion curve, you know people are very avant guarde and take it right away, going through to the middle ground, and then a few laggards, who were very slow to take it up. That all comes from Rogers. Now you can think of that in two ways. The way it's always thought of is of a particular technology; so are the farmers using the latest and best fertiliser? Are the obstetricians using the latest treatment of a particular thing, shall we say of antenatal steroids? That's one way to look at it. The diffusion of that technology. But of course underneath all that lies an epistemological issue about what is perceived by the society of experts, the society of farmers, or



? Rogers EM. (1962) Diffusion of Innovations. NY: Free Press. (4th edn 1995)

Rogers + Shoemaker (1971) Communication of innovations: a cross-cultural approach. NY: Free Press.

# Diffusion of Innovation Theory

**One of the greatest pains to human nature is the pain of a new idea. It...makes you think that after all, your favorite notions may be wrong, your firmest beliefs ill-founded... Naturally, therefore, common men hate a new idea, and are disposed more or less to ill-treat the original man who brings it.**
**-Walter Bagehot *Physics and Politics***

## Definition of Diffusion of Innovation

In his comprehensive book *Diffusion of Innovation*, Everett Rogers defines diffusion as the process by which an innovation is communicated through certain channels over time among the members of a social system. Rogers' definition contains four elements that are present in the diffusion of innovation process.
The four main elements are:

(1) innovation - an idea, practices, or objects that is perceived as knew by an individual or other unit of adoption.

(2) communication channels - the means by which messages get from one individual to another.

(3) time - the three time factors are:
(a) innovation-decision process
(b) relative time with which an innovation is adopted by an individual or group.
(c) innovation's rate of adoption.

(4) social system - a set of interrelated units that are engaged in joint problem solving to accomplish a common goal.

**Make a better mousetrap, and the world will beat a path to our door.**
**-Ralph Waldo Emerson**

## Background on Diffusion of Innovation

The original diffusion research was done as early as 1903 by the French sociologist Gabriel Tarde who plotted the original S-shaped diffusion curve. Tardes' 1903 S-shaped curve is of current importance because "most innovations have an S-shaped rate of adoption". (Rogers, 1983) The variance lies in the slope of the "S". Some new innovations diffuse rapidly creating a steep S-curve; other innovations have a slower rate of adoption, creating a more gradual slope of the S-curve. The rate of adoption, or diffusion rate has become an important area of research to sociologists, and more specifically, to advertisers.

In the 1940's, two sociologists, Bryce Ryan and Neal Gross "published their seminal study of the diffusion of hybrid seed among Iowa farmers" renewing interest in the diffusion of innovation S-curve. The now infamous hybrid-corn study resulted in a renewed wave of research. "The rate of

adoption of the agricultural innovation followed an S-shaped normal curve when plotted on a cumulative basis over time". This rate of adoption curve was similar to the S-shaped diffusion curve graphed by Tarde forty years earlier.

Ryan and Gross classified the segments of Iowa farmers in relation to the amount of time it took them to adopt the innovation, in this case, the hybrid corn seed. The five segments of farmers who adopted the hybrid corn seed, or adopter categories are:

(1) innovators,

(2) early adopters,

(3) early majority,

(4) late majority, and

(5) laggards.

"The first farmers to adopt (the innovators) were more cosmopolite (indicated by traveling more frequently to Des Moines) and of higher socioeconomic status than later adopters". One of the most important characteristics of the first segment of a population to adopt an innovation, the innovators, is that they require a shorter adoption period than any other category. Rogers identifies several additional characteristics dominant in the innovator type:

(1) venturesome, desire for the rash, the daring, and the risky,

(2) control of substantial financial resources to absorb possible loss from an unprofitable innovation.

(3) the ability to understand and apply complex technical knowledge, and

(4) the ability to cope with a high degree of uncertainty about an innovation.

Characteristics Rogers identified in the Early Adopters:

(1) integrated part of the local social system,

(2) greatest degree of opinion leadership in most systems,

(3) serve as role model for other members or society,

(4) respected by peers, and

(5) successful.

Characteristics Rogers identified in the Early Majority:

(1) interact frequently with peers,

(2) seldom hold positions of opinion leadership,

(3) one-third of the members of a system, making the early majority the largest category.

(4) deliberate before adopting a new idea.

the society of obstetricians, what is it that they perceive as being authoritative knowledge in a period of time? What I believe and we can discuss whether later if you wish, what I believe is this, that not only have obstetricians and indeed other people, it's exactly the same with a group of cardiologists for example, where similar studies have been done, not only have specialists taken on the idea of particular treatments like clot-busting drugs in cardiology or antenatal steroids in obstetrics, but they have taken on the idea that you should change your practice quite expeditiously in line with the evidence. So the notion of evidence-based practice has also been solved. I believed that through my professional career there has been a sea change in that respect, and so I don't think we need to be quite so pessimistic in the future as we have been in the past about the uptake of new practice. That is the first part of my last point.

The second part of this is that not only has there been a change in the hearts and minds of practitioners, but there has also been a change in response to that about in a societal sense how we organize ourselves to receive new evidence. So for example, in the case of all those trials that were done on antenatal steroids, back in the 1970s and 1980s and so on, the trials were done, so the idea of doing trials had been solved, with an original idea that came from people like Brian Bateman, Austin Bradford Hill. Those ideas were coming

Hammersmith Hospital from 1952 to 1976. See also a videotape interview with Professor Charles Fletcher by Max Blythe, held at the Royal College of Physicians of London. See note 9.

### Dr Harold 'Bill' Foreman

FRCP (1898–1980) was physician-superintendent of Sully Hospital, a sanitorium that became a centre for cardiothoracic medicine in south Wales. He had been a prisoner of war with Archie Cochrane and was instrumental in the relocation of Archie's epidemiology and medical statistics course to Sully Hospital from Richmond Road, Cardiff in 1962. See Robson K. (1984) Harold Mason Foreman. *Munk's Roll* **7**: 189–190. See also See note 20, 176–178.

### Dr John Gallacher

AfBPsS, CPsychol (b. 1956) was a member of the MRC Epidemiology Unit from 1977 until 1997 when he became a lecturer in epidemiology in the University of Wales College of Medicine, Cardiff. He introduced psychosocial questionnaires, audiometry and noise exposure into Phase II of the Caerphilly study and a series of tests of cognitive function into Phase III and IV. He continues to work with Peter Elwood on these data and is organizing the cognitive tests for Phase V.

### Dr John Gilson

CBE FRCP (1912–1989) served at the RAF Physiological Laboratory in Farnborough during the Second World War because of his interest in respiratory physiology, where he developed oxygen masks that improved air flow. He joined the MRC Pneumoconiosis Research Unit in 1946, becoming Director in 1952 until his retirement in 1976. See Kilpatrick G S. (1994) John Carey Gilson. *Munk's Roll* **9**: 197.

### Dr Philip D'Arcy Hart

CBE FRCP (b. 1900) trained in medicine at University College Hospital, London, where he became a Consultant Physician. Interested in developing a career in medical research, and encouraged by Sir Thomas Lewis, he became a member of the MRC's staff, and in 1937 undertook the survey he here describes (see page 3). In 1948 he became the Director of the MRC Tuberculosis Research Unit until his retirement in 1965, to become a grant-holder of the MRC in the laboratories of the National Institute for Medical Research, London.

### Dr Julian Tudor Hart

(b. 1927) was first an epidemiologist working in the Epidemiology Research Unit in 1961, before moving to general practice in 1961 until 1988. See Mullan F. (1995) Interview with Julian Tudor Hart, February 1995. Primary Care Oral History Project, 1995–98. Modern Manuscripts Collection, National Library of Medicine, Bethesda, MD, USA. Dr Tudor Hart's practice records from 1965 to 1992 are held as CMAC/GP/13 in Archives and Manuscripts, Wellcome Library, London.

### Mr Nick Henderson

MRCVS FIPR (b. 1926) was a veterinary surgeon and is Executive Director of the European Aspirin Foundation. He is a Liveryman of the Society of Apothecaries.

### Professor Ian Higgins

Was one of the three original scientific staff appointed to the Epidemiological Research Unit in 1961.

### Sir Austin Bradford Hill

Kt FRS (1897–1991) was Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine from 1945 until his retirement in 1961. His series of 17 articles in the *Lancet* in 1937 introduced the medical researcher to the use of statistics (reprinted as *Principles of Medical Statistics*. London: *The Lancet*, 1937). He was made an Honorary Fellow of the Royal College of Physicians in 1963. See Doll R. (1994) Austin Bradford Hill. *Biographical Memoirs of Fellows of the Royal Society* **40**: 129–140.

### Sir Harold Himsworth

KCB FRCP FRS (1905–1993), a distinguished clinical scientist, was Professor of Medicine and Director of the Medical Unit at University College Hospital, London, from 1939 to 1949 and Secretary of the MRC from 1949 until his retirement in 1968. See Black D A K, Gray J. (1995) Sir Harold Percival Himsworth KCB. *Biographical Memoirs of Fellows of the Royal Society* **41**: 201–218. Gray J, Booth C. (1994) Sir Harold Himsworth. *Munk's Roll* **9**: 238–241.

into quite widespread use in the 1970s, that's why all these trials have been done. What we didn't have was a method, a societal method to receive the results of the trial. So the trial would be done and that would be that. And then no one knew what to do with it. How do you react to these trials? When is the trial evidence sufficient for a guideline to be developed? Now what I did in a way, I suppose, back in the college in those early days of 1992, was to start to provide some kind of societal mechanism to pick up the results of research, and it's not surprising it took us a while to learn how to do this, and of course that's now been formalised much more, some would say too much, with organizations such as NICE and its equivalents in other parts of the world. Thank you very much.

Williams: For practising clinicians another anything new and accelerated factor which is a thing called the clinical negligence scheme for trusts which gives a discount in your insurance for a hospital if you are following evidence-based guidelines and can show that you have these in place and to actually achieve CMST grade-one status, you have to jump through a lot of hoops and it's all about practising evidence-based guidelines. I think that's a new accelerating factor in the application of research into practice.

### Professor Jane Harding

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

### Dr John Hayward

xxxx (b. 19xx) was in general practice for 16 years before re-training in public health. From 1994/6 he led the Effective Care Project in maternity services for the Camden and Islington Health Authority. He has been the Director of Public Health in Newham, London, since xxxx. See Hayward (2001).

### Dr Edmund Hey

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

### Professor Ross Howie

### Dr Ian Jones

52.

### Professor Richard Lilford

xxx (b. 19xx) xx

### Professor Sir William Liley

KCMG FRS(NZ) (1929–83) was trained at Otago University, New Zealand, did research under Professor John Eccles on neuromuscular transmission, switching to obstetrics at the Women's National Hospital, Auckland, from 1959 as a New Zealand Medical Research Council Senior Research Fellow, then at the Auckland University Medical School as Research Professor in Perinatal Physiology from 1969 until his sudden[?premature?unfortunate?] death in 1983. His diagnostic procedure for rhesus haemolytic disease of the newborn was perfected so that he could predict which could remain in the uterus and which could not; led the team that performed the first successful intrauterine transfusion, and believed in the rights of the unborn child. See Hawgood (2005).

### Professor Sir Graham (Mont) Liggins

FRCOG FRCS (Edin) PhD (b. 19xx)



a 2-3 sentence biographical note is needed here, please.

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WITNESS SEMINARS

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************

1. NAME **Professor Richard Lilford FRCOG FRCP FFPH**

2. ADDRESS
   **Department of Public Health & Epidemiology**
   **University of Birmingham**
   **Edgbaston**
   **Birmingham B15 2TT**

3. WITNESS SEMINAR: **Prenatal Corticosteroids for Reducing Morbidity and Mortality**
   **15 June 2004**

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   I confirm that I am the author and legal owner of my contribution to the proceedings of the Witness Seminar and of any comments I may have made on any draft transcript ("my Contribution"), and I assign to the Trustee of the Wellcome Trust ("the Trust") the copyright in my Contribution.

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Signed..... Date 23/06/05

Rec'd: 14/6/05

Please sign and return by 27 June 2005
Rec'd 28/6/05.

Professor Richard Lilford FRCOG FRCP FFPH,
1 Ampton Road
Edgbaston
BIRMINGHAM
B15 2UP

Lois Reynolds
*l.reynolds@ucl.ac.uk*
*www.ucl.ac.uk/histmed*
Tel: *020 7679 8123*
Fax: *020 7679 8192*

30 June, 2005

Dear Professor Lilford,

**Witness Seminar: Prena[illegible] 4**

Thank you very much for the corrections t[illegible] e meeting and the return of the signed copyright form.

Annette Evans.

Enclosed is a second proof of your contribution, [illegible]ghlighted with further queries.

I particularly like the paragraph on diffusion theo[illegible] (page 75), which has been re-ordered to tally with the references. If you would like to make further changes, this is the time to do it.

Is there an illustration (photograph, table, chart) that would give the non-specialist reader some feel for the excitement of the period? Although you mention Tables 1–4 from the Wilson *et al.* (2002) paper, these would require a great deal of explanation.

Again, many thanks for your help with the transcript.

Yours sincerely,

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
cc: top copy sent to University of Birmingham

Professor Richard Lilford FRCOG FRCP FFPH,
1 Ampton Road
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BIRMINGHAM
B15 2UP

Lois Reynolds
*l.reynolds@ucl.ac.uk*
*www.ucl.ac.uk/histmed*
Tel: *020 7679 8123*
Fax: *020 7679 8192*

30 June, 2005

Dear Professor Lilford,

**Witness Seminar: Prenatal Corticosteroids, 15 June 2004**

Thank you very much for the corrections to your contribution at the above meeting and the return of the signed copyright form.

Enclosed is a second proof of your contribution, with sections highlighted with further queries.

I particularly like the paragraph on diffusion theory (page 75), which has been re-ordered to tally with the references. If you would like to make further changes, this is the time to do it.

Is there an illustration (photograph, table, chart) that would give the non-specialist reader some feel for the excitement of the period? Although you mention Tables 1–4 from the Wilson *et al.* (2002) paper, these would require a great deal of explanation.

Again, many thanks for your help with the transcript.

Yours sincerely,

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
cc: top copy sent to University of Birmingham

**Lois Reynolds**

**From:** Library [Library@RCOG.ORG.UK]
**Sent:** 30 June 2005 10:22
**To:** ucgarey@ucl.ac.uk
**Subject:** RE: RCOG Guidelines : query

Dear Mrs Reynolds,

Thank you for your enquiry. I've looked through the various editions of College guidance on prenatal corticosteroids, and found the following:

In December 1992 advice from the RCOG Scientific Advisory Committee entitled "Antenatal corticosteroid administration reduces the incidence of neonatal repiratory distress syndrome" was mentioned in the President's newsletter, saying that copies were available from the College. The advice is a single A4 typed sheet.

The first greentop guideline on this topic was published in 1996, and has subsequently been revised in 1999 and 2004. These editions were all entitled "Antenatal corticosteroids to prevent respiratory distress syndrome". The current version is available on our website at http://www.rcog.org.uk/index.asp?PageID=511

Rather than the whole series of guidelines being republished as green-top guidelines in 2002, each individual guideline is updated or withdrawn at varying times, with new titles being introduced on an on-going basis. In general, a topic is reviewed every 3 years. The first three green-tops, "For the use of ritodrine", "Use of gonadotrophic hormone preparations for ovulation induction", and "In-patient treatment - D&C in women age 40 or less" were published in April 1994.

The series of national evidence-based guidelines funded by the NHS Executive were much longer documents than the green top guidelines, on topics such as:
Management of menorrhagia in primary and secondary care
Management of infertility in primary, secondary and tertiary care
Male and female sterilisation
Care of women requesting induced abortion
Induction of labour
Use of electronic fetal monitoring.

Some of these have now been superseded, but you can see details of the current editions at
http://www.rcog.org.uk/index.asp?PageID=73&BookCategoryID=2&BookTypeID=5 , or
http://www.rcog.org.uk/index.asp?PageID=1046

I hope this information will be of use for your publication. If you would like to see copies of any of the guidelines, or the item in the President's newsletter please let me know.

Regards,
Elaine Garrett

**********

Elaine Garrett
Reader Services Librarian
Royal College of Obstetricians and Gynaecologists
27 Sussex Place
Regent's Park
London NW1 4RG
Tel: 020 7772 6214
Fax: 020 7262 8331
Email: EGarrett@rcog.org.uk

All: 1 Review: 0

1: Toschke AM, Ehlin AG, von Kries R, Ekbom A, Montgomery SM. Related Articles, Links

Maternal smoking during pregnancy and appetite control in offspring.
J Perinat Med. 2003;31(3):251-6.
PMID: 12825482 [PubMed - indexed for MEDLINE]

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-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 29 June 2005 15:57
To: Library
Subject: RCOG Guidelines : query

Dear RCOG Library,

Professor Richard Lilford spoke at our Witness Seminar meeting on Prenatal Corticosteroids on 15 June 2004. We are preparing the transcript of that meeting for publication in November 2005. His contribution to discussion mentioned the background to the first 21 guidelines that were sent out to all practitioners under the President's signature. He implies that was during his time as Chairman of the Audit Committee.

I would be grateful if you could let me have the full reference for the original first document and, if there was a more formal publication?

The present draft footnote on the guidelines follow, and I would be very grateful for your comments and suggestions.

Best wishes from Lois Reynolds

0-0-0-0-0-0

The Royal College of Obstetricians and Gynaecologists (RCOG) guidelines were first produced in 1994 [XXXX, updated as 22 'green-top' guidelines in September 2002] and two years later, funded by the Department of Health, a series of national evidence-based guidelines were produced [xxxx, see also Mann T. (1999) Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS. Leeds: NHS Executive; Scottish Intercollegiate Guidelines Network. (1999) SIGN Guidelines: An Introduction to SIGN Methodology for the Development of Evidence-based Clinical Guidelines. Edinburgh; 1999. Publication No. 39].

0-0-0-0-0

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www.ucl.ac.uk/histmed/witnesses.html

**Lois Reynolds**

**From:** Richard Lilford [r.j.lilford@bham.ac.uk]
**Sent:** 03 October 2005 17:41
**To:** ucgarey@ucl.ac.uk; Richard Lilford
**Subject:** RE: Witness Seminar: prenatal corticosteroids : Corrections???

Oh DEAR DEAR DEAR. I AM A MAN MOST REMISS. AND I HAVE LOST IT. IF YOU SEND AGAIN I PROMISE I WILL DO IN PLANE TOMORROW.

RICHARD

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 29 September 2005 18:14
To: Richard Lilford
Subject: RE: Witness Seminar: prenatal corticosteroids : Corrections???

Hi Prof Lilford,
It is urgent that we receive the corrections on the document sent to you on 10 August 2005. If you have not received it, please let me know. Best wishes from Lois

-----Original Message-----
From: Richard Lilford [mailto:r.j.lilford@bham.ac.uk]
Sent: 26 July 2005 17:31
To: ucgarey@ucl.ac.uk; r.j.lilford@bham.ac.uk
Subject: RE: Witness Seminar: prenatal corticosteroids : Corrections???

Ok will try to do tonight

richard

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 26 July 2005 17:26
To: r.j.lilford@bham.ac.uk
Subject: Witness Seminar: prenatal corticosteroids : Corrections???

Dear Prof Lilford,
I hope that you received the corrected pages sent to your home address on 30 June. The final proofs are scheduled to be sent to participants next week and I would be glad of any comments you might have.
Best wishes from Lois

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
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www.ucl.ac.uk/histmed/witnesses.html

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**Lois Reynolds**

**To:** Richard Lilford
**Subject:** RE: Witness Seminar: prenatal corticosteroids : Corrections???

Dear Professor Lilford
Thank you for your e-mail. Lois had to travel to Montana to visit her sick parents and will not be back until 17 October. I will send a copy of the draft for your corrections/comments.
With kind regards
Daphne Christie

4/10/05 SC.

-----Original Message-----
From: Richard Lilford [mailto:r.j.lilford@bham.ac.uk]
Sent: 03 October 2005 17:41
To: ucgarey@ucl.ac.uk; Richard Lilford
Subject: RE: Witness Seminar: prenatal corticosteroids : Corrections???

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www.ucl.ac.uk/histmed/witnesses.html

Faxed Lilford collection rec'd 1pm 9/11/05



Universite de Paris], the fellow who is still publishing on 'beware, beware,' and I cannot counter that.[53] I'm glad he's looking at it, and I just think we have to be vigilant and [?that?] those of us who spend more time with this have to keep track of the babies.

**Lilford:** Since this is a history meeting, and while you have been talking about the early 1970s, I have been thinking back into the recesses of my own mind. I was a young doctor in Cape Town and news about this crossed the Indian Ocean and people were interested there. As I can recall it, there seemed to be a notion that many babies would, in retrospect, be found not to have needed antenatal steroids because their lungs were very mature. And so the idea that was being put around then was that one should test first to see if the lungs were already mature. And the person who did that testing was me. So if somebody needed early delivery, then I would do an amniocentesis. We had a thing called a bubble test and I would take the fluid off to a side room and I would mix it with alcohol.[54] I would shake it and then there was this chart on the wall where the bubble density could be related to maturity. If there were more than a certain number of bubbles, then we could safely proceed with the delivery the next day. If there weren't, then we gave steroids. We would re-test two days later and if there were now bubbles we knew we could go ahead with delivery. So there must have been another scientific climate running at that time which said that [?we should?] discriminate more before we shove these steroids in. But as far as I know, that line of thought ran into the sands, it didn't progress in any way. I just mention that for your edification.

VA 9/11/05

---

[53] [Prof Avery, is this the correct Burri ref? If not could you suggest one?] Corroyer S, Schittny J C, Djonov V, Burri P H, Clement A. (2002) Impairment of rat postnatal lung alveolar development by glucocorticoids: involvement of the p21CIP1 and p27KIP1 cyclin-dependent kinase inhibitors. *Pediatric Research* 51: 169–76. See also Avery M E. (1975) Pharmacological approaches to the acceleration of fetal lung maturation. *British Medical Bulletin* 31: 13–17.

[54] Prof Lilford, could you expand on the bubble test? Our readers would find this technique of interest.

was to promulgate guidelines. So I told the council how I was going to do this, and they must have had something else in their mind that day, because they nodded it through, and moved on to the next item. I now had a mandate to produce guidelines for dissemination. The next thing to decide on was the context of the guidelines. Iain Chalmers along with his colleagues had recently published his book, *Effective Care in Pregnancy and Childbirth*, and so I thought, 'That's what we will do: we will go through all these trials, and come out with lots of guidelines.' So I called a small group together – Marc Keirse, who was an obstetrician and an associate of Iain's, now working in Australia, and a chap called Jim Thornton, my clinical partner – and we went through this whole data set in a day. [From the floor: In a day?] Yes, in a day, a long day I can tell you, but it was a day. I remember that it went on into the evening and Marc came round to our house for supper after. I thought we would have, say, 100 guidelines, as the book was very thick, but when we went through it, we could make only 21 'yes' or 'no' statements. That really surprised me, as I had no idea it would be as few as that.

How many trials were there in those days? There would have been about 20 000 trials [Chalmers: Three and a half thousand]. From these 3500 trials, what do you get? Twenty-one guidelines, which you can say categorically 'do this' or 'do not do that'. Even some of these were not completely uncontentious. The one that worried me most was the Ventouse. In any account most of the guidelines were based on very [???convincing???] evidence and these included the injunction to prescribe steroids in the case of premature labour. Anyway this was our yield, 21, and we showed them to a bemused council who approved dissemination. So it was that the guidelines were distributed to all the people practising obstetrics and gynaecology in the country, under the President's signature.[117] Of course, as so often happens in life in our modern complex society, a number of other dissemination activities occurred at around this time. Liam Donaldson, who was then a regional director of public health, published a commentary in the *British Medical*

[117] Was this published in a journal? If so, we would be very grateful for a reference.

No – Lett President's letter

*Journal* on the use of steroids, although, as we shall see, his was an ~~[???]~~ ecological study.[118] Then there was a publication from the British Association of Perinatal Medicine (BAPM), and in 1993 there were letters in the *Lancet*.[119] An NHS Management Executive letter, EL93 1115, was [also] dispatched in 1993.[120] There was NIH consensus development conference in 1994.[121] So there was quite a lot of buzz going on, and I didn't realize that my idea was so unoriginal until Edmund Hey made me aware of these other activities, but there again that's life. So anyway we did disseminate our guidelines, and I rested myself content.[122] In fact we went on to produce further guidelines about communication in maternity services and organizational standards, but those were studiously ignored. With Lesley Page, Professor of Midwifery Practice at Queen Charlotte's Hospital, I then applied for a prize from BUPA, who give an annual prize to he or she who communicated best during the year.[123] We

[118] Donaldson (1992).

[119] British Association of Perinatal Medicine (???Toschke AM, Ehlin AG, von Krie: R, Ekbom A, Montgomery SM. (2003) Maternal smoking during pregnancy and appetite control in offspring. J Perinat Med. 2003;31(3):251-6.???) xxxx. (1993) xxxxxx *Lancet* xxxxxxx?????? [Please suggest appropriate references, or where these might be found.]

[120] Is this the correct letter? It is not on the website which lists Department of Health Executive Letters at http://www.dh.gov.uk/PublicationsAndStatistics/LettersAndCirculars/ExecutiveLet ers/fs/en (visited 2 August 2005).

[121] National Institute of Child Health and Human Development. (1994).

[122] The Royal College of Obstetricians and Gynaecologists (RCOG) *President's Newsletter* of December 1992 noted the single-page advice from the RCOG Scientific Advisory Committee that 'Antenatal corticosteroid administration reduces the incidence of neonatal respiratory distress syndrome'. See also note 141. The series of national evidence-based guidelines funded by the Department of Health, which started in 1996, are much longer documents than the green top guidelines. For the current antenatal corticosteroid advice, see www.rcog.org.uk/index.asp?PageID=73&BookCategoryID=2&BookTypeID=5 (visited 30 June 2005). See also Mann T. (1999) *Clinical Guidelines: Using Clinical Guideline. to Improve Patient Care Within the NHS*. Leeds: NHS Executive; Scottish Intercollegiate Guidelines Network. (1999) *SIGN Guidelines: An Introduction to SIGN Methodology for the Development of Evidence-based Clinical Guidelines*, no. 39. Edinburgh: 1999.

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

didn't get it, and the reason we didn't, again quite properly, was that all we had done was to propagate these guidelines, we hadn't investigated what effect they had. So then I applied for a grant to do a study on the uptake of guidance with Jenny Hewison, Jim Thornton, Ian Watt, David Bromholt: and Michael Robinson. Edmund Hey also sent me a paper by a very nice man called John Sinclair, and in it he says,

> Despite the evidence of efficacy and effectiveness of steroids in reducing RDS and death rates, the use by obstetricians of antenatal corticosteroids has remained low by many accounts.[124]

For example, in the Canadian multicentre trial of neonatal surfactant, it was found that many of the mothers had not had steroids. This was in the early 1990s.[125] So the question was what happened after that – did the ????? move following dissemination of the guidelines and the other activities in the early 1990s? After all, if it wasn't necessary to have systematic reviews, if it wasn't necessary to put them into databases, and if it wasn't necessary to show that they had societal endorsement, then whyembark on all these activities? That was what our study was designed to find out. We took four guidelines: the Ventouse, stitching up of the perineum using the correct materials, antenatal steroids, and antibiotics in preterm labour. Then we added one on the hoof, because during the course of the study, Lelia Duley and her colleagues published a spectacular trial – it must be *the* trial of the 1990s – which showed that magnesium was the optimum treatment for eclampsia.[126] So we quickly took the opportunity of observing the effect of this seminal publication. The results of the study have been published.[127] There is one thing to say about these results with particular reference to corticosteroids and that is this. We realized, right from the start that simply looking at [mothers] who had given

[124] Sinclair (1995).

[125] Canadian trial reference?

[126] [Is this the correct study????] Duley L, Neilson J. (1997) Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomized trials. *British Journal of Obstetrics and Gynaecology* 104: 756–8.

[127] Wilson *et al.* (2002).

preterm birth to see whether or not they had had corticosteroids, was not going to give the right information. This would produce an ecological ~~??logical??~~ fallacy, because not all women who give birth prematurely would have had indicators for steroids. What we really needed to know ~~[is the proposition [i.e. was the proportion??]~~ of women receiving steroids (a) who were recognized to be in preterm labour; (b) in whom birth was not so immenent as to negate any possible benefit; and (c) ~~to~~ whom there were no contra-indications.

The same situation arises in the audit of treatment of people with a heart attack.[128] We know that one of the tenets of good care if you are having a heart attack is that you should be given aspirin and a clot busting drug like streptokinase. Some studies have shown that only 50 per cent of people who had a heart attack received the clot busting drug. But this gives a considerable underestimate of proper care, because the clot busting drug can only be given for a short period of time after the onset of pain (a day or so). Furthermore some people do not have clear evidence of heart attach on admission, such as raised ST segments on the ECG. The clot busting drug can have some nasty side-effects (brain haemorrhage) and it is properly withheld in these cases. So you need to look at people who have presented with clear features of heart attack, not those coded as having had a heart attack.

We took a lot of trouble and your money to really make sure that the people who were judged not to have received antenatal steroids should have had them. What we showed in respect of all four guidelines was a massive change in the uptake and if you have got a copy of the paper you can see it in the graphs:[129] a massive change in practice in line with the evidence over the period of study [1988–96]. So the notion that the doctors do not use the evidence is no longer true, there is massive change.

Now is it perfect? No. With reference to steroids, for example, only 80 per cent of eligible women received the correct treatment, so there was a 20 per cent

---

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

[129] Wilson *et al.* (2002). See Figures 1–4 on page 178.

who protected the result a.

too late



shortfall. On some of the other standards, it's more like 70 per cent compliance, so there is still work to be done. I am not saying everything is perfect. And indeed, when this result was published it was carried in a newspaper, the *Observer* ~~I think,~~ a shameful ~~result~~.[130] The result can be 'spun' either way. But one thing that it did show was the amount of change in line with the evidence.

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

I have one last thought to leave with you. The whole notion of diffusion of information into a community of experts is one that has been studied for a long time. I understand that it started with two sociologists, Ryan and Gross, who were looking at the uptake of effective agriculture practice among farmers back in the 1930s.[131] Later a man called Everett Rogers analysed the original 'diffusion curve' in terms of communications theory, showing that some people are very avant-garde and adopt a new method right away, some are in the middle ground, and then a few laggards, who are very slow to take it up.[132] Now you can think of that in two ways: one tends to be thought of in terms of a particular technology: are the farmers using the latest and best fertilizer? are the obstetricians using the latest treatment for a particular condition? That's one way: the diffusion of a specific technology. But, of course, underneath all that lies an epistemological issue: what is perceived by the society of experts, the society of farmers, or the society of obstetricians, as constituting

Please check highlighted area, which has been altered to suit the references.

thank you - fine ✓

[130] *Observer* piece? Was the publication of the Leeds University maternity audit in 2002 was followed by a Sunday newspaper piece?

[131] Ryan B, Gross N C. (1943) The diffusion of hybrid corn in two Iowa communities. *Rural Sociology* 8: 15–24.

[132] Rogers E M. (1962) *Diffusion of Innovations*. New York, NY: Free Press. Fourth edn, 1995. See also Rogers E, Shoemaker F. (1971). *Communication of Innovations*. New York, NY: Free Press.

Sorry I do not have ref.

University of Auckland, in 19xx, specializing in Endocrinology and Fetal Physiology. His most important discovery was that the time of birth was controlled by the fetus, not the mother.

### Professor Richard Lilford

Phd FRCOG FRCP FFPH (b. 1950) was Consultant Obstetrician and Gynaecologist to Queen Charlotte's Hospital, London, before moving to the University of Leeds in 19xx as Professor of Obstetrics and Gynaecology and Chairman of the Epidemiology Research Institute (19xx–1995). He has been Professor of Clinical Epidemiology and Head of the Division of Primary Care, Occupational Health and Public Health in the Medical School of the University of Birmingham since 1995. He is also the Director of the Patient Safety Research Programme for the Department of Health in England and is Director of Research Methods Programme, NHS Executive, West Midlands, since 1995[?].

### Professor Miranda Mugford

[Hons?] (b. 19xx), an economist and health services researcher, joined the National Perinatal Epidemiology Unit at the University of Oxford in 19xx. She has been Professor of Health Economics in the School of Medicine and Health Policy and Practice at the University of East Anglia (UEA), since 19xx and Chair of convenors of the Campbell and Cochrane Collaboration Economics Methods Group. Her special interest lies in methods used in economic evaluations, especially how methods for systematic review of literature can be incorporated into economic evaluation techniques. See Macfarlane and Mugford (1984).

### Mrs Brenda Mullinger

BSc (b. 1949), an xxx, joined international clinical research, based in the UK (Glaxo from 19xx to 19xx) and subsequently Canada (Squibb from 19xx to 19xx). She co-ordinated the UK RDS trial in the 1970s [?details?]. On her return to the UK, she moved into medical writing and editing, working as an independent freelance before joining a healthcare communications agency. See, for example, Mullinger (xxxx).

### Professor Colin Normand

FRCP HonFRCPCH (b. 1928) trained in paediatrics at the Hospital for Sick Children, Great Ormond Street, London; Johns Hopkins Hospital, Baltimore; and University College Hospital, London, between 1959 and 1971. He was Professor of Child Health at the University of Southampton from 1971 to 1993 and Dean of Medicine (1990–1993). His many publications in the neonatal field have mainly related to the absorption of lung liquid in the neonatal lung and to the biochemistry of pulmonary surfactant.

### Professor Ann Oakley

PhD (b. 1944) joined the National Perinatal Epidemiology Unit, University of Oxford, as Consultant in 1979, becoming a Wellcome Research Fellow the following year, and was appointed Senior Research Officer in 1983. She moved to the Thomas Coram Research Unit, University of London, in 1985 as



64

1998?

2004

for NHS R+D

# The Wellcome Trust Centre for the History of Medicine at University College London

24 Eversholt Street • London • NW1 1AD
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UCL

Dr Jerold Lucey
Editor in Chief, Pediatrics
University of Vermont College of Medicine
Given E203
89 Beaumont Avenue
Burlington
VT 05405-006
USA

Dr Daphne Christie
d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

11 March 2004

Dear Dr Lucey

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2pm-6pm**

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I attach a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and lists our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

Sir Iain Chalmers has suggested we invite you to this meeting, but unfortunately we do not have the funds to assist with travel from overseas to attend. I'm therefore writing to let you know of our plans, and to emphasise that if you happen to be in Britain at the time, we would be delighted to have you join us.

It really would be a great opportunity to document this obstetric success story. I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

Daphne Christie

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

atts.

**Wendy Kutner**

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 19 March 2004 15:38
**To:** Lucey, Jerold F
**Cc:** Wendy
**Subject:** RE: Witness Seminar

Dear Dr Lucey
Thank you for your e-mail. We are sorry that you are unable to attend the witness meeting on 15 June.
With best wishes,
Daphne Christie

-----Original Message-----
**From:** Lucey, Jerold F [mailto:Jerold.Lucey@uvm.edu]
**Sent:** 19 March 2004 15:05
**To:** d.christie
**Cc:** shey; ichalmers
**Subject:** Witness Seminar

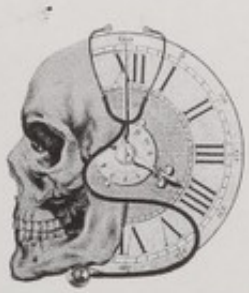
Dear Dr. Christie:

I want to congratulate you on what I think is a wonderful project.

I wish that I could participate but I cannot. I have to attend two weddings and one graduation just before and after June 15th.

I'll try to dredge my memory of events surrounding the paper and if I can I'll put something in writing.

Sincerely,
Jerold F. Lucey, MD
Editor in Chief, Pediatrics




# The Wellcome Trust Centre for the History of Medicine at University College London

24 Eversholt Street • London • NW1 1AD
www.ucl.ac.uk/histmed • +44 (0) 20 7679 8100


UCL


Professor Sally Macintyre OBE
Director
MRC Social and Public Health Sciences Unit
University of Glasgow
Glasgow G12 8QQ
Scotland

Dr Daphne Christie
d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193


25 March 2004

Dear Professor Macintyre

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

encs.

MRC Medical Research Council

Dr. Daphne Christie
Senior Research Assistant to Dr Tilli Tansey
The Wellcome Trust Centre for the History of Medicine
At University College London
24 Eversholt Street
London
NW1 1AD

26th March 2004.

Dear Dr. Christie

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**

Thank you for your letter inviting Professor Macintyre to the above meeting. Professor Macintyre is at present on sick leave, and is not expected back at work until around the beginning of May. I will, however, pass your letter to her at the earliest opportunity.

Yours sincerely

F. McDonald

Fiona McDonald, Personal Assistant to Professor Sally Macintyre

e-mail:fiona@msoc.mrc.gla.ac.uk

Rec 5/4/04

MRC Medical Research Council

Dr. Daphne Christie
Senior Research Assistant to Dr Tilli Tansey
The Wellcome Trust Centre for the History of Medicine
At University College London
24 Eversholt Street
London
NW1 1AD

1st April 2004.

Dear Dr. Christie

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**

Further to my letter of 26th March I have now had a chance to speak with Professor Macintyre re your invitation to her to attend the Witness Seminar on 15th June. I'm afraid that Professor Macintyre will be out of the country on that day and therefore unable to accept the invitation.

Best wishes,

Yours sincerely

F. McDonald.

Fiona McDonald, Personal Assistant to Professor Sally Macintyre

e-mail:fiona@msoc.mrc.gla.ac.uk

## Wendy Kutner

**To:** WydawnictwoKontekst
**Cc:** ucgachr@ucl.ac.uk
**Subject:** RE: Witness Seminar

Dear Anita, Our Witness Seminar: Prenatal corticosteroids for reducing morbidity andmortality associated with preterm birth is being held on Tuesday 15th June (not the 5th). Am I correct you wish to attend this particular meeting on this date? If you do want to attend please send me your title e.g. Dr/ Ms/ etc. and contact details whilst here at the Centre as places are limited and I would need the place if you find you are unable to attend, even at the last minute. Thank you. Wendy

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
24 Eversholt Street
LONDON NW1 1AD

Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

-----Original Message-----
**From:** WydawnictwoKontekst [mailto:wydawnictwokontekst@neostrada.pl]
**Sent:** 20 May 2004 09:09
**To:** w.kutner
**Subject:** Witness Seminar

Dear Wendy,

I know that it may be too late, but I would like to ask about possibilities of participation in the Witness Seminar on 5th June"?
I am in Poland yet, but from 3rd June to 23rd June thanks to the Wellcome Travel Grant I will have an affiliation status at the Wellcome Centre. You could remember me from the last year visit..

Yours sincerely

Anita Magowska

anitamagowska@wp.pl

## Wendy Kutner

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 21 May 2004 09:16
**To:** Anita Magowska
**Cc:** Wendy
**Subject:** RE: Witness Seminar

Dear Anita
Thank you for your e-mail and interest in our witness seminar programme. We have noted that you would like to attend the witness seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15 June. Please note that this is an historical meeting. Space is limited so please let us know should you not be able to attend.
Yours sincerely
Daphne Christie

-----Original Message-----
**From:** Anita Magowska [mailto:anitamagowska@wp.pl]
**Sent:** 21 May 2004 00:30
**To:** d.christie
**Subject:** Witness Seminar

I would like to ask you about the possibility of attendance the Witness Seminar.
I am afraid it is too late, but if I don't ask, I won't learn.
I am in Poland, but since 3rd June until 23rd June, thanks to the Wellcome Travel Grant, I will have the affiliation at the Wellcome Centre for the History of Medicine.
Yours sincerely

Anita Magowska

## Wendy Kutner

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 25 May 2004 08:53
**To:** Anita Magowska
**Cc:** Wendy
**Subject:** RE: Witness Seminar

Thank you. We look forward to seeing you on the 15th June.
Daphne Christie

-----Original Message-----
**From:** Anita Magowska [mailto:anitamagowska@wp.pl]
**Sent:** 21 May 2004 21:18
**To:** d.christie
**Subject:** Re: Witness Seminar

Dear Daphne,
thank you very much for this acceptance. The seminar is one of important reasons for which I decided to visit the Wellcome Centre on June. I am sure that I will be able to attend the seminar.
Yours sincerely

Anita Magowska

----- Original Message -----
**From:** Dr Daphne Christie
**To:** Anita Magowska
**Cc:** Wendy
**Sent:** Friday, May 21, 2004 10:16 AM
**Subject:** RE: Witness Seminar

Dear Anita
Thank you for your e-mail and interest in our witness seminar programme. We have noted that you would like to attend the witness seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15 June. Please note that this is an historical meeting. Space is limited so please let us know should you not be able to attend.
Yours sincerely
Daphne Christie

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**From:** Anita Magowska [mailto:anitamagowska@wp.pl]
**Sent:** 21 May 2004 00:30
**To:** d.christie
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I am in Poland, but since 3rd June until 23rd June, thanks to the Wellcome Travel Grant, I will have the affiliation at the Wellcome Centre for the History of Medicine.
Yours sincerely

Anita Magowska

## Wendy Kutner

**From:** Anita Magowska [anitamagowska@wp.pl]
**Sent:** 03 June 2004 08:28
**To:** w.kutner
**Subject:** Witness Seminar

Dear Wendy,
I will be affiliated as a assistant researcher at the Wellcome Centre for the History of Medicine since tomorrow for three weeks. I know the correct date (15th June) and I am sure I will be able to attend the Seminar.
Some days ago, having no your answer I contacted with Dr. Daphne Christie. She was so kind to accept my participation in this event.
My title is: Dr.
In Poland I have the post named "docent", it is equal with the Reader in the UK or the Assistant Professor in the US. I think that "Dr." is enough.

Yours sincerely

Anita Magowska

## Wendy Kutner

**To:** Anita Magowska
**Cc:** ucgachr@ucl.ac.uk
**Subject:** RE: Witness Seminar

Dear Anita, Thank you for your reply. Once I read all my e-mails by the end of yesterday I saw that you had been in touch with Daphne, so sorry about the duplication. I will add your name to those attending and we look forward to seeing you at the meeting. Wendy

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
24 Eversholt Street
LONDON NW1 1AD

Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

-----Original Message-----
**From:** Anita Magowska [mailto:anitamagowska@wp.pl]
**Sent:** 03 June 2004 08:28
**To:** w.kutner
**Subject:** Witness Seminar

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My title is: Dr.
In Poland I have the post named "docent", it is equal with the Reader in the UK or the Assistant Professor in the US. I think that "Dr." is enough.

Yours sincerely

Anita Magowska

Dr Jonathan Mant
Dept of Primary Care & General Practice
Primary Care Clinical Sciences Building
University of Birmingham
Birmingham B15 2TJ

Dr Daphne Christie
d.christie@ucl.ac.uk
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Fax: +44 (0) 20 7679 8193

19th March 2004

Dear Dr Mant

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

encs.

rcd 25.3.04

THE UNIVERSITY
OF BIRMINGHAM

**Division of Primary Care
Public and Occupational Health**

**Department of Primary Care
and General Practice**

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**Head of Department**
Richard Hobbs FRCGP
Professor of Primary Care and
General Practice

24th March 2004

Dr D Christie
Senior Research Assistant
The Wellcome Trust Centre
24 Eversholt Street
London
MW1 1AD

Dear Dr Christie,

**Re: Wellcome Trust's History of 20th Century Medicine Group Witness Seminar: prenatal corticosteroids.**

Thank you very much for your invitation to attend this meeting. I would have been very interested in taking part in what sounds a really fascinating piece of work. Unfortunately, I am examining on that day, which is a commitment I can't avoid. During the early 1990s, I was involved in some work in Oxford, which was aimed at increasing uptake of this therapy. For your interest, I enclose a copy of the three publications that arose out of this work.

I am sorry that I am unable to join you in June, and I wish you well with your work,

Yours sincerely,

**Dr. Jonathan Mant,**
**Senior Lecturer,**
Department of Primary Care & General Practice,
Primary Care Clinical Sciences Building,
University of Birmingham B15 2TT
Tel: 0121 4142657
E-mail: j.w.mant@bham.ac.uk

Dr Jonathan Mant
Senior Lecturer
Department of Primary Care & General Practice
Primary Care Clinical Sciences Building
University of Birmingham
B15 2TT

Dr Daphne Christie
d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

25 March 2004

Dear Dr Mant

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

Thank you for your letter of 24th March, which I received today. I am sorry that you are unable to attend the above meeting, but would like to thank you for the copies of your publications, which will be very helpful when we come to edit the proceedings for publication.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

## Wendy Kutner

**From:** Matterson ,Ms Clare [c.matterson@wellcome.ac.uk]
**Sent:** 14 May 2004 10:28
**To:** w.kutner
**Subject:** RE: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesday 15 June 2004

✓ No

Dear Wendy
I would have loved to have come to this. Extremely interesting and I would have been facinated to hear some of the stories first hand. Unfortunately it clashes with the BOard of Governors Residential. Can you ensure that I am on the list for the publication when it comes. And tell Tilli that I hope it all goes well
Clare Matterson
Director, Medicine, Society & History

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 12 May 2004 16:33
To: Catalyst; *Press Office; *Strategic Planning and Policy Unit; *MSH/Admin; *MSH/Biomedical Ethics; *MSH/Public Engagement Development Group; *MSH/HoMGrants; *MSH/HoMGrants; *MSH/Public Engagement Development Group; *MSH/InfoService; *MSH/Library; *MSH/MFAC; *MSH/PhotoLibrary; *Science Funding Division
Subject: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesday 15 June 2004

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, Professor Patricia Crowley, Professor James Drife, Professor John Gabbay, Professor Harold Gamsu, Dr John Muir Gray, Mrs Gill Gyte, Dr Stephen Hanney, Dr John Hayward, Professor Richard Lilford, Professor Miranda Mugford, Mrs Brenda Mullinger, Professor Ann Oakley, Dr David Paintin, Professor Osmund Reynolds, 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

Mrs Wendy Kutner
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www.ucl.ac.uk/histmed

## Wendy Kutner

**To:** Michaud ,Miss Kathryn
**Subject:** RE: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesday 15 June 2004

Dear Miss Michaud
Thank you for your email. We look forward to seeing you at the meeting.
Best wishes
Daphne Christie

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
24 Eversholt Street
LONDON NW1 1AD

Tel: 020 7679 8106
Fax: 020 7679 8193
w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

-----Original Message-----
From: Michaud ,Miss Kathryn [mailto:k.michaud@wellcome.ac.uk]
Sent: 13 May 2004 10:50
To: w.kutner
Subject: RE: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesday 15 June 2004

As someone who was administered steroid injections prior to the birth of my premature daughter I am looking forward to attending this seminar!

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 12 May 2004 16:33
To: Catalyst; *Press Office; *Strategic Planning and Policy Unit; *MSH/Admin; *MSH/Biomedical Ethics; *MSH/Public Engagement Development Group; *MSH/HoMGrants; *MSH/HoMGrants; *MSH/Public Engagement Development Group; *MSH/InfoService; *MSH/Library; *MSH/MFAC; *MSH/PhotoLibrary; *Science Funding Division
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Witness Seminar - Tuesday 15th June, 2004

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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, Professor Patricia Crowley, Professor James Drife, Professor John Gabbay, Professor Harold Gamsu, Dr John Muir Gray, Mrs Gill Gyte, Dr Stephen Hanney, Dr John Hayward, Professor Richard Lilford, Professor Miranda Mugford, Mrs Brenda Mullinger, Professor Ann Oakley, Dr David Paintin, Professor Osmund Reynolds, 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

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20 February 2004

Professor Mugford

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Sir Iain Chalmers is assisting us in the organization of the meeting.

Sir Iain has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

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We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion. We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

encs.

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Dr Daphne Christie
Senior Research Assistant
The Wellcome Trust Centre
University College London
24 Eversholt Street
LONDON
NW1 1AD

26 Feb. 04

Dear Dr Christie

Thank you for your invitation to the Wellcome Trust's History of 20th Century Medicine Group Witness Seminar on prenatal corticosteroids on Tuesday 15 June. I should be very glad to attend.

If wondering why things happened as they did, you might consider the role of public health and health commissioning in the process of adoption of the treatment, as this "technology" arrived in that arena during the time of the purchaser/provider split in the NHS. I am not sure who to recommend as a witness, but suggest Dr. John Gabbay might provide interesting insights. He is at the University of Southampton.

With best wishes

Yours sincerely

Miranda Mugford

MIRANDA MUGFORD
Professor of Health Economics

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26 April 2004

Dear Professor Mugford

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004, 2pm–6pm**

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

pp **Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

enc.

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12 May 2004

Dear Professor Mugford

**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Venue: Franks II, Mezzanine Floor, The Wellcome Building, 183 Euston Road, London NW1**
**Tuesday 15th June 2004: 2.00 pm – 6pm**

We are delighted that you are able to attend the above meeting and are happy to tell you that plans for the meeting are proceeding well. A copy of our publicity material has been sent to you under separate cover and I am now enclosing a draft programme. A full attendance list will be available at the meeting.

We would be very grateful if you would be prepared for the Chairman to call upon you to say a few words, for about 5 minutes, on 'Cost-effective analyses'. We like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

The Wellcome Trust Centre for the History of Medicine at UCL will reimburse your travel costs of a second class, preferably an Apex or Saver rail fare and/or underground fare supported by suitable receipts. Please note that University College London will reimburse your travel costs for a second class, preferably Apex or Saver rail fare, underground ticket or taxi only if supported by suitable receipts. They are inflexible in this matter.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

Please note that informal drinks will be served immediately after the meeting. We look forward to seeing you on the 15th June.

Yours sincerely

Daphne Christie

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

enc.

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## Wendy Kutner

**To:** Mugford Miranda Prof (MED) w241
**Cc:** Daphne Christie
**Subject:** RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Professor Mugford, Thank you for your reply. We look forward to seeing you at the meeting. Wendy

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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-----Original Message-----
From: Mugford Miranda Prof (MED) w241 [mailto:M.Mugford@uea.ac.uk]
Sent: 03 June 2004 14:29
To: 'w.kutner'
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Wendy Kutner

Thank you for the invitation and previous correspondence. I will come to the meeting prepared to speak for less than five minutes about cost effectiveness analysis, and would like very much to accept the invitation to supper after the meeting.

With best wishes, Miranda

Miranda Mugford
Professor in Health Economics
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http://www.uea.ac.uk/menu/acad_depts/hsw/hpp/hegwelc.htm

http://www.uea.ac.uk/menu/acad_depts/hsw/hpp/healecon/cochrane.html

>-----Original Message-----
>From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
>Sent: 03 June 2004 12:32
>To: m.mugford
>Cc: Daphne Christie
>Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004
>
>
>Dear Professor Mugford, further to our recent correspondence
>about the above meeting, Dr Tilli Tansey and Dr Daphne
>Christie would like to invite you to join them for an early
>supper at a local restaurant after the meeting. Supper should
>be finished by 9pm to give you ample time to return home.
>Please let me know on 020 7679 8106 or by e-mail
>w.kutner@ucl.ac.uk whether you are able to attend the supper.
>Yours sincerely, Wendy Kutner

## Wendy Kutner

**From:** Mugford Miranda Prof (MED) w241 [M.Mugford@uea.ac.uk]
**Sent:** 14 June 2004 12:30
**To:** 'w.kutner@ucl.ac.uk'
**Subject:** Prenatal corticosteroids 15th June

**Follow Up Flag:** Follow up
**Flag Status:** Flagged


Wellcome15june.doc


Econ fig1 wellcome15june.ppt

Dear Wendy

Following my phone call, I attach two documents mentioned. I do understand that these may not be handed out at the meeting. If one sheet alone is allowed, then the figure would be useful.

My home phone number is 01603 759324

Best wishes

Miranda

(mugford)

**Background material**
**Prepared for Wellcome Trust's Prenatal Corticosteroids**
**Witness Seminar**
**15 June 2004**

## Economics and health care decisions

1. Economics is the study of the ways in which resources are used and applied to producing benefits. Health economics is the application of economics concepts to the subject matter of health.

2. Resources are the inputs needed to produce the outputs, which in turn yield benefits.

3. Resources are usually limited and so choices have to be made about their use.

4. The most efficient choices are those that maximise benefits for the given combination of resources.

5. Benefits are derived from the outputs (goods and services) produced using resources, and may also be sacrificed in choosing one project over another.

6. Money aids the process of exchange and production, and is used as the unit of accounting used in most economic calculations.

7. Money values are not always a good reflection of the 'true' social value of an output or input, and for this reason, 'free market' provision of services is not always considered the best social arrangement. Public provision of services is often driven by such 'market failure'.

8. Where market forces do not operate, economic efficiency is still relevant. If more benefit can be gained from limited resources without any accompanying loss, then there is a moral or ethical argument in favour of moving to that solution. In the private sector, the need to at least 'break even' is an incentive to efficiency in production and distribution. Public accountability for taxpayers' money sometimes drives the quest for efficiency in public sector.

9. This leaves a great many questions about how and when to measure, combine and compare inputs and outputs, and their associated costs and benefits, for any particular aspect of health care.

## Economic evaluation in health care

10. A large and developing 'science' of economic evaluation has been developing in health economics over the previous 20 years. This was initiated in the UK by Professor Alan Williams, Professor Tony Culyer and colleagues, supported initially by DHSS and SSRC, and now increasingly from pharmaceutical industry. The techniques have been adopted in technology assessment guidelines processes since the late 1990s, such as those of NICE in the UK. Parallel influences in the USA included through the OTA, and other agencies.

11. Cost effectiveness (CEA) or cost consequences evaluation are forms of economic evaluation, used where there is a single agreed defined health outcome to be maximised.

12. Cost utility (CUA) and cost benefit (CBA) evaluation are needed when a range of interventions and outcomes are compared. An early and pioneering health economics study of introduction of regionalised intensive care illustrates use of these methods (Boyle et al 1983, abstract attached).

*Miranda Mugford, UEA Norwich, June 2004*

N Engl J Med. 1983 Jun 2;308(22):1330-7.

## Economic evaluation of neonatal intensive care of very-low-birth-weight infants.

**Boyle MH, Torrance GW, Sinclair JC, Horwood SP.**

We evaluated the economic aspects of neonatal intensive care of very-low-birth-weight infants, using outcomes and costs of care before and after the introduction of a regional neonatal-intensive-care program. Neonatal intensive care increased both survival rates and costs. For newborns weighing 1000 to 1499 g, the cost (in 1978 Canadian dollars) was $59,500 per additional survivor, $2,900 per life-year gained, and $3,200 per quality-adjusted life-year gained; intensive care resulted in a net economic gain when figures were undiscounted but a net economic loss when future costs, effects, and earnings were discounted at 5 per cent per annum. For infants weighing 500 to 999 g, the corresponding costs were $102,500 per additional survivor, $9,300 per life-year gained, and $22,400 per quality-adjusted life-year gained; intensive care resulted in a net economic loss. By every measure of economic evaluation, the impact of neonatal intensive care was more favorable among infants weighing 1000 to 1499 g than among those weighing 500 to 999 g. A judgment concerning the relative economic value of neonatal intensive care of very-low-birth-weight infants requires a comparison with other health programs.

PMID: 6405272 [PubMed - indexed for MEDLINE]

# 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


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16 June 2004

Dear Professor Mugford

**The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth**

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne Christie

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**


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3 Jan 2005

Dear Daphne

Thank you for sending me the draft transcript of this witness seminar. I have marked suggested editing in the document, and hope this is clear enough. I have suggested four references to make it easier for anyone who would like to follow up what I said.

On page 61, I felt that I rambled somewhat, and so have suggested shortening the text. I'm willing to discuss this.

I attach my short biography.

I look forward to seeing the next proof version,

With best wishes

Yours sincerely

Miranda

Miranda Mugford

**Hey**: I think we had better draw this to a closure. I want you back in say 15 minutes time, because we haven't got as far as we should have. Death isn't the only outcome, there are cost-benefits apart from that and we must move on I think.

TEA BREAK

Dr Hey.....[not recorded].

**Mugford**: My background is a degree in economics. I graduated ~~from the University of Stirling~~ in 1972 ~~and the relevance of that is that~~ when health economics as a discipline ~~didn't they~~ did it exist. I think the first Penguin book of reading for students of health economics was published in 1972 ~~and I looked at it and wished that I had studied health economics.~~ There wasn't at that stage ~~even~~ a postgraduate training in ~~it~~ health economics. I finished my economics quite disillusioned with the subject, because it was very much centred on the formal economy ~~that is about how people trade goods and services using the money mechanism and adjustments of it through the public services as a method.~~ ? [note to editor: I am happy for this to be left in, but it is not essential. It was intended to illustrate the serendipity of having a health economics analysis of antenatal steroids.] ~~So I finished a Masters in Money Economics and then dabbled a bit in bits of health of~~ economics research and had ~~some children. And this is a very personal, indulgent, and I shall go on, but~~ and self I joined the NPEU in Oxford, the National Perinatal Epidemiology Unit, as a researcher in statistics, medical statistics, with Alison

Macfarlane
~~McFarlane~~ but also to work in the unit on other topics, including on incorporating economics alongside randomized trials with Adrian Grant, and this very new notion of building economic evaluations using evidence from syntheses of evidence of effectiveness, building on the work that Iain Chalmers and others were pioneering in the Oxford database of perinatal trials as it became but wasn't yet when I first joined the unit in 1981. So I think early in the time, in the early 1980s, when I was still working on the book with Alison Macfarlane ~~McFarlane~~ of statistics of pregnancy and childbirth, Iain Chalmers asked me to keep a file in my filing cabinet on neonatal intensive care, because it was an issue that was rising in the health services and it was going to be of certainly economic importance. And so I did. At that time health economics was emerging and that's another whole historical story which has been documented elsewhere,* but my connection with it was really that Alan Williams, who is and was a professor at York who probably was the founding father of health economics in the UK, visited the unit. I think he was examining a dissertation in Oxford with Iain, and I asked him how did I qualify as a health economist, he said what you have to be able to do is if you are a graduate economist and you can stand up and say that in front of a bunch of doctors, you are a health economist. So I girded my loins and just worked on subjects that seemed to be relevant to our brief in the NPEU and to the incredible enthusiasms of people within the unit, including the systematic review of steroids ~~which~~ I remember, I think, the day when the results were being worked through by Patricia[1] and Iain[2] and the coffee room was buzzing, and this was very exciting. So that was before it was published. At the same time I was host and supervisor to a series of students from York where they had a new health economics master's

move to footnote

[ 1. Crowley
2. Chalmers } (for editors' info) ]



* Croxson B.

degree and they looked for placements for their students during the summer to do dissertations, ~~and~~ one of them, James Piercy, came to me and his topic was to work on the economics of antenatal corticosteroids and he did some observational work in the neonatal unit in Oxford to try to assess the costs of treating babies at risk of preterm delivery and eligible for steroids. In fact, the surfactant question was also, I was going to say bubbling around at that time. And so he and I with Iain Chalmers wrote a paper which was a modelling exercise, a very, very simple decision modelling exercise, based on different assumptions about initial birth weight and mortality risk, based on the cost data which James had gathered for his dissertation and based on the evidence of effectiveness from the systematic review. That was published by *Archives of Disease in Childhood*, having been rejected by the *British Medical Journal*. That was published in 1991, I think, ~~1990~~, it was after the systematic review. So as far as I am concerned, that wasn't quite the end of the story because the Oxford Regional Health Authority was introducing the ~~the~~ getting research into practice programme ~~grip~~. We are going to hear more about that I think.

One of the things I was asked to do by the public health doctors was to model what would be the impact in the Oxford region of this particular policy of increasing uptake beyond current uptake, which I think we assumed conservatively to be about 10 per cent, I can't remember. We worked out that implementing the policy in the Oxford region might ~~reduce~~, not only reduce mortality, but also reduce costs of neonatal intensive care after paying for the drugs, which were not a great cost to the health service, and that probably it would be in the region of 10 per cent of the cost of neonatal intensive care for those babies.** Although when I talked to the finance director in the Oxfordshire Health

* ~~Ref~~: Mugford M, Piercy J, Chalmers I. Cost implications of different approaches to the prevention of respiratory distress syndrome. Arch. Disease in Childhood 1991; 66: 757-64

** Mugford M. Steroids for women expected to deliver prematurely: estimates of the impact of wider use. ~~NPEC~~ ORHA, Oxford 1994.

Authority, as it then was, he was a bit dismissive and he said well if you cannot tell us how many cots we can close, it's not really very interesting to us, because those paediatricians will just fill the cots anyway, they will put someone else into them. I said well that's not the point of the economics. The point of the economics is that if you can do more with what you have got, it's a better thing to do.

**Hey**: Yes, your study came in just when if you didn't give steroids you might have to end up giving surfactants, and surfactant was £250 per ampoule, wasn't it?

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

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

[Note to editor: I don't think I disagreed with Dr Hey]

**Mugford**: No. There's just one other thing which I think Mary Ellen Avery referred to, and Patricia too, that the analysis we did was quite unsophisticated, but we did make some effort to model the impact in the smaller babies and the more preterm babies, and in that case there isn't a predicted cost saving. One of the problems we had with people was the assumption that that is not then cost effective, which isn't true, because society has shown that it is willing to pay for neonatal

care, and ~~they are~~ willing to pay for the benefits of having survivors. So it's not just that they need to save money, it's that there's a willingness to pay for the benefits ~~and that is~~ can go beyond the straight evident cost savings. But it's just ridiculous that anyone should just not look at this. Economists, it's not very fashionable to look at areas where in fact there is a win–win situation. The exciting academic work all goes on at the fringes ~~of~~ where benefits perhaps might not be worth the costs.

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

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

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

**Mugford:** We can say that over the last 20 years the resources devoted to neonatal intensive care, (you have had a different seminar on this subject, and I haven't looked at the living witness results on that seminar,) ~~but~~ having incredibly expanded, and there are very, very many more nurses, doctors, ventilators and techniques for the care of preterm babies than there were 20 years ago.*

**Hey:** I think we shall move straight on, because we need to move on to getting things into research into practice. So I am going to ask Iain just to explain how it becomes that he managed to steal a totally early and very out of date version of Patricia's metaanalysis as late as 1992, at a time when there were twice as many trials involved in her analysis as you wanted for your logo.

**Chalmers:** It's very good that Patricia has already described some of the history that I might have covered, but given that I am going to be talking about the Cochrane logo, I might as well start off with Archie Cochrane, who wrote a book which was published in 1972, called *Effectiveness and Efficiency, Random Reflections on Health Services*. I read it in 1973, and basically it changed my life. Whereas previously I had not even been aware of the term randomized control trials, I had

* Ref: Macfarlane A, Johnson A, Mugford M. Epidemiology. ~~Eds~~ Chap. 1 in Roberton NRC, Rennies J. Textbook of Neonatology (3rd Edn.) Churchill Livingstone 1999: 3-33.

experience, counts at least, and of course what the great and the good around you are saying, your local opinion leaders, counts at least as much as what we would like people as rational scientists, what we would like them to use as evidence. I would like to hear more about that interaction between different forms of evidence in people's minds as they develop their policies.

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

**Chalmers:** Alex Turnbull was Professor of Obstetrics in Oxford at the time. He was also one of the people looking at the maternal mortality

experiences for the report and I know that he was very influenced by a particular woman who had died of septicaemia, who had received corticosteroids, and that was I think the basis for his opposition. It's right that if you have seen someone have a haemorrhagic stroke after you have given streptokinase, it makes it far more difficult to say that this is a policy that we should adopt, because you actually don't know which of your patients would have died if you hadn't have given it to them. But in fact it wasn't the case in St Davids. In St Davids they had adopted steroids on the basis of the trials. This study that Roger did was a retrospective assessment which didn't, they didn't take it up, they had taken it up to a greater extent than University Hospital of Wales, and that was as you said in fact based on the Liggins and Howie trial.

Hayward: I wonder whether it might be useful briefly describing intervention that I led on over a two-year period, which was partly triggered by Richard's list of suggested effective interventions that should be used for perspective audit by obstetricians under the banner of the RCOG. I will need about four minutes to describe it. I am Director of Public Health in Newham, but I am really here because I was then a public health specialist in training at Camden and Islington health authority, and I have known Iain for years, because I am married to his sister. It took me 10 years to really get a grip on what he had been going on about, about evidence. But there's nothing like a convert late in life to become a passionate advocate, so having at last seen the light after 10 years it made me very interested to know quite why other people were having equivalent problems.

consultant colleague. Last year that woman whose baby got severe respiratory distress and has survived with cerebral palsy, and this woman got 4000 euros compensation in an out-of-court settlement because I had failed to give her antenatal steroids. The decision by the protection society and the legal team was that whereas everybody else might be able to defend themselves against not giving her antenatal steroids, that they had seen what I had written about antenatal steroids prior to 1985 and that I would not be able to defend myself. So a very, very disabled child, that's the bottom line and that's what matters really. But a lot of suffering on the part of the parents, and a question mark about whether the disability is in fact due to the complications of respiratory distress or perhaps for a completely different reason.

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

**Mugford:** It follows on from Patricia's story and also what I was saying, that the impacts on the economic side that we measured were purely the health services facts and many economic studies are just cost-effectiveness analyses from the point of view of the health service for the efficient running of health services. But the impact on family is terrific and there's a long-term impact of children with cerebral palsy. We did a study in the NPU with another MSc student who

looked at the cost of babies going home on oxygen. And it was terrific. Parents gave up their whole careers to look after their children and ~~again~~ if we redid the steroid analysis taking account of family and household impact it would just emphasize the same answer, it's even more of a "win-win" ~~win-rim (?)~~ we don't really need to do the study, but sometimes you have to do the study to have the impact.

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

**Brocklehurst**: I am a bit conscious that I have been asked to speak about current research and where the gaps are in a session which is about twentieth century medicine. So we are already a bit beyond the twentieth century in terms of what I needed to discuss, although hopefully in a few years time this will be history and you can tell me that I was completely wrong in guessing where we were going to go. I want just to talk about some of the issues that have come up to day in terms of how we are now looking at the evidence that we have got and what is beginning to come out. I am going to get onto the issue of multiple courses of steroids, but there are another couple of issues which I wanted to touch on, which have been brought up this morning, one of which is the choice of agent that we use for antenatal corticosteroids. There's been a very interesting paper published in the

*American Journal of Obstetrics and Gynecology* by Alan Jones and Roger Soll, which is looking at the available trials and separating them into those have used dexamethasone and those that have used betamethasone, and the interesting thing is there have been no head to head comparisons of dexamethasone or betamethasone, which have looked at substantive neonatal outcomes. There have been ones that look at antenatal fetal heart rate tracings that seems to be hugely irrelevant if they are not related to the outcome for the baby. And they suggested that betamethasone is preferable to dexamethasone, because the betamethasone trials compared with placebo have a marked reduction in the incidence of death, and dexamethasone has no statistically significant effects on neonatal death, although probably one of the things they invoked is the fact that the number of trials using betamethasone is substantially larger than the number of trials using dexamethasone, and the numbers in each trial are larger. However, they have suggested some biological plausibility of this, and I am sure we are going to see a lot more on what agent we should be using and interestingly one of the issues that they brought up is because no drug companies are licensing steroids for antenatal indications, the ability to get hold of dexamethasone and betamethasone in the USA is becoming more and more difficult, because no company is producing it, because it doesn't have a licence. So people are using all sorts of other steroids, potentially, some of which clearly do not cross the placental barrier and may not be effective at all. They also raise issues about whether all steroids may be as good as intramuscular steroids and also different ways of giving the steroids to the baby, whether you can give it into….. amniotic fluid and they will take it, or give it directly intramuscularly into the fetal

thigh which seems a little bit more invasive than a quick intramuscular injection into the mother's thigh. But I suspect we are going to see a lot more about the choice of the agent in the future. We have heard a lot about the long-term follow up of the single dose of steroids and I think that the 30-year follow up of the original Liggins and Howie trial will be extremely useful and I think we probably need to do some more follow up, much longer term follow up of the other trials which have been done to try to strengthen that evidence-base about the long-term effects if only to be hugely reassured that there are no adverse effects even though the death rate has been decreased and therefore one might expect a worse outcome in the steroid arm.

The other issue is one of twins and the ongoing debate about what you should do with twins and high-order births. I was very interested when I saw the title of a research project that was presented to the *American Journal of Obstetrics and Gynecology* in 2002, which was looking at twins. Unfortunately it was comparing prophylactic multiple doses of steroids with steroids when the women presented in preterm birth, which showed no difference. But it certainly didn't elucidate whether the dose that they were using or whether it was benefiting twins, and we are still, I think I am certain of that, although trials of the individual patient meta-analysis at the existing trials may well take us forward on that issue, if we can ever get the data or the money to do it.

Finally, I want to just touch briefly on the issue of repeated doses of steroids which have been brought up time and time again and I think here there is a bit of a lesson to be learnt. As Patricia said, within a

very short space of time of us using steroids, we were then splashing it around with gay abandon and giving it to everybody we possibly could and often on a weekly basis, to the point where we were giving prophylactics, lots of us were giving prophylactic steroids weekly to twins from 20 weeks, and certainly lots of users were given it to their triplets weekly from 20 weeks, until they get to 34 weeks or the risk of preterm delivery is not thought to be present. Because of that a great amount of effort went into designing a number of trials around the world to look at the comparisons with a single course of steroids and multiple courses of steroids to look at the outcome on the baby. And when we originally thought about this, following your survey of practice in 1977, there were five trials that were designed, which would have added up to a total of 10 000 women randomized, yes five trials around the world, one of which we have already heard about in Australia, two in the USA, one in Canada and one in the UK, in Europe, which I was going to be leading for the MPU. I just want to briefly update you on where those trials are, because I think it is crucial in telling us whether we will ever get an answer to the single dose or multiple course of steroids debate. The largest of those trials was ours, which was the teams trial which was going to include 4000 women and had a primary acumen at age two. We did planning for a pilot trial, but unfortunately we went to the MRC at the time when the MRC had no money, you may remember that event, so despite achieving the highest grade that we could possibly get for the quality of our trial, there was no money to fund it. That trial now would almost have been finished if we had got the funding. The Canadian trial, which aims to recruit over 2000, is recruiting. It was due to finish three years ago, has got 900. Whether it will ever get to 1900 I

don't know because it might take as long again. The Australian trial is getting close to the 980 it wanted to recruit, although looking at long-term outcomes 980 is too small. While the USA trial which aimed to recruit 1000 was stopped early by the Data Monitoring Committee at 500, because they decided it was futile to continue, because they wouldn't be able to detect the short-term benefit they wanted to detect. Then the other large trial of 2500, at the maternal and fetal medicine's network, was also stopped by the Data Monitoring Committee at 500, because they found a slightly lower birthweight in the group receiving multiple courses of steroids. So it looks likely at the end of this that we may end up with about 3000 women recruited around the world in trials on multiple courses of steroids versus the single course, instead of the 10 000, and I am very sceptical that in five years time we will actually have enough to question in terms of we need to know which is the long term acumens. The short-term respiratory acumens look as if they may be favourable for multiple courses of steroids, but clearly that is only part of the question. So the fact that we didn't get these original trials into practice very quickly we are still not necessarily improving on past performance when it comes to antenatal corticosteroids.

The other thing to mention, I suppose, is in the absence of trials evidence of long-term ~~acumen~~ outcome and what people are going to rely on is observational studies of long-term ~~acumen~~ outcome. The one observational study with repeat courses of steroids which has been published is from the western Australian group, which suggested a statistically significantly in decreased incidence of cerebral palsy with multiple courses of steroids versus a single course, but a statistically significant increase in significant behavioural problems among the children who

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

**Brocklehurst:** I think there is an issue, because I remember the Canadian study got in touch with us about our team's trial, and said how did you get a placebo for your betamethasone, because it's cloudy and we went it's not. Ours is completely clear. That's because you are not using a long-acting betamethasone. You are not giving what was used in the original trial and you never read the original trial. Because the original trial doesn't specify what the betamethasone preparation was and we were using betamethasone which is what was used in this country, and in the UK you can only buy betamethasone which is a solution.

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

Hey: Perhaps we had better clarify that. They used, rather than having a negative placebo in the original Liggins trial, a corticosteroid which was only one seventieth as powerful, because it didn't cross the placenta.

Gamsu: It did cross but in much smaller quantities.

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

Harding: If I could just comment on that? The cortisone acetate, the placebo, Mont did actually check its effects on the babies, and in I don't know how many women, but he measured cord blood steroid levels and showed that it had that twice the dose that they used as placebo had no effect on cord blood steroid levels and that reassured him that that was an appropriate placebo. To come back to Peter Brocklehurst's point about how come they chose the best dose and the best drug. I don't think we know that they did. Nobody's looked and almost all of the issues that Peter rose, the repeat steroids, which dose, which drug, how often, at what gestation, to which pregnancy,

Biography

Miranda Mugford

Professor of Health Economics in the School of Medicine and Health Policy and Practice at the University of East Anglia (UEA), also, Chair of convenors of the Campbell and Cochrane Collaboration Economics Methods Group. Economist and health services researcher with special interest in methods used in economic evaluations, especially how methods for systematic review of literature can be incorporated into economic evaluation techniques. Before 1997, she was economist at the National Perinatal Epidemiology Unit at the University of Oxford. Since moving to UEA she has continued work on perinatal health services, including the 2 volume book 'Birth Counts' co-authored with Alison Macfarlane and others, published by The Stationery Office.

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MUGFORD



# PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

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

EDITED BY D A CHRISTIE AND E M TANSEY

## 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

**Dr Edmund Hey:** I was always taught that before I stood up to speak I would check my references. Most of us haven't had a chance to check any of our references, but it may be that after today's meeting, some of us will go scurrying away to do just that. I was provoked into checking up what the Wellcome History of Medicine people had to say about Sir Peter Medawar, and his statement that most scientific papers are a fraud. I would encourage you to read what he actually wrote, because it isn't quite how it gets quoted nowadays. He gave that as an unscripted talk, which I find quite terrifying, on the third programme (yes it was called the third programme back in 1963) and since we are in reminiscing mood, I had just started my first job as a MRC physiologist/clinician/animal worker, working with Kenneth Cross. I heard his talk on the day and it had an absolutely profound effect on me. I thought I might read a bit of it, but then I decided I found another talk in which he was actually interviewed just three years later, defending this, and I think we will come back to this at the end of the day. The issue is what he meant about research being fraudulent. I will just read a couple of sentences. The interviewer says, arising out of your paper is the scientific paper of fraud, which was written under the influence of Karl ... philosophy, you said it is a fraud. So how many of your scientific papers have been a fraud. And he said,

> Well, most of my scientific papers have been moderately fraudulent, but I would really rather put it this way. I have never pretended that the research I reported in the scientific paper was done in the inductive style, that's to say you just wander around collecting facts and then you

> suddenly tumble into putting them into a picture. I know I haven't practised what I have preached, but then I think I am not the first person who's failed to do so.

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

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

I am not sure that's true. Sir Peter Medawar was a Nobel Prize winner, he knew more than most, he made many very brilliant discoveries himself. But I am going to come back at the end of the afternoon and just ask whether in actual fact we cannot see of the germs that produced the idea that Mont Liggins came up with. If we did, we are then left spending most of today realising that great ideas are one per cent inspiration and 99 per cent perspiration, and I suspect we are going to spend the vast part of today wondering why we perspired quite as heavily as we have over this particular inspiration and why it is that some of us are still mopping our brow and realising that we still haven't got things sorted.

I think that we should start by asking Mel who has come all the way from Boston, although I think she's been in the Rhine until a few days ago, to set the scene, because 30, 40 years ago clinicians and physiologists and animal research workers were much closer together

than they are often are nowadays. Certainly in the UK. It's very uncommon that you meeting somebody who spends some days in the lab and some days on the farm or in the animal laboratory, but you can tell us the story, because years ago, much of what we understand now about the lung came from the combination of those interests, didn't it?

**Dr Mary Ellen (Mel) Avery:** I bring you a personal view of the discovery of (?) maturation of the lung; the preterm, ….has to be delivered for one reason or another which of course had had an enormous impact on the survival of some very low birthweight infants. The story really begins as you have noticed with Mont Liggins and I am happy to acknowledge the fact that he has been a most generous supporter and friend and we have been in close touch I say with years ago, not the last decade, but during the 1960s and 1970s, when this story evolved.

I was asked to give a personal point of view and I will tell you how I got into the act. The studies of babies were initiated largely, I think, ?uk/us in this country, with the Barcroft and Baron combination with Maureen Young as well and later with Nescia and Bataglia, who were just given a big award in the USA for this very thing. I was finishing a double shift (?) supported by the National Institutes of Health in 1957 to 1959 and then a Marcol (?) Fellow, the John and Mary Marcol Foundation in New York would select people for five years on a reasonably good salary and say, 'Go do whatever you want to do'. Can you imagine? They even gave the people I wanted to work with

some support to pay for my hardware and software and what have you. So I was set free. I decided to go to the UK, because I had been associated with Clement Smith and knew that he felt great fondness for English research and animal research and, of course, that was ordered within a month with Leonard Strang. I brought Colin Norman back with me. I am sorry he's not here today because he spent a year in Johns Hopkins where I was then a fledgling investigator. But we learned some techniques. We set out to map the course of events in the developing ewe, the animal of choice, I have often wondered why. I think it's because babies and lambs are about the same size at birth and the equipment you had for one worked for the other. I don't know if that's quite true or not, but that's my thought on the matter. There's a hiatus here. I began to get interested in other things, but the group in the lab continued and the names that come into mind Florence Moog, a brilliant anatomist, embryologist who was studying the intestine of rats in St Louis. We were both members of the same National Institutes of Health Study section, so this was a coffee break conversation. What do you do? What do I do? She tells me she can accelerate the maturation of the intestine of, I think it was rats, measured by the appearance of alkaline phosphatase. I said, 'Accelerated maturation, who would like to do that?' Well, that was 1962. Then we said we have to know about the normal appearance of various enzymes and so on in the developing lamb. That's when all the people in the laboratory, which then numbered 15 or 20, produced a paper about what the timing was of various enzymes and other events in the normal lamb. I concluded that presentation at a meeting of the Society of Obstetricians and the Paediatric Society. Mont Liggins was there and

**Harding:** They truly did start randomizing at the end of 1969 and it really was the beginning of the trial. Mont in his usual way decided that the animal studies were conclusive and that they should move on to trials and when I asked him why it was so short a period, because it was only a few months, between concluding the animal studies and starting the trial, he was convinced that it needed to be a randomized trial. Ross was very much of that mind and they devised the protocol together. It didn't take them long to get the drug. There were no ethics committees in 1969, but the hospital senior medical staff committee approved all trials. It functioned as an ethics committee at that time, and the hospital medical committee approved it without further discussion. Mont was very keen to get started, because the head of department was actually planning a different trial that would have precluded this one and Mont was going to get in first, which he did.

**Professor Richard Lilford:** I wonder what would have happened if Professor Avery hadn't transclaimed that conservation. It sounds from the way you speak, as though Mont regarded this as a sideline and there wasn't a need to pursue it himself.

**Harding:** In the end he did pursue it, but I think you are right. I think the interest elsewhere, particularly from Mel's group and the San Francisco group probably on the effects of steroids on lung

maturation, not so much rekindled, as accelerated his interest in the topic, and he recognized the importance of pursuing this and what a clinical impact it might have had. He took Ross along with him, because it was a sideline for Ross as well.

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

**Harding:** The funding situation was easy. We had a public health system and there was no direct charge to patients and that has always been the case for newborn intensive care in New Zealand. It's fair to say that the state of intensive care varied around the country. The National Women's Hospital was opened in 1964 from memory, but I would need to check that, specifically to both enhance the care of women and their babies and to encourage research in this field. It was the only intensive care unit in the country where babies were ventilated and Ross started ventilating babies in the mid-1960s with a primitive ….ventilator and started using (?) in the 1970s which was before Gregory's publication on (?) because again the link to San Francisco, both he and Ross knew the San Francisco group well and had seen the data before it was published and were convinced that this was a useful thing to do. So the ~~sceper~~ CPAP was just beginning to be used

follow up happened, and he himself therefore was never right through I think into the early 1980s recommending that anybody else should act on the basis of their trial alone, and was very encouraging of other trials. I was asked about the follow up and the NIX trial, which we will no doubt come to, and the follow up was still going on at the time that the Auckland trial follow up was completed, I asked Ross if he knew about this and he said he couldn't remember if he had known about it, but if he had he certainly would have encouraged them to proceed, because again he thought it was important that other groups replicated, looked under other circumstances, and checked what specifically was and wasn't helpful about this treatment.

Hey: I guess perhaps that it is time that we move on and ask Patricia Crowley to tell us something of how for the first time the various trials that did get done in the 1970s and early 1980s got put together. But I suspect after that we need to go back over some of these individual trials and in particular explore with Mel's help some of the thinking that went into the USA collaborative trial and how it got interpreted and how it got analysed. Let's just have the overview first.

Professor Patricia Crowley: If you forgive me by starting with a little bit of personal recollection. I first heard about antenatal cure steroids in an undergraduate lecture in 1974 and it obviously made an immense impact on me because a few weeks after hearing about antenatal steroids the first baby I ever delivered as an undergraduate died, a neonatal death, from respiratory distress syndrome despite weighing 7

lbs and being born at 36 weeks, because we didn't have the kind of ventilation for premature babies in Ireland at that time. And so perhaps things were set for being interested in this topic. In 1977 as a senior house officer in paediatrics, I attended a lecture given by Mel Avery, a visitor to Dublin, as a guest of the Irish Perinatal Society, and again the impact was enhanced by the fact that the lecture was given by a very attractive woman, and that was unusual in those days to hear a good lecture given a woman at all. But for a woman to be the keynote speaker and that's probably why I remember it, plus at the fact that at that time I was working in neonatal paediatrics and seeing babies die from this condition. I was working in the National Maternity Hospital, which was a very authoritarian place, with a very necalictic attitude towards any kind of intervention or treatment except for ones ordained from the bosses in that institution. And I counselled a woman whose previous baby had died from respiratory distress syndrome, and with the paediatric registrar's we had to go as a deputation to the master of the hospital to get permission to give this one woman a course of antenatal steroids and that was the first and only time in a two-year spell in obstetrics and paediatrics that I was allowed to prescribe antenatal steroids.

I then went to work in the Hammersmith Hospital in London and in 1978, the public meeting, the follow-up presentation of the Royal College of Obstetricians preterm labour working group, where Rob (?)….. had attended in 1977, and presented a very comprehensive review of all these results of all the trials that had been done up until then, containing all the entire 1200 women that had been randomized to antenatal steroids. This work was presented in 1978 and I was fortunate enough to be there and I was very impressed by

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3. WITNESS SEMINAR: Prenatal Corticosteroids for Reducing Morbidity and Mortality
   15 June 2004

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17 Aug 05

Dear Lois

I enclose my copy of the Transcript of the Prenatal Corticosteroids witness seminar.

I hope this annotated version is self explanatory. I have completed the two references you omitted. The reference in footnote on page 92 (Hallam et al 1996) is in the NPEU publications list, and you may be able to get a copy from them. This journal is not available in electronic form that far back.

If possible, I would be grateful to edit my contribution on pages 59-61 as marked. I have a sloppy style of speech which does not read well. I would also like to remove complete irrelevances (which I don't deny I said!).

PTO.

rec'd 23/8/05 ack. 1/9/05

Please let me know if you have
further queries. Many thanks for all
your efforts to interpret my contribution.

With best wishes

Miranda

# STEROIDS FOR WOMEN EXPECTED TO DELIVER PREMATURELY

## Estimates of impact of wider use

*

Miranda Mugford
National Perinatal Epidemiology Unit

May 1993

Oxford Regional Health Authority

**ESTIMATED IMPACT ON HEALTH SERVICE RESOURCES IN ENGLAND AND WALES OF EXTENSION OF POLICY TO GIVE ANTENATAL CORTICOSTEROIDS TO WOMEN WHERE PRETERM DELIVERY IS ANTICIPATED**

1. **Introduction**
This is a simple analysis based on available data and therefore conclusions must be read as conditional estimates with a possible range of alternative values. Sensitivity analysis is still to be done.

2. **Antenatal steroids are effective in reducing respiratory distress and mortality.**
A policy of giving corticosteroids (24mg betamethasone, 24mg dexamethasone, or 2g hydrocortisone) by injection to women for whom preterm delivery is anticipated reduces the incidence of respiratory distress syndrome (RDS) in newborn babies by between 40 and 60 percent, and early neonatal deaths by between 25 and 50 percent (Crowley et al 1990).

3. **Costs of neonatal care for babies with RDS are around twice costs for babies without RDS.**
Table 1 shows estimated costs at 1989 prices for neonatal hospital care by birthweight category and presence of RDS. These costs are based on estimated costs in one hospital (Mugford et al 1991), but are similar to costs in other UK centres (Howard and Mugford 1992) All costs exclude the cost of surfactant treatment (see below)

4. **Less than 20 percent of preterm deliveries have been preceded by antenatal steroids.**
In England and Wales, this policy of care is not widely used. In most hospitals in the Northern Region, less than 10 percent of women having preterm births had been given steroids, with the exception of the regional referral centre where less than 30 percent of preterm deliveries had been preceded by antenatal steroid treatment (Donaldson 1992). In a very large multicentre trial of alternative treatments for babies with high risk of RDS, which included about half of the very low weight babies in the UK over the period of the study, less than 20 percent of all babies entered had been born of mothers who had had steroids before the birth (OSIRIS 1992).

5. **Estimating the number of births that could benefit from such treatment.**
The total number of preterm births in England and Wales cannot be directly measured from routine sources, because gestational age is not recorded for live births. The numbers are approximated by the number of low weight births, for which data are available from birth registration statistics (OPCS 1992). (A certain proportion of babies of low weight would be small for dates but not necessarily preterm, and would have different risks of RDS. A more sophisticated model with better data would take account of this factor.)

   Table 2 shows numbers of births by birthweight category. The following analysis is based on numbers of births with stated birthweights of less than 2500g. There may be considerable numbers in the 'not stated' category who are at increased risk of RDS and could have benefited from antenatal corticosteroids.

6. **Estimating current incidence and workload due to RDS**
Routinely collected statistics from the NHS are not of sufficient completeness or quality to give numbers of babies with diagnostic codes for respiratory distress, nor to give numbers of days of care at different levels of intensity for babies of different birthweights. Both these sets of data should have been possible if the recommendations of the Korner committee had been implemented

properly.

It is therefore necessary to estimate the likely incidence of RDS based on estimates of the risk of RDS from Halliday et al (1985), and gestation for weight data from Scotland (Macfarlane and Mugford 1984). Assumed incidence of RDS by birthweight group is given in Table 3.

7. **Estimated impact of increased antenatal steroid use on numbers of cases of RDS**
Assuming that antenatal steroids reduce the risk of RDS by 50 percent Table 4 shows estimated current numbers of cases (assuming 20 percent of women have treatment before preterm birth), and the expected numbers if a) 50 percent and b) 75 percent of women received corticosteroid treatment. This table is based on the assumption of no neonatal surfactant therapy (see below).

8. **Changes in resource use as a result of different levels of use of antenatal corticosteroids.**
Table 5 gives the results of calculations based on Tables 1,3 and 4. It shows that increasing use of steroids from the current 20 percent of preterm births to 50 percent would, in theory release over £2.5m of neonatal care resources, and that a further increase in steroid use to 75 percent would reduce costs by a further £2.2m. This represents between about 2 and 5 percent of current spending on neonatal hospital care.

9. **The policy would reduce neonatal mortality.**
Table 6 lays out expected changes in mortality resulting from extension of antenatal corticosteroid use. If 50 percent of women with preterm birth received corticosteroids, around 230 deaths might be averted, with a further 195 averted if coverage were as high as 75 percent.

10. **Extension of corticosteroid use would reduce the NHS costs of surfactant therapy**
As surfactant is now in widespread use for babies at high risk of RDS, and as it is very costly (at about £1000 per baby treated), it is also relevant to consider the effects of antenatal steroids on surfactant use. It is now clear that it is beneficial to give surfactant early, before the onset of RDS, in very preterm babies, and as a treatment, on onset of RDS for babies of lower initial risk (OSIRIS 1992). Table 7 shows estimated surfactant costs arising as a result of applying this policy with different assumptions about antenatal corticosteroid coverage. The need for and cost of surfactant is reduced by greater use of steroids antenatally.

11. Surfactant use reduces the risk of death by a probable, further, 45 percent. The effects of the further reduction in RDS and increased survival on neonatal costs is not yet clear (Mugford and Howard in press) but is the subject of current research in a national multicentre study (Tarnow Mordi et al).

12. **Implications for health service managers**

a. Current regional targets for neonatal mortality might be more attainable if antenatal steroid use were extended.
b. Midwifery and obstetric clinical managers should consider the implications for their local practices.
c. Audit of obstetric and midwifery care should assess the use of antenatal corticosteroids.
d. Enquiries into infant deaths should also assess this factor.
e. Data systems should be improved to support such audit.
f. Purchasing contracts for maternity services could include policy for antenatal steroid use as a quality requirement.
g. Pharmacy and neonatal managers at neonatal care provider units should monitor surfactant costs and review the number of babies

receiving surfactant whose mothers did not have antenatal corticosteroids.

Miranda Mugford, NPEU, Oxford 19 April 1993.

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Tarnow-Mordi WO, Halliday H, Hey E, Malek M, Mugford M et al. The economics of neonatal surfactant therapy. MRC News 1992;57:16-17.

Table 1 Neonatal care costs per case by birthweight, £ at 1989 prices, to nearest £100

| | No RDS | RDS |
|---|---|---|
| <1500g | 4800 | 6800 |
| 1500-1999 | 2400 | 3900 |
| 2000-2499 | 1200 | 1400 |

Table 2 Births by birthweight England and Wales 1990

| Birthweight | Livebirths |
|---|---|
| <1500g | 6 500 |
| 1500-1999 | 8 924 |
| 2000-2499 | 30 631 |
| >=2500g | 632 319 |
| not stated | 27 766 |

Table 3 Assumed risks of RDS by birthweight category

| Birthweight | Percent with RDS | Estimated numbers in England and Wales[1] |
|---|---|---|
| <1500g | 70 | 4 550 |
| 1500-1999g | 55 | 4 908 |
| 2000-2499g | 15 | 4 595 |
| (>=2500 | 1 | 6 323 |
| not stated | ? | ? |

1 Assuming no steroids are given antenatally

Table 4 Estimated numbers of cases of RDS with different assumptions about proportion receiving corticosteroids before birth

| | Percent of women receiving steroids prior to preterm birth | | | |
|---|---|---|---|---|
| Birthweight | 0 | 20 | 50 | 75 |
| <1500g | 4 550 | 4 095 | 3 413 | 2 844 |
| 1500-1999 | 4 908 | 4 415 | 3 681 | 3 068 |
| 2000-2499 | 4 595 | 4 135 | 3 446 | 2 872 |

Table 5 Cost implications of change in coverage of antenatal steroid use

| | Net change in NHS hospital costs |
|---|---|
| Increase from 20 percent to 50 percent: | -£2.6m |
| Increase from 20 percent to 75 percent | -£4.8m |

Table 6 Estimated change in numbers of deaths occurring with different policies for use of antenatal corticosteroids

| | Percent of women receiving antenatal corticosteroids | | | |
|---|---|---|---|---|
| | 0[2] | 20[1] | 50[2] | 75[2] |
| Birthweight | | | | |
| <1500g | 1 534 | 1 415 | 1 235 | 1 085 |
| 1500-1999g | 241 | 223 | 194 | 171 |
| 2000-2499g | 217 | 200 | 175 | 154 |

1 Neonatal deaths in England and Wales 1990

2 Estimated based on Crowley at al, and assuming that the effect they showed for early neonatal deaths also applies to neonatal deaths.

Table 7 Costs of surfactant treatment with different policies for antenatal steroid use

| | Percent of women receiving steroids prior to preterm birth | | |
|---|---|---|---|
| Policy for surfactant | 20 | 50 | 75 |
| Treatment of RDS | £12.6m | £10.5m | £8.8m |
| 'Early use in <1550g, and treatment of RDS for all others | £14.4m | £13.0m | £11.8m |

Annotated 17 Aug 05 Mugford

(attached copy
check
Still to do ~~PBT~~, ORHA report – for % uptake of steroids assumed.
LP92: Ref to nurse on oxygen study

* Hallam L, Lindbeck B, Bradley M.
Journal of Neonatal Nursing 1996; 2(3) 25-30: NPEU publication number 769.

asked NPEU.

please see pages V7, 59-63, 77, 91
and blog note on p 115

# PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

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

Edited by L A Reynolds and E M Tansey

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spare pages removed 28/9/05
corrected 28/9/05

please return by 7 Sept 05.

# Prenatal Corticosteroids for Reducing Morbidity and Mortality In Preterm Birth

## Participants

Dr Mary Ellen (Mel) Avery
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)
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, Professor Alison Macfarlane, Dr David Paintin, Professor Maureen Young

## Apologies include:

Professor Sir Robert Boyd, Dr Clive Dash, Professor Geoffrey Chamberlain, Dr Pamela Davies, Professor Sir Liam Donaldson, Professor Peter Dunn, Dr Jonathan Grant, 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, Professor Jim Neilson, Dr Cliff Roberton, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

†Died 31 August 2004

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

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

**Harding**: In the end he did pursue it, but I think you are right. I think the interest elsewhere, particularly from Mel's group and the San Francisco group [who were??????] probably on the effects of steroids on lung maturation, not so much rekindled, as accelerated his interest in the topic, and he recognized the importance of pursuing this and what a clinical impact it might have had.[25] He took Ross along with him, because it was a sideline for Ross as well.

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

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[25] The San Franciso group included xxx and xxx and xxx. See, for example, Platzker A C, Kitterman J A, Mescher E J, Clements J A, Tooley W H. (1975) Surfactant in the lung and tracheal fluid of the fetal lamb and acceleration of its appearance by dexamethasone. *Pediatrics* 56: 554–61.

**Harding:** The funding situation was easy. We had a public health system so there was no direct charge to patients and that has always been the case for newborn intensive care in New Zealand. It's fair to say that the state of intensive care varied around the country. The National Women's Hospital was opened in 1964 from memory, but I would need to check that, specifically to both enhance the care of women and their babies and to encourage research in this field. It had the only intensive care unit in the country where babies were ventilated and Ross started ventilating babies in the mid-1960s with a primitive bird ventilator and started using continuous positive airway pressure (CPAP) in the 1970s. That was before Gregory's publication on CPAP, again because of the link to San Francisco, both he and Ross knew the San Francisco group well and had seen the data before it was published and were convinced that this was a useful thing to do.[26] So the CPAP was just beginning to be used at the time of the trial. Ventilation was initiated, but outcomes were still poor and in the paper from Ross, which I think everybody has a copy of, he describes the change in perinatal mortality over that time.[27] I think he also describes in that paper, but certainly to me, at the end of the trials he went to Geneva in 1975 to talk to the World Health Organization about the funding of the follow up, and while he was away two large preterm babies died of uncomplicated RDS, because nobody else could care for them. He was extremely upset about that. So it was a unique position in a sense that this was the only place that it could have been done, in New Zealand certainly, and the only people who could do it.

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

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[26] Gregory *et al.* (1971). See also Dunn *et al.* (1971); Dunn (1974). For the source of Gregory's inspiration, see Christie and Tansey (eds) (2001): 25.

[27] See note 18. [OR as appendix??]

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

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

**Mugford**: My background is a degree in economics. I graduated from the University of Stirling in 1972 ~~and the relevance of that is that~~ health economics as a discipline didn't exist then. I think the first Penguin book of readings for students of health economics was published in 1973.[92] I looked at it and wished that I had studied health economics. There wasn't at that stage even postgraduate training in it. I finished my economics [?degree?] quite disillusioned with the subject, because it was very much centred on the formal economy, that is how people trade goods and services using the money mechanism ~~and adjustments of it through the public services as a method. So I finished a Masters in Monetary Economics and then dabbled in bits of health of economics research and had some children. And this is very personally indulgent, and I shall go on, but~~ I joined the NPEU in Oxford, as a researcher in statistics, ~~medical statistics~~ with Alison Macfarlane, but also to work in the unit on other topics, including incorporating economics alongside randomized trials with Adrian Grant, this very new notion of building economic evaluations using evidence from syntheses of evidence of effectiveness, building

[92] Cooper M H, Culyer A J. (1973) *Health Economics: Selected readings*. Harmondsworth: Penguin.

on the work that Iain Chalmers and others were pioneering in the Oxford Database of Perinatal Trials, as it later became but wasn't when I first joined the unit in 1981.

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

At that time health economics was emerging and that's another whole historical story which has been documented elsewhere.[93] My connection with it was really through Professor Alan Williams at York, who was probably the founding father of health economics in the UK, and his visit to the unit. I think he was examining a dissertation in Oxford with Iain and I asked him how I could qualify as a health economist? He replied, 'What you have to be able to do if you are a graduate economist is to stand up and say that you are a health economist in front of a bunch of doctors.' So I girded my loins and worked on subjects that seemed to be relevant to our brief in the NPEU to the enthusiasms of people within the unit, including the systematic review of steroids. I remember the day when the results were being worked through by Patricia and Iain before it was published. The coffee room was buzzing and this was very exciting. At the same time I was host and supervisor to a series of students from York where they had a new health economics Master's degree and they looked for placements for their students during the summer to do dissertations. One of them, James Piercy, came to me ~~with his topic~~ on the economics of antenatal corticosteroids ~~and~~ he did some observational work in the neonatal unit in Oxford to try to assess the costs of treating babies at risk of preterm delivery and eligible for steroids. In fact, the surfactant question was also, I was going to say bubbling around at that time. He and I with Iain wrote

[93] ~~Prof Mugford, was this~~ Croxson (1998).

a paper which was a modelling exercise, a very, very simple decision modelling exercise, based on different assumptions about initial birth weight and mortality risk, based on the cost data, which James had gathered for his dissertation, and the evidence of effectiveness from the systematic review. That was published by *Archives of Disease in Childhood*, having been rejected by the *British Medical Journal*, in 1991, after the systematic review.[94] So as far as I am concerned, that wasn't quite the end of the story because the Oxford Regional Health Authority had introduced the Getting Research Into Practice Programme [and Purchasing?] (GRIP).[95] We are going to hear more about that later, I think.

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

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

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[94] Mugford *et al.* (1991).

[95] Dopson and Gabbay (1995).

* The report has reference: Mugford M. Steroids for women expected to deliver prematurely: estimates of the impact of wide use. Oxford: ORHA, 1993.

Oxford Regional Health Authority

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

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

**Mugford**: No. There's just one other thing which I think Mary Ellen Avery referred to, and Patricia too, and that was the analysis we did was quite unsophisticated, but we did make some effort to model the impact in the smaller babies and the more preterm babies, and in those cases there wasn't a predicted cost saving. One of the problems we had with people was the assumption that that is not then cost effective, which isn't true, because society has shown that it is willing to pay for neonatal care, and they are willing to pay for the benefits of having survivors. So it's not just that they need to save money, it's that there's a willingness to pay for the benefits ~~and that it can go~~ beyond the straight, evident cost savings. ~~But it is ridiculous that anyone should just not look at this.~~ Economists, it's not very fashionable to look at areas where in fact there is a win–win situation. The exciting academic work goes on at the fringes, where benefits perhaps might not be worth the costs.

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

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

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

**Mugford**: We can say that over the last 20 years the resources devoted to neonatal intensive care, you had a different seminar on this subject[96] – I haven't looked at the ~~living witness results on [?]transcript of?]~~ that seminar – but ~~[?what has expanded?]having incredibly expanded and~~ there are very many more nurses, doctors, ventilators and techniques for the care of preterm babies than there were 20 years ago.[97]

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

**Chalmers**: It's good that Patricia Crowley has already described some of the history. Given that I am going to be talking about the Cochrane logo, I might as well start with Archie Cochrane, whose famous book – *Effectiveness and Efficiency: Random reflections on health services* – was published in 1972.[98] I read

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[96] See the Witness Seminar, 'Origins of Neonatal Intensive Care in the UK', Christie and Tansey (eds) (2001), also freely available online at www.ucl.ac.uk/histmed following the link to Publications.

[97] Macfarlane A, Johnson A, Mugford M. (1999) Epidemiology, in Roberton N R C, Rennies J. (eds) *Text book of Neonatology*, 3rd edn. Edinburgh: Churchill Livingstone, 3–33.

[98] Cochrane (1972).

it in 1973 and it changed my life![99] In spite of the fact that I had been 'licensed to kill' six years earlier after studying at the Middlesex Hospital Medical School, London, to qualify as a doctor, I had not previously been aware of the term 'randomized controlled trial (RCT)'. Cochrane showed me how I might adjudicate among incompatible clinical opinions about treatments, a common situation faced by me and other junior doctors, and it was after reading Cochrane's book that I started to collect reports of RCTs. A librarian in Cardiff, Steve Pritchard, designed a Medline search to identify these studies for me, and I started noting those in my special area of interest (perinatal care) during my reading of journals and books.

In 1976, because it was clear that this was an insufficiently systematic method of finding reports of RCTs, I outlined a plan for using a more systematic approach both for finding published reports, and for identifying unpublished studies (because biased under-reporting of RCTs means that unpublished studies tend to have less dramatic results than those that get into print). This plan, which was set out in a letter to Martin Richards, a psychologist in Cambridge, also stated an intention to use statistical synthesis of the results of similar by separate studies (meta-analysis) to reduce Type 2 errors (false negatives) in estimating treatment effects. My letter to Martin Richards happened to be sent to him during the same year as the term 'meta-analysis' was introduced by the American social scientist Gene Glass.[100]

The first opportunity that I took to do a systematic review using meta-analysis related to different ways of monitoring babies during labour.[101] Electronic fetal heart rate monitoring had been introduced in obstetrics not long previously, sometimes accompanied by fetal scalp blood sampling to assess fetal acid-base status, particularly if the heart rate trace had raised concerns. It was being suggested by some people that these more intensive methods of intrapartum

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[99] Chalmers (1999).

[100] Glass (1976).

[101] Chalmers (1979).

**Williams:** For practising clinicians a new accelerating factor is the Clinical Negligence Scheme for Trusts which gives a discount in your insurance for a hospital if you are following evidence-based guidelines and can show that you have these in place. To actually achieve CNST grade-one status, you have to jump through a lot of hoops and it's all about practising evidence-based guidelines.[134] I think that's a new accelerating factor in the application of research into practice.[135]

**Gabbay:** I like Richard's analysis at the end, but when you talked about the epistemological change I thought you were going to say something slightly different, which I would think is the case and that is that what people count as evidence and what we as researchers and members of the Cochrane collaboration may wish them to count as evidence may not be the same thing. I was very struck by the wonderful vignette earlier on from our colleagues in Wales, John and Roger, when they were faced with the dilemma of whether to move to using steroids or not, and what seemed to sway things in the first case that Roger described, was a very unscientific retrospective analysis of a case series, which was done locally and which was quite persuasive, and John was saying that it was probably as persuasive as the trials and systematic reviews that we as researchers would wish people to use.[136] So I just wanted to add to Richard's analysis that it's also a shift in what people count as legitimate evidence and the kind of mechanism that John has just described, where it has to be scientifically based evidence in order to get your brownie points and get more money or whatever it is you are after.

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[134] For further details of the scheme, see www.nhsla.com/Claims/Schemes/CNST/ (visited 5 August 2005).

[135] For a review of this field, see Hicks N R, Mant J. (1997) Using the evidence: putting the research into practice. *British Journal of Midwifery* 5: 396–9. See also Mant J, Hicks N R, Dopson S, Hurley P. (1999) Uptake of research findings into clinical practice: a controlled study of the impact of a brief external intervention on the use of corticosteroids in preterm delivery. *Journal of Evaluation in Clinical Practice* 5: 73–9.

[136] See page xx for a correction on the case of St David's Hospital (near note 140).

Maybe part of the mechanism we need is to shift people's views of what evidence is, because in the work I have been doing, watching clinicians using evidence, stories, anecdotes, personal experience, and of course what the great and the good around you are saying – local opinion leaders – counts at least as much as what we as rational scientists, would like them to use as evidence.[137] I would like to hear more about that interaction between different forms of evidence in people's minds as they develop their policies.

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

**Chalmers:** Alec Turnbull was Professor of Obstetrics and Gynaecology in Oxford at the time. He was also one of the people looking at the maternal mortality experiences for the report on *Confidential Enquiries into Maternal Deaths.*[138] I know that he was very influenced by a particular case, a woman who had died of septicaemia, who had received corticosteroids, and I think that

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[137] Gabbay and le May (2004).

[138] Department of Health and Social Security (DHSS) (1986).

had different policies. I was learning what those policies were and then I was passing on this information to the junior members of their team, so that they could also practice non-evidence-based medicine. That was a long time ago, but I think it is still the case that many people believe that doctors and other experts know what they are doing.

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

Crowley: As an obstetric senior registrar in 1985, I took over the care of a woman who was having an antepartum haemorrhage at 37 weeks gestation. We thought she was 37 weeks because of an error in estimating the dates made earlier in the pregnancy. Because of continuing antepartum haemorrhage I induced labour following consultation with a supervising consultant. She had not had antenatal steroids. She was, in fact, only 33 weeks gestation and the baby went on to develop severe RDS and after prolonged ventilation survived with severe cerebral palsy. His mother sued the hospital, my consultant colleague and myself. The patient was awarded Euros 4000 million compensation in an out-of-court settlement because I had failed to give her antenatal steroids. The decision by the protection society and the legal team was that whereas other obstetricians might be able to defend themselves against not giving antenatal steroids in 1985, the papers I had published demonstrating the evidence in favour of antenatal steroids prior to 1985 rendered my failure to prescribe antenatal steroids indefensible. So a very disabled 20-year-old man and his parents have suffered a lot as a result. This

medico–legal event contributed a further chapter to my 30-year personal involvement with the antenatal steroid story.[159]

**Hey**: One of the good things was that came out of the book, *Effective Care in Pregnancy and Childbirth*, was a version which has been widely read by parents, wasn't it?[160] Not many other branches of medicine have pursued it through to that point yet, have they?

**Mugford**: Following on from Patricia's story and also what I was saying earlier, that the impacts on the economic side that we measured were purely the health services facts ~~and~~ many economic studies are just cost-effectiveness analyses from the point of view of the health service for the efficient running of the health services. But the impact on family is terrific and there's a long-term impact of children with ~~cerebral palsy~~.[161] We did a study in the NEPU with another York MSc student who looked at the cost of babies going home on oxygen. And it was terrific. Parents gave up their whole careers to look after their children and if we redid the steroid analysis taking account of family and household impact it would just emphasize the same answer, it's even more of a 'win-win'. We don't really need to do the study, but sometimes you have to do the study to have the impact.

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

---

[159] May we have a date on this?

[160] Dr Hey, could you elaborate?

[161] Prof Mugford, could you provide a reference here?

See * on front page of this volume.

He was Director of Public Health in Newham, London, from 2002 until 200x. See Hayward (2001).

### Dr Edmund Hey

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

### Professor Ross Howie

### Mr Ian Jones

(b. 1945) has been Publisher at the Wellcome Trust since 19xx.

### Dr William ('Bill') Henry Kitchen

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

### Professor Sir William Liley

KCMG FRS(NZ) (1929–83) was trained at Otago University, New Zealand, did research under Professor John Eccles on neuromuscular transmission, switching to obstetrics at the Women's National Hospital, Auckland, from 1959 as a New Zealand Medical Research Council Senior Research Fellow, then at the Auckland University Medical School as Research Professor in Perinatal Physiology from 1969 until his sudden[?premature?unfortunate?] death in 1983. His diagnostic procedure for rhesus haemolytic disease of the newborn was perfected so that he could predict which could remain in the uterus and which could not; led the team that performed the first successful intrauterine transfusion, and believed in the rights of the unborn child. See Hawgood (2005).

### Professor Sir Graham (Mont) Liggins

FRCOG FRCS (Edin) PhD (b. 19xx) graduated in medicine at University of Otago in 1949. He was appointed to a personal chair at the Postgraduate School of Obstetrics and Gynaecology,

University of Auckland, in 19xx, specializing in Endocrinology and Fetal Physiology. His most important discovery was that the time of birth was controlled by the fetus, not the mother.

### Professor Richard Lilford

Phd FRCOG FRCP FFPH (b. 1950) was Consultant Obstetrician and Gynaecologist to Queen Charlotte's Hospital, London, before moving to the University of Leeds in 19xx as Professor of Obstetrics and Gynaecology and Chairman of the Epidemiology Research Institute (??–1995). He has been Professor of Clinical Epidemiology and Head of the Division of Primary Care, Occupational Health and Public Health in the Medical School of the University of Birmingham since 1995. He is also the Director of the Patient Safety Research Programme for the Department of Health in England and is Director of Research Methods Programme, [???NHS Executive, West Midlands, since 1995???].

### Professor Miranda Mugford

[Hons?] (b. 19xx), an economist and health services researcher, joined the National Perinatal Epidemiology Unit at the University of Oxford in 19xx. She has been Professor of Health Economics in the School of Medicine and Health Policy and Practice at the University of East Anglia (UEA), since 19xx and Chair of convenors of the Campbell and Cochrane Collaboration Economics Methods Group. Her special interest lies in methods used in economic evaluations, especially how methods for systematic review of literature can be incorporated into economic evaluation techniques. See Macfarlane and Mugford (1984).

### Mrs Brenda Mullinger

BSc (b. 1949), an xxx, joined international clinical research, based in the UK (Glaxo from 19xx to 19xx) and subsequently Canada (Squibb from 19xx to 19xx). She co-ordinated the UK RDS trial in the 1970s [??details??]. On her return to the UK, she moved into medical writing and editing, working as an independent freelance before joining a healthcare communications agency. See, for example, Mullinger (xxxx).

### Professor Colin Normand

FRCP HonFRCPCH (b. 1928) trained in paediatrics at the Hospital for Sick Children, Great Ormond Street, London; Johns Hopkins Hospital, Baltimore; and University College Hospital, London, between 1959 and 1971. He was Professor of Child Health at the University of Southampton from 1971 to 1993 and Dean of Medicine (1990–1993). His many publications in the neonatal field have mainly related to the absorption of lung liquid in the neonatal lung and to the biochemistry of pulmonary surfactant.

### Professor Ann Oakley

PhD (b. 1944) joined the National Perinatal Epidemiology Unit, University of Oxford, as Consultant in 1979, becoming a Wellcome Research Fellow the following year, and was appointed Senior Research Officer in 1983. She moved to the Thomas Coram Research Unit, University of London, in 1985 as

Mugford M. Steroids for women expected to deliver prematurely: estimates of the impact of wider use. Oxford: ORHA, 199X 3

# PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

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

Edited by L A Reynolds and E M Tansey

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

...

**Mugford:** My background is a degree in economics. I graduated from the University of Stirling in 1972: health economics as a discipline didn't exist then. I think the first Penguin book of readings for students of health economics was published in 1973.[1] I looked at it and wished that I had studied health economics. There wasn't at that stage even postgraduate training in it. I finished my economics degree quite disillusioned with the subject, because it was very much centred on the formal economy, which is how people trade goods and services using the money mechanism and adjustments of it through the public services as a method. So I finished a Masters in Monetary Economics and then dabbled in bits of health of economics research. I joined the NPEU in Oxford, as a researcher in statistics with Alison Macfarlane, but also to work in the unit on other topics, including incorporating economics alongside randomized trials with Adrian Grant. This was a very new notion of building economic evaluations using evidence from syntheses of evidence of effectiveness, building on the work that Iain Chalmers and others were pioneering in the Oxford Database of Pe[rinatal Trials, as it was then]. It wasn't when I first joined the unit in 1981.

In the early 1980s when I was still working on the [...] childbirth with Alison Macfarlane, Iain Chalmers a[nd ...] cabinet on neonatal intensive care, because it was ar[...] in the health services and it was going to be of econo[mic importance? And so I did.]

At that time, health economics was emerging and [...] which has been documented elsewhere.[3] My con[nection with it was really through] Professor Alan Williams at York, who was prob[ably the founding father of health]

MUGFORD (W) edited 1/6/05.

[1] Cooper and Culyer (1973).

[2] Macfarlane and Mugford (eds) (1984).

[3] Croxson (1998).

# PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

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In the early 1980s when I was still working on the book of statistics of pregnancy and childbirth with Alison Macfarlane, Iain Chalmers asked me to keep a file in my filing cabinet on neonatal intensive care, because it was an issue that was of increasing interest in the health services and it was going to be of economic importance.[2] And so I did.

At that time, health economics was emerging and that's another whole historical story which has been documented elsewhere.[3] My connection with it was really through Professor Alan Williams at York, who was probably the founding father of health

---

[1] Cooper and Culyer (1973).

[2] Macfarlane and Mugford (eds) (1984).

[3] Croxson (1998).

economics in the UK, and his visit to the unit. I think he was examining a dissertation in Oxford with Iain and I asked him how I could qualify as a health economist? He replied, 'What you have to be able to do if you are a graduate economist is to stand up and say that you are a health economist in front of a bunch of doctors.' So I girded my loins and worked on subjects that seemed to be relevant to our brief in the NPEU and to the enthusiasms of people within the unit, including the systematic review of steroids. I remember the day when the results were being worked through by Patricia and Iain before it was published. The coffee room was buzzing and this was very exciting. At the same time I was host and supervisor to a series of students from York, where they had a new health economics Master's degree and they looked for placements for their students during the summer to do dissertations. One of them, James Piercy, came to me to work on the economics of antenatal corticosteroids. He did some observational work in the neonatal unit in Oxford to try to assess the costs of treating babies at risk of preterm delivery and eligible for steroids. In fact, the surfactant question was also, I was going to say 'bubbling' around, at that time. He and I with Iain wrote a paper which was a modelling exercise, a very, very simple decision-modelling exercise, based on different assumptions about initial birth weight and mortality risk, based on the cost data, which James had gathered for his dissertation, and the evidence of effectiveness from the systematic review. That was published by *Archives of Disease in Childhood*, having been rejected by the *British Medical Journal*, in 1991, after the systematic review.[4] So as far as I am concerned, that wasn't quite the end of the story because the Oxford Regional Health Authority had introduced the Getting Research Into Practice and Purchasing (GRIPP) programme.[5] We are going to hear more about that later, I think.

One of the things I was asked to do by the public health doctors was to model the impact in the Oxford region of this particular policy [GRIPP], increased uptake beyond current uptake, which I think we assumed conservatively to be about 10 per cent, I can't remember.[6] We worked out that implementing the policy in the Oxford region might reduce not only mortality but also the costs of neonatal intensive care after paying for the drugs, which were not a great cost to the health service, and that reduction would probably be in the region of 10 per cent of the cost of neonatal intensive care for those babies. Although when I talked to the finance director in the health authority, as it then was, he was a bit dismissive and said, 'If you cannot tell us how many cots we can close, it's not really very interesting to us, because those paediatricians will just fill the cots anyway, they will put someone else into them'. I replied that this was not the point of the economics. The point of the economics is that it is better if you can do more with what you have got.

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

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[4] Mugford *et al.* (1991).

[5] Dopson and Gabbay (1995).

[6] Mugford (1993).

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

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

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

...

**Mugford**: We can say that over the past 20 years the resources devoted to neonatal intensive care – you [the History of Twentieth Century Medicine Group] had a different Witness Seminar on this subject,[7] but I haven't looked at that transcript – have expanded incredibly. There are very many more nurses, doctors, ventilators and techniques for the care of preterm babies than there were 20 years ago.[8]

...

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

...

**Mugford**: Following on from Patricia's story and also what I said earlier, that the impacts on the economic side that we measured were purely the health services facts. Many economic studies are just cost-effectiveness analyses from the point of view of the health

---

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

[8] Macfarlane *et al.* (1999).

service for the efficient running of the health services. But the impact on family is terrific and there's a long-term impact of children with disabling chronic lung disease. We did a study in the NPEU with another York MSc student, Birgitta Rudbeck, who looked at the cost of babies going home on oxygen. [9] And it was terrific. Parents gave up their whole careers to look after their children. If we redid the steroid analysis taking account of family and household impact it would just emphasize the same answer, it's even more of a 'win–win'. We don't really need to do the study, but sometimes you have to do the study to have the impact.

....

## References include:

Dopson S, Gabbay J. (1995) *Evaluation of GRIPP (Getting Research into Practice and Purchasing). Report for the Department of Health*. London: Department of Health.

Hallem L, Rudbecke B, Bradley B. (1996) Resource use and costs of caring for oxygen-dependent children: a comparison of hospital and home-based care. *Journal of Neonatal Nursing* **2**: 25-30. NPEU Publication No. 769.

Hanney S, Mugford M, Grant J, Buxton M. (2005) Assessing the benefits of health research: lessons from research into the use of antenatal corticosteroids for the prevention of neonatal respiratory distress syndrome. *Social Science and Medicine* **60**: 937–47.

Macfarlane A, Mugford M. (eds) (1984) *Birth Counts: Statistics of pregnancy and childbirth*, 2 vols. London : Stationery Office. Second edition published 2000.

Macfarlane A, Johnson A, Mugford M. (1993) Epidemiology, in Roberton N R C, Rennie J. (eds) *Textbook of Neonatology*, 3rd edn. Edinburgh: Churchill Livingstone, 3–33.

Mugford M. (1993) *Steroids for Women Expected to Deliver Prematurely: Estimates of the impact of wider use*. Oxford: Oxford Regional Health Authority (ORHA).

Mugford M, Piercy J, Chalmers I. (1991) Cost implications of different approaches to the prevention of respiratory distress syndrome. *Archives of Disease in Childhood* **66**: 757-64.

Biographical note: This is the date used in the text. Is it correct? yes

## Professor Miranda Mugford

DPhil (b. 1950), an economist and health services researcher, joined the National Perinatal Epidemiology Unit at the University of Oxford in 1981. She has been Professor of Health Economics in the School of Medicine and Health Policy and Practice at the University of East Anglia (UEA), since 1997 and Chair of Convenors of the Campbell and Cochrane Collaboration Economics Methods Group. Her special interest lies in methods used in economic evaluations, especially how methods for systematic review of literature can be incorporated into economic evaluation techniques. See Macfarlane and Mugford (1984).

[9] Hallam *et al.* (1996).

**Lois Reynolds**

**From:** Mugford Miranda Prof (MED) w241 [M.Mugford@uea.ac.uk]
**Sent:** 18 October 2005 17:00
**To:** ucgarey@ucl.ac.uk
**Subject:** RE: Wellcome Witnesses: Prenatal corticosteroids : further query

Dear Lois, It is correct as you have put it, ie:

0-0-0-0
Professor Miranda Mugford: I am a health economist. I just wanted to ask what the clinical situation was with neonatal intensive care at that time in New Zealand? Was it at different states of development in different countries? Just the background to what was normally done with babies at an early stage of gestation when they were born. What was the funding situation for their care?
0-0-0-0

√ checked 25/10/05

Best wishes, Miranda

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: Tuesday, October 18, 2005 2:57 PM
To: Mugford Miranda Prof (MED) w241
Subject: RE: Wellcome Witnesses: Prenatal corticosteroids : further query

Dear Prof Mugford,
A further query on your contribution follows.
Many thanks from Lois

0-0-0-0
Professor Miranda Mugford: I am a health economist. I just wanted to ask what the clinical situation was with neonatal intensive care at that time in New Zealand? Was it at different states of development in different countries? Just the background to what was normally done with babies at that gestation [???at an early stage of gestation???] when they were born. What was the funding situation for their care?
0-0-0-0

-----Original Message-----
From: Mugford Miranda Prof (MED) w241 [mailto:M.Mugford@uea.ac.uk]
Sent: 30 September 2005 10:38
To: ucgarey@ucl.ac.uk; M.Mugford@uea.ac.uk
Subject: RE: Wellcome Witnesses: Prenatal corticosteroids : your pages

Dear Lois

Sorry about the confusion. I've checked this and annotated with a couple of small things in red type. The referencing and footnotes are correct in your version. The Mugford (1993) ref is correctly included at footnote number 6.

Many thanks, and best wishes

Miranda

>-----Original Message-----
>From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
>Sent: Thursday, September 29, 2005 12:47 PM
>To: M.Mugford@uea.ac.uk
>Subject: Wellcome Witnesses: Prenatal corticosteroids : your pages
>
>Dear Prof Mugford,
> Thank you for your corrections. Attached are your pages for a
final
>look, as I was confused by the addition of a reference [Mugford M.
>(1993) Steroids for women expected to deliver prematurely: estimates of

>the impact of wider use.
>Oxford: OHTA, 1993] inserted on a separate page, quite near the
>paragraph discussing Birgitta.
> I would be glad of your views.
> Best wishes from Lois
>
>
>
>Mrs Lois Reynolds
>Research Assistant to Dr Tilli Tansey
>History of Twentieth Century Medicine Group Wellcome Trust Centre for
>the History of Medicine
> at UCL
>210 Euston Road,
>LONDON
>NW1 2BE
>
>Tel: 020 7679 8123
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>
>The Wellcome Trust Centre is supported by the Wellcome Trust, a
>registered charity, no. 210183.
>
>

rec: 5/5/04
ack: 5/5/04 (t)

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Shipbourne, Tonbridge, Kent TN11 9PL
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FAX TO: Wendy Kutner 020 7679 8193.
History of (20) Medicine Group

FROM: Brenda Mullinger
01732 811101

Re: Prenatal Corticosteroids meeting 15th June.

Many thanks for your phone call.

Do you have a map/directions that you could fax me please. In particular, which is the nearest tube station?

Many thanks

Brenda Mullinger

# The Wellcome Trust Centre for the History of Medicine at University College London

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www.ucl.ac.uk/histmed • +44 (0) 20 7679 8100

UCL

Mrs Brenda Mullinger
Larches
Green Road
Shipbourne
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Kent TN11 9PL

Dr Daphne Christie
d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

16 June 2004

Dear Ms Mullinger

**The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth**

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne Christie.

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

rec'd 11.1.05
ack "

Larches
Green Road
Shipbourne
Tonbridge
Kent TN11 9PL

Dr Daphne Christie
Senior Research Assistant
The Wellcome Trust Centre for the History of Medicine at UCL
Euston House
24 Eversholt Street
London NW1 2YZ

6 January 05

Dear Dr Christie

**Witness Seminar: Prenatal Corticosteroids for Reducing Morbidity and Mortality**

Thank you for your letter of 7 December 2004. Please find enclosed the signed copyright form, a brief biographical piece, and copies of those pages from the transcript that have minor corrections.

As you may know, Prof Harold Gamsu died on 31 August 2004; I have therefore undertaken to check his short contributions. I know that Prof Gamsu was disappointed that the background to the UK multicentre trial in the prevention of RDS received very little airing. I would therefore like to add a brief footnote, also attached, which might appropriately appear on page 38 (or elsewhere as you see fit).

Prof Gamsu was also disappointed that we did not learn more from Prof Jane Harding of the follow-up data from the original Liggins and Howie study in New Zealand, even though this was promised in the earlier part of the Witness Seminar. Will it be possible to include a brief synopsis of their findings? The idea of undertaking a follow-up of babies born in the UK study was mentioned at the seminar – this is a real possibility because Prof Gamsu was diligent in retaining all the trial record forms (and randomisation codes) long after others' interest in the study had ceased.

Regarding illustrations of early work, it may be possible to provide you with the original protocol and case record forms for the UK multicentre trial, if this is of any interest.

Please let me know if I can make any further contribution to the proceedings.

Yours sincerely

Brenda Mullinger

Brenda Mullinger (Mrs)

Brenda Mullinger BSc d.o.b. 19.6.49

Brenda spent 12 years in international clinical research, based in the UK (Glaxo) and subsequently Canada (Squibb); she co-ordinated the UK RDS trial in the '70s. On her return to the UK, she moved into medical writing and editing, working as an independent for 13 years before joining a healthcare communications agency 5 years ago.

**Footnote: Witness Seminar Prenatal Corticosteroids - page 38.**

The UK multicentre trial was conducted from mid-1975 to February 1978; 251 women were randomised to double-blind treatment with either betamethasone phosphate (4mg every 8h for a maximum of 6 doses) or matching placebo, each given by intramuscular injection. Betamethasone treatment reduced the incidence of RDS relative to placebo – the greatest benefit was seen in those infants born before 34 weeks' gestation. *Br J Obstet Gynaecol 1989;96:401-10*

**Mrs Brenda Mullinger:** At the time of the UK multicentre trial,* I was working for Glaxo and I coordinated the trial in the UK. What I wanted to say relates to what Professor Crowley said about uptake. Although we originally coordinated the study after different clinicians had approached Glaxo, we found that we needed more centres to join the study, and so we did actually try approaching other centres in the UK and looking at the paper because I cannot remember, we got underway in mid-1975, but I was told by Dr Clive Bash, who unfortunately cannot be here, who was the medic at Glaxo, that many of the UK centres who were approached wouldn't join the study because they were already using betamethasone and they felt that it wasn't ethical to have control groups. So that although your uptake maybe was only 10 per cent, certainly the research centres, the sort of centres that might have joined the study, were starting to think about using it by the mid-1970s in the UK.

* Insert footnote (see separate WORD document)

**Avery:** I think we have to think in terms of 1970s versus the 1990s and over 2000, because up until the seventies the control trials were very supportive of efficacy of prenatal glucocorticoids, but that was an era when we didn't have lots of babies under 800 g. Now the story's different. We have babies of 600 g and 700 g and 800 g, who are getting glucococorticoids, and we assumed that they wouldn't have any serious toxicity. But along came Pepra Hoopie from Geneva who worked with us at Harvard and who had developed a great experience with imagining studies of the brains of these babies and there is no

Crowther out of Adelaide for the last seven years. We hope we will finish recruiting this month. It's 980 women, and we have been doing huge detailed studies of the babies in Auckland, Auckland again being the second largest centre recruiting to this trial. But early on in that trial it occurred to us that we still didn't have good data about risks and benefits for that group, the group who don't stand to achieve the greatest benefit for the infant and are potentially at the greatest risk. Once again we thought you know the data isn't out there but I bet it is in the original trial. Once again we were able to go back to the original data, look specifically at that group, write a new metaanalysis which has also been published after many rejections, after a very long time, which showed, in fact, that there may be adverse effects in that group. Therefore people need to randomize them to the new trials. We were in fact trying to help recruitment of the randomized trials. It took so long to publish that, I think it's had very little effect on recruitment to the trial, but the data is nevertheless out there. Yet another outcome that was not relevant at the time. The question has come up subsequently.

**Hey:** Would Glaxo still be able to find the data from the UK trial?

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

*(died: 31.8.04)

unexplained deaths in hypertensive women from Liggins's original report which turned out to spurious.

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

Hanney: We have been looking at the benefits from health research for about ten years now, and this particular stream of work seems to us to have been one of the most interesting, and I have worked on it with Miranda and Martin Buxton and Jonathan Grant, and I apologise for I will check on my notes from time to time, because I am trying to pick up on what various people have said today on what I think is an interesting session. For instance, John, we at least read your work. There is a paper that set out most of the list of the detail in press and is going to be published in *Social Science and Medicine*. So I will just highlight all the key points for now. Apologies, perhaps

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

**Brocklehurst:** I think there is an issue, because I remember the Canadian study got in touch with us about our team's trial, and said how did you get a placebo for your betamethasone, because it's cloudy and we went it's not. Ours is completely clear. That's because you are not using a long-acting betamethasone. You are not giving what was used in the original trial and you never read the original trial. Because the original trial doesn't specify what the betamethasone preparation was and we were using betamethasone which is what was used in this country, and in the UK you can only buy betamethasone which is a solution.

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

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   15 June 2004

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Mrs Brenda Mullinger

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

Mullinger B. (1995) Keeping up with change in clin
*Pharmaceutical Physician* 7(2):24–30 and 7(3): 40–

MULLINGER
edited 1/6/05.

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Mullinger B. (1995) Keeping up with change in clinical research. Parts I and II. *Pharmaceutical Physician* 7(2):24–30 and 7(3): 40–46.

Nuffield

See also page 109.

Please see pages 38-39 and notes on pages 19, 38, 54 and blog notes on 115b

for Prof Gamsu, see 54-56, 63, 84-85, 115
with missing text on page 55

Sorry I can't help you with Prof Gamsu's blog

# PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

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

Edited by L A Reynolds and E M Tansey

11.8.05

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# Prenatal Corticosteroids for Reducing Morbidity and Mortality In Preterm Birth

## Participants

Dr Mary Ellen (Mel) Avery
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)
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, Professor Alison Macfarlane, Dr David Paintin, Professor Maureen Young

## Apologies include:

Professor Sir Robert Boyd, Dr Clive Dash, Professor Geoffrey Chamberlain, Dr Pamela Davies, Professor Sir Liam Donaldson, Professor Peter Dunn, Dr Jonathan Grant, 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, Professor Jim Neilson, Dr Cliff Roberton, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

†Died 31 August 2004

Universite de Paris], the fellow who is still publishing on 'beware, beware,' and I cannot counter that.[53] I'm glad he's looking at it, and I just think we have to be vigilant and [?that?] those of us who spend more time with this have to keep track of the babies.

**Lilford:** Since this is a history meeting, and while you have been talking about the early 1970s, I have been thinking back into the recesses of my own mind. I was a young doctor in Cape Town and news about this crossed the Indian Ocean and people were interested there. As I can recall it, there seemed to be a notion that many babies would, in retrospect, be found not to have needed antenatal steroids because their lungs were very mature. And so the idea that was being put around then was that one should test first to see if the lungs were already mature. And the person who did that testing was me. So if somebody needed early delivery, then I would do an amniocentesis. We had a thing called a bubble test and I would take the fluid off to a side room and I would mix it with alcohol.[54] I would shake it and then there was this chart on the wall where the bubble density could be related to maturity. If there were more than a certain number of bubbles, then we could safely proceed with the delivery the next day. If there weren't, then we gave steroids. We would re-test two days later and if there were now bubbles we knew we could go ahead with delivery. So there must have been another scientific climate running at that time which said that [?we should?] discriminate more before we shove these steroids in. But as far as I know, that line of thought ran into the sands, it didn't progress in any way. I just mention that for your edification.

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[53] [Prof Avery, is this the correct Burri ref? If not could you suggest one?] Corroyer S, Schittny J C, Djonov V, Burri P H, Clement A. (2002) Impairment of rat postnatal lung alveolar development by glucocorticoids: involvement of the p21CIP1 and p27KIP1 cyclin-dependent kinase inhibitors. *Pediatric Research* 51: 169–76. See also Avery M E. (1975) Pharmacological approaches to the acceleration of fetal lung maturation. *British Medical Bulletin* 31: 13–17.

[54] Prof Lilford, could you expand on the bubble test? Our readers would find this technique of interest.

**Mrs Brenda Mullinger**: At the time of the UK multicentre trial, I was working for Glaxo and I coordinated the trial in the UK.[55] What I wanted to say relates to what Professor Crowley said about uptake. Although we originally coordinated the study after different clinicians had approached Glaxo, we found that we needed more centres to join the study, and so we did actually ~~[try]~~ ~~approaching [~~[approach]~~]~~ other centres in the UK. Looking at the paper ~~[now?]~~ we got underway in mid-1975, but I was told by Dr Clive Dash, the medic at Glaxo who unfortunately cannot be here, that many of the UK centres who were approached wouldn't join the study because they were already using betamethasone and they felt that it wasn't ethical to have control groups. So that although your uptake maybe was only 10 per cent, certainly the research centres, the sort of centres that might have joined the study, were starting to think about using it by the mid-1970s in the UK.[56]

I see

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

[56] Dr Clive Dash wrote: 'The UK multicentre study [Gamsu *et al.* (1989)] was designed in 1974, largely stimulated by the publication of Liggins and Howie (1972) and their prior animal studies. The idea for a UK study was an amalgam of interest from some obstetricians and neonatal paediatricians and from within the Medical Department of Glaxo in the UK because of the organizational link with the Antipodes. A taxing question in the design and analysis of the UK study was the imprecision in estimating gestational age at the time of recruitment. Maternal dates and obstetrical palpation were the only antenatal assessments available then – so different from the current techniques! The clinicians documented both estimates for the analysis. These were augmented (or confounded) by neonatal assessment [Farr *et al.* (1966); Dubowitz *et al.* (1970)], which was also recorded. Clinicians' views can change during the planning and conduct of long-term studies (about 4 years to plan and complete recruitment and follow-up for the UK study). All the clinicians involved in the early planning recognized that more clinical work was needed to confirm the results from New Zealand. Everyone involved in the study's planning recognized that it was important to have commitment from an obstetrician and paediatrician at each participating hospital. By the time the study recruitment started (about one year later), some of the clinicians did not wish to recruit patients to the study for various reasons, even after Ethics Committee approval.' E-mail to Dr Daphne Christie, 10 January 2005.

**Avery**: We have to think in terms of the 1970s versus the 1990s and up to 2000, because up until the 1970s the control trials were very supportive of the efficacy of prenatal glucocorticoids, but that was an era when we didn't have lots of babies under 800g. Now the story is different. We have babies weighing 600g, 700g and 800g, who are getting glucococorticoids, and we assumed that they wouldn't have any serious toxicity. But along came Petra Huppi from Geneva, who worked with us at Harvard and had developed a great experience with imaging studies of the brains of these babies. There is no question that there can be white matter problems which she has documented and published.[57] I'm not prepared to take a stand, I'm only saying this is one group where there could be toxicity, and where we really don't know the cost–benefit of accelerating the lung versus some white matter problems in the baby. This is a new frontier, and I just wanted to put this on the table. I don't know any more about it than I have just said.

**Crowley**: Through all the systematic trials we have kept an eye on intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL). There is good evidence that these adverse outcomes are reduced by antenatal steroids across the gestational ages. The use of early postnatal steroids is associated with an increased risk of adverse outcome. Antenatal steroids are protective in terms of neonatal neurology, whether you look at the brain at autopsy or with imaging techniques for PVL. Would you agree with that, Jane?

**Harding**: If I could come back briefly to address Richard Lilford's point and then go back to some of the reasons perhaps why steroids weren't used. I have just dragged out the report of the 70th Ross Conference on Paediatric Research, which was I think about 1979, but I don't have a date on the paper.

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[57] Prof Avery, is the correct Huppi reference?? Murphy B P, Inder T E, Huppi P S, Warfield S, Zientara G P, Kikinis R, Jolesz F A, Volpe J J. (2001) Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. *Pediatrics* **107**: 217–21.

[From the floor: 1976].[58] It was one of the places where Mont Liggins reported the outcomes of the Auckland trial. He also reports the outcomes of ratios in amniotic fluid before and after steroid treatment, and points out that they don't change consistently, so that amniotic testing for fetal lung maturation did not reflect clinical lung maturation. I was reminded of his concluding paragraph, which is why I dragged it out:

> We have not attempted to select patients on the basis of assessment of pulmonary maturation from amniotic fluid analyses. In pregnancies beyond 34 weeks, in which the risk of respiratory distress syndrome (RDS) is low, a strong case can be made for giving glucocorticoids only when the results of amniocentesis indicate pulmonary immaturity. Before 32 weeks the likelihood of RDS is so high, and finding a mature pattern in amniotic fluid is so low that treatment without prior amniocentesis is probably justified.[59]

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

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

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[58] Liggins G C. (1976) Prenatal glucocorticoid treatment: prevention of RDS by maternal betamethasone administration. Moore T D. (ed.) *Lung Maturation and the Prevention of Hyaline Membrane Disease.* Report of the 70th Ross Conference on Pediatric Research. Columbus, OH: Ross Laboratories, 97–103. [highlighted title differs from Ross Howie's list]

[59] Page number of quote??

trial completed and published more than five years ago, that they can still find the original raw paperwork? One of the most amazing things that I found in reading around before today's meeting, was to come across this paper by a Jane Harding in the *American Journal of Obstetrics and Gynecology* on just this subject, published in 2001, and this is control trial data, and it has sat there all that time.[82]

Harding: Yes. I think there are a number of messages. One is the data was still there and still in a form that we could use, which I think is very impressive. The second is that new questions have come up that the trials weren't necessarily designed to answer at the time, but it's terribly important that the data is still there.[83] Thirdly, someone might like to comment on the length of time it took us to get that paper published. The study was done in 1996–97, we wrote it up in 1998, it was rejected by two journals, submitted to the *American Journal of Obstetrics and Gynecology* in 1999, and it was eventually published in 2001. I do think the people who publish have something to contribute to this very prolonged process.

If I could just go onto the other issue that was raised, what about the women who get steroids and don't deliver? We have been concerned about this with respect to the repeat steroid issue. There has been a multi-centre randomized trial being run by Caroline Crowther out of Adelaide for the last seven years.[84] We hope to finish recruiting this month. It includes 980 women, and we have been doing huge detailed studies of the babies in Auckland, the second largest centre recruiting to this trial. It occurred to us early on in that trial that we still

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[82] Harding *et al.* (2001).

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

[84] See also Crowther C A, Harding J. (2003) Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester: John Wiley & Sons, Ltd.

didn't have good data about risks and benefits for that group [?:which??], the group who don't stand to achieve the greatest benefit for the infant and are potentially at the greatest risk. Once again we thought the data wasn't out there but I bet it was in the original trial. Once again we were able to go back to the original data, look specifically at that group, write a new meta-analysis which has also been published after many rejections, after a very long time, which showed, in fact, that there may be adverse effects in that group.[85] Therefore people need to randomize them to the new trials. We were in fact trying to help recruitment of the randomized trials. It took so long to publish that. I think it's had very little effect on recruitment to the trial, but the data are nevertheless there. Yet another outcome that was not relevant at the time, the question has come up subsequently.

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

**Professor Harold Gamsu**: Oh yes, I have all the data in my office.[86] It's still there, all the data sheets, because I was hoping to do a long-term follow up on

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[85] McLaughlin *et al.* (2003).

[86] Gamsu *et al.* (1989). See? Protocol and case record, in Figure ??? Dr Clive Dash wrote: 'The retention of clinical trial data in the 1970s–80s was poor. This has changed in recent years. When Harold Gamsu persuaded us to do a detailed analysis of the UK study, the computer software had changed and so had most personnel acquainted with the prior system. Luckily, Alex Paton at Glaxo was able to interrogate the database and through her efforts we were able to meet Harold's expectations and answer his critical questions. Also, Harold volunteered to keep safe the original case record forms and other study documentation when Brenda Mullinger and I left Glaxo to pursue other career opportunities. I believe Harold always hoped to trace the babies in adult life to address the question of the long-term safety. It is due to his diligence and enthusiasm that he persuaded us (again, pleasantly) in 2001 to begin the process towards a 30+ years follow-up. His untimely death occurred in August 2004, soon after this Witness Meeting. We hope to continue this project with the support of NPEU in Oxford provided external support can be mobilized and plan to dedicate any outcomes to his memory.' E-mail to Dr Daphne Christie, 10 January 2005.

Add footnote from page 19

this because I know a little bit about the history[28] of the National Women's Hospital in Auckland and it doesn't have a very good history itself in terms of ethics of trials. So I just wondered what the original protocol for this trial said about seeking consent and giving information to the parents of these babies.

**Harding:** I have to tell you I have never seen a detailed trial protocol. I have seen the paper that went to the senior medical staff committee and it does say that women would be asked to consent to randomization. It would have been verbal consent.[29] And like you and a number of other people, I wondered how real and how effective that process was at the time. We will talk further later I am sure, but we have just completed the 30-year follow up of these babies, and one of the things that we had some concerns about is about how people would react to being approached 30 years later about a trial where we weren't sure how informed the consent was.[30] We have been overwhelmingly impressed with how positive people were about the trial. In the end we traced 72 per cent of the original participants and a number of the children, now 30-year-olds, who obviously did not know they were part of this trial, and who went back to

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[28] Prof Oakley, could you elaborate further about this? It would make a good footnote.

[29] See Appendix xxx, page xx.

[30] Dalziel S R, Walker N K, Parag V, Mantell C, Rea H H, Rodgers A, Harding J E. (2005) Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomized controlled trial. *Lancet* 365: 1856–62. Niven G R, Harding J E. (1995) Another outcome of neonatal intensive care: first year mortality and hospital morbidity. *Journal of Paediatrics and Child Health* 31: 137–42. Harding J E, Howie R N. (1987) First year mortality and hospital morbidity after newborn intensive care. *New Zealand Medical Journal* 100: 548–52.

Mrs Brenda Mullinger, who had worked with Prof Gamsu, wrote: 'Prof Gamsu was ~~also~~ disappointed that we did not learn more from Prof Jane Harding of the follow-up data from the original Liggins and Howie in New Zealand, ~~even though this was~~ promised in ~~the earlier~~ part of the Witness Seminar. ~~Will it be possible to include a brief synopsis of their findings?~~ The idea of undertaking a follow-up of babies born in the UK study was mentioned at the seminar – this is a real possibility because Prof Gamsu was diligent in retaining all the trail record forms (and randomization codes) long after others' interest in the study had ceased.' Letter to Dr Daphne Christie, 6 January 2005.

their mothers and sometimes we traced the mothers rather than the children. There were a few women who did not recall being part of the trial. I think that's not surprising given the circumstances. Remember that the tocolytic used during the first three years of the trial was ethanol. IV ethanol was the tocolytic used until about 1971.[31] However, the vast majority of women did recall that they were in the trial and recalled it very positively. A number of the subjects, the offspring, the children – now adults, I don't know how to call them because of that difficulty – came along because they said their mothers told them they had to come. Their mothers were so grateful that they had been part of the trial, that their preterm baby had survived as a result of this trial, as they perceived it, and were very positive about it. That's a slightly long answer to your question. I think consent really did happen, it was verbal consent, and the reaction of the majority of people involved was very positive 30 years later.

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

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

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[31] Dr Clive Dash wrote: 'The UK study was being planned at the time of the move from ethanol as a tocolytic to various newly introduced β-agonists. We decided to use salbutamol, if a tocolytic was clinically necessary, so as to standardize one of the management modalities – and also because salbutamol had been developed by Glaxo.' E-mail to Dr Daphne Christie, 10 January 2005.

the adults, and in fact things haven't turned out that way, but that's still available for people to do if they would like to.

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

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

**Hey**: So are everybody's, but if people have kept their data, there are more that can be analysed that has not yet been done. Could anybody find the NIH data? Would the NIH people share their data?

**Avery**: I have no idea.

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

**Brocklehurst**: I cannot tell you very much more, because I heard it presented in Glasgow about six weeks ago, but I have seen nothing in the press yet.[87] My recollection is that it was in animals, but we'll be able to explore this further

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[87] Professor John Newnham from the King Edward Memorial Hospital, University of Western Australia, Perth, Australia, delivered the Society Lecture, 'Antenatal Steroids and Outcome', at the British Maternal and Fetal Medicine Society's Ninth Annual Conference, 1–2 April 2004, held at the Scottish Exhibition and Conference Centre (SECC), Glasgow. He presented results from human and animal studies where infants had been exposed to steroids before birth. See the full report by Dr Margaret M Ramsay, Honorary Secretary, BMFMS at www.bmfms.org.uk/presssummaryofglagow04.doc (visited 18 July 2005).

when the study is published.[88] Having tried to do one of the large trials of multiple courses of steroids, I think one of the issues with clinicians about the use of multiple courses of steroids is that their threshold for starting antenatal steroids is lower, because if they are wrong, and the woman doesn't deliver soon, they have felt that they can always give a second course. If people are restricted to giving a single course of steroids they may delay starting until there is stronger evidence, if you like, of impending preterm birth. So the groups of women selected into these trials is likely to be quite different from the multiple steroids group and that will make the interpretation of the results interesting.

**Lilford:** I recently had a debate with my 14-year-old daughter Philippa about whether history is just an interesting thing to read, or whether it helps us to design our own futures. Listening to Jane speak makes me think that there really are occasions when history has a lesson for the future. Hearing you speak about finding these records has been very interesting, but I suspect that many people in this room were amazed that you really could find those source materials after 30 years, that you could find the trial documents and so on. When Harold Gamsu moves the documents from his office, goodness knows where they might go. So the lesson that we might want to learn from this is the importance of some sort of systematic paid for-archive for trial information and I don't know if you might want to comment. I know that the Economic and Social Research Council (ESRC) archive their most precious data and build the cost of so doing into the grant.[89] The more I hear the more I think this might be something we ought to try to take forward as a matter of some urgency.

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[88] The lecture will be published in 2006 as: Newnham J P. (in press) The steroid story: iconic advance or ticking bomb? *Yearbook of Obstetrics and Gynaecology*, vol. 12. London: The College.

[89] The Economic and Social Data Service (ESDS) Qualidata is a specialist service of the ESDS led by the UK Data Archive (UKDA) at the University of Essex. The service provides access and support for a range of social science qualitative datasets. Established in 1967 the UKDA holds the largest collection of digital data in the social sciences and humanities in the UK, funded by the ESRC,

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

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

**Mugford**: We can say that over the last 20 years the resources devoted to neonatal intensive care, you had a different seminar on this subject[96] – I haven't looked at the living witness results on [??transcript of??] that seminar – but [?what has expanded?]having incredibly expanded and there are very many more nurses, doctors, ventilators and techniques for the care of preterm babies than there were 20 years ago.[97]

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

**Chalmers**: It's good that Patricia Crowley has already described some of the history. Given that I am going to be talking about the Cochrane logo, I might as well start with Archie Cochrane, whose famous book – *Effectiveness and Efficiency: Random reflections on health services* – was published in 1972.[98] I read

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[96] See the Witness Seminar, 'Origins of Neonatal Intensive Care in the UK', Christie and Tansey (eds) (2001), also freely available online at www.ucl.ac.uk/histmed following the link to Publications.

[97] Macfarlane A, Johnson A, Mugford M. (1999) Epidemiology, in Roberton N R C, Rennies J. (eds) *Text book of Neonatology*, 3rd edn. Edinburgh: Churchill Livingstone, 3–33.

[98] Cochrane (1972).

it in 1973 and it changed my life![99] In spite of the fact that I had been 'licensed to kill' six years earlier after studying at the Middlesex Hospital Medical School, London, to qualify as a doctor, I had not previously been aware of the term 'randomized controlled trial (RCT)'. Cochrane showed me how I might adjudicate among incompatible clinical opinions about treatments, a common situation faced by me and other junior doctors, and it was after reading Cochrane's book that I started to collect reports of RCTs. A librarian in Cardiff, Steve Pritchard, designed a Medline search to identify these studies for me, and I started noting those in my special area of interest (perinatal care) during my reading of journals and books.

In 1976, because it was clear that this was an insufficiently systematic method of finding reports of RCTs, I outlined a plan for using a more systematic approach both for finding published reports, and for identifying unpublished studies (because biased under-reporting of RCTs means that unpublished studies tend to have less dramatic results than those that get into print). This plan, which was set out in a letter to Martin Richards, a psychologist in Cambridge, also stated an intention to use statistical synthesis of the results of similar by separate studies (meta-analysis) to reduce Type 2 errors (false negatives) in estimating treatment effects. My letter to Martin Richards happened to be sent to him during the same year as the term 'meta-analysis' was introduced by the American social scientist Gene Glass.[100]

The first opportunity that I took to do a systematic review using meta-analysis related to different ways of monitoring babies during labour.[101] Electronic fetal heart rate monitoring had been introduced in obstetrics not long previously, sometimes accompanied by fetal scalp blood sampling to assess fetal acid-base status, particularly if the heart rate trace had raised concerns. It was being suggested by some people that these more intensive methods of intrapartum

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[99] Chalmers (1999).

[100] Glass (1976).

[101] Chalmers (1979).

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

May I just mention the main conclusions from this particular piece of work? Don't expect this sort of study to get it into the *British Medical Journal*. It won't be accepted. Secondly, advocates are really important when it comes to getting guidelines adopted and I think opinion leaders are really important within institutions, but the important thing is that the guidelines have got to be written in such a way to be usable, understandable and accessible to those who are going to implement them. That means clear inclusion and exclusion criteria. Another important agent for change are the users, and if you have women asking these sorts of questions, after a while people do get a bit embarrassed coming up with the same answers that clearly won't be supported by evidence or by colleagues. I would like to see women users being far more involved in ways in which we can encourage the implementation of best practice. I am not surprised that there was no sign of managers actually implementing any change in Richard's study. It's a scary business. There was blood all over the carpet when we were dealing with the ECV meetings, and it required somebody – like the users who were tough, or somebody like me who's a public health specialist and who has been a GP and is not afraid of consultants – to hold the line if necessary. Managers cannot do that, and I don't think we should expect them to. I think it's exceedingly difficult. The

most important barrier, the most important influence to achieve change, is the personal experience of the person making the clinical decision. When new interventions are being rolled out we must encourage people to be at the centre of it, so they get feedback of the positive results. Then it is much easier to get change implemented.

**Hey**: That rings true for a lot of us, I think. You went over time, but I think you said something very important. We are beginning to get very tight for time and so I am going to ask Stephen Hanney to speak next. But Harold [Gamsu], while you were out of the room we did hear that quite a lot of units said that they couldn't join your trial, because they were already using it so widely and that occurred at the time when in actual fact we know that less than 6 per cent were really using steroids nationally 1. Did being involved in the trials themselves influence the centres? Did the centres that had been involved in the research take up the outcome of that research more than those who only read about it?

**Gamsu**: I don't know the answer to that I am afraid. We didn't follow that point up, but as far as I know Brenda Mullinger might know something about it. All I can say is that there were local reasons that indicated against the use of steroids. There was quite a lot of gossip about this and we have heard some examples of this today. The risk of infection especially in ruptured membranes, and the unexplained deaths in hypertensive women from Liggins's original report which turned out to be spurious.

The other thing that I found was influencing obstetricians was the increased risk of pulmonary oedema which people widely accepted as a complication of steroid therapy. In fact it was a complication of tocolytic agents that were used, especially when those agents were given in large volumes of fluid. As far as I know, steroids given alone ~~were not tocolytic agents and~~ did not result in pulmonary oedema. So I think we had quite a lot of persuading to do even in

those places that accepted that they would be in the trial. I know that Brenda Mullinger and Clive Dash from Glaxo had a lot of difficulty keeping the momentum up, trying to recruit women, ~~even though ..... [?] were reaching the volunteers.~~ As you possibly remember from the paper, 60 per cent of the cases came from patients who were recruited from three hospitals, the rest of ~~them~~ just put it away.

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

For instance, John [Hayward], we at least read your work. There is a paper that sets out most of this in detail in press and will be published in *Social Science and Medicine*.[147] I will just highlight all the key points for now. Perhaps it's just worth spending a minute, going over our payback framework so you can see how we tried to drop this stream of work into a frame [?model?] that we had already developed. Apologies to those who have already heard this many times before. Basically, there are two aspects to our payback framework: a multidimensional categorization of benefits, and a model to examine how they arrive. The categories which we suggest are five: knowledge production; the targeting of future research and building research capacity; better informing policies, with the term policies being widely interpreted; health gain and benefits to the health sector; and the broad economic benefits. There's a series of stages in the model in which we think these various benefits can be identified. A key feature of our model is to attempt to identify actual levels of uptake so that we can then say what the benefit has been, and this, of course, links with previous discussions.

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[147] Hanney *et al.* (2005).

There's always a problem when doing this type of analysis as to where you start. Various initial presentations today showed clearly that research builds on previous research etc., and so whenever one makes [?chooses?] a start[ing] point, it is always artificial. On the other hand I do think the nature of the discussions [?today?], and what Mary Ellen says, does provide [?has provided?] a realistic basis for saying we will start by looking at the work of Liggins and Howie. In terms of knowledge production clearly the 1969 paper from Liggins, [and] the 1972 paper from Liggins and Howie, were very important.[148] There are lots of weaknesses in citation analysis, but it does indicate whether people have taken notice, and these are two very highly cited papers, especially the 1972 paper which has been cited over 1200 times.[149]

There has been some bibliometric analysis in this field undertaken by the Policy Unit here at the Wellcome Trust.[150] Various generations of papers were traced backwards and showed again that this was the most important work in this field in several generations. Clearly knowledge production [is] very high. In terms of affecting future research, again citations indicate that it has influenced much subsequent work. It's also interesting that many of the other pieces of work, trials etc., actually start with a reference to the work of Liggins and Howie, which again I think emphasizes their importance for further work. And it's also been mentioned that Ross Howie felt that further trials should be undertaken rather than necessarily saying that people should act on the findings. Nevertheless, there was quite an uptake in some places, on the basis of this very important trial and the ensuing publications from it. In the UK the

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[148] Liggins (1969); Liggins and Howie (1972).

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

[150] Grant *et al.* (2003).

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✓ 27/9/05

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Replace with Mullinger 1995

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### Sir Iain Chalmers

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

### Professor Archie Cochrane

CBE MBE FRCP FFCM (1909–88), medical scientist and epidemiologist, whose first clinical trial was conducted as a prisoner of war in Salonika. Following the war he was appointed to the Medical Research Council's Pneumoconiosis Research Unit in 1948. In 1960 he was appointed David Davies Professor of Tuberculosis and Diseases of the Chest at the Welsh National School of Medicine, Cardiff, becoming Director of the Epidemiology Research Unit there in 1961 until his retirement in 1974. His papers are available for study at the Cochrane Archive, Llandough Hospital, Penarth, Cardiff. See Cochrane (1976); Cochrane [ALC] (1988). See also Ness *et al.* (2002).

### Dr Patricia Crowley

FRCOG FRCPI (b 1951) has been a consultant Obstetrician Gynaecologist at the Coombe Women's Hospital, Dublin, and Senior Lecturer at the Department of Obstetrics and Gynaecology, Trinity College Dublin since 19xx.

### Dr Clive Dash

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

### Professor Geoffrey Dawes

CBE FRCOG FRCP HonFACOG FRS (1918–96), qualified at Oxford in 1943, spent a year? at Harvard in 1946. He was Director of the Nuffield Institute for Medical Research, Oxford, from 1948 to 1985., as well as a Governor of Repton, 1959–88, and Vice President of the Royal Society, 1976–77. See Liggins G (1998). Geoffrey Sharman Dawes, *Biographical Memoirs of Fellows of the Royal Society* **44**: 110–25.

### Professor John Gabbay

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

he was former director. His recent research has focused on the implementation of evidence in clinical practice.

### Professor Harold Gamsu

FRCP FRCPCH (1931–2004) graduated in Johannesburg in 1954. His training in paediatrics commenced there, and continued at the University of Sheffield and xx in Cleveland, Ohio. He was appointed as Wates Fellow at King's College Hospital, London, in 1965, then Senior Lecturer, Reader in Paediatrics and Director of the Neonatal Unit, 1979, and in 1994 Professor of Neonatology until his retirement in xxxx, later Emeritus. He established the London Perinatal Group in the 1970s, later known as the Thames Regional Perinatal Group.

### Dr Dino Giussani

PhD (b. 1967) received his PhD in Fetal Medicine at UCL and has conducted post-doctoral work at the University of Chile and Cornell University. He was appointed university lecturer at the University of Cambridge in 1993; has been Fellow of the Lister Institute for Preventive Medicine there, since 2001 and a Reader in Developmental Cardiovascular Physiology and Medicine since 200x, and Director for Studies in Pre-clinical Medicine at Gonville and Caius College, Cambridge, since 200x.

### Mrs Gill Gyte

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

### Dr Stephen Hanney

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

### Professor Jane Harding

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

### Dr John Hayward

FFPH(b. 1946) was in general practice for 16 years before re-training in public health. From 1994/6 he led the Effective Care Project in maternity services for the Camden and Islington Health Authority.

Mrs Brenda Mullinger

✓ 29/9/05.

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

He was Director of Public Health in Newham, London, from 2002 until 200x. See Hayward (2001).

### Dr Edmund Hey

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

### Professor Ross Howie

### Mr Ian Jones

(b. 1945) has been Publisher at the Wellcome Trust since 19xx.

### Dr William ('Bill') Henry Kitchen

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

### Professor Sir William Liley

KCMG FRS(NZ) (1929–83) was trained at Otago University, New Zealand, did research under Professor John Eccles on neuromuscular transmission, switching to obstetrics at the Women's National Hospital, Auckland, from 1959 as a New Zealand Medical Research Council Senior Research Fellow, then at the Auckland University Medical School as Research Professor in Perinatal Physiology from 1969 until his sudden[?premature?unfortunate?] death in 1983. His diagnostic procedure for rhesus haemolytic disease of the newborn was perfected so that he could predict which could remain in the uterus and which could not; led the team that performed the first successful intrauterine transfusion, and believed in the rights of the unborn child. See Hawgood (2005).

### Professor Sir Graham (Mont) Liggins

FRCOG FRCS (Edin) PhD (b. 19xx) graduated in medicine at University of Otago in 1949. He was appointed to a personal chair at the Postgraduate School of Obstetrics and Gynaecology,

University of Auckland, in 19xx, specializing in Endocrinology and Fetal Physiology. His most important discovery was that the time of birth was controlled by the fetus, not the mother.

### Professor Richard Lilford

Phd FRCOG FRCP FFPH (b. 1950) was Consultant Obstetrician and Gynaecologist to Queen Charlotte's Hospital, London, before moving to the University of Leeds in 19xx as Professor of Obstetrics and Gynaecology and Chairman of the Epidemiology Research Institute (??–1995). He has been Professor of Clinical Epidemiology and Head of the Division of Primary Care, Occupational Health and Public Health in the Medical School of the University of Birmingham since 1995. He is also the Director of the Patient Safety Research Programme for the Department of Health in England and is Director of Research Methods Programme, [???NHS Executive, West Midlands, since 1995???].

### Professor Miranda Mugford

[Hons?] (b. 19xx), an economist and health services researcher, joined the National Perinatal Epidemiology Unit at the University of Oxford in 19xx. She has been Professor of Health Economics in the School of Medicine and Health Policy and Practice at the University of East Anglia (UEA), since 19xx and Chair of convenors of the Campbell and Cochrane Collaboration Economics Methods Group. Her special interest lies in methods used in economic evaluations, especially how methods for systematic review of literature can be incorporated into economic evaluation techniques. See Macfarlane and Mugford (1984).

### Mrs Brenda Mullinger

See attached

BSc (b. 1949), an xxx, joined international clinical research, based in the UK (Glaxo from 19xx to 19xx) and subsequently Canada (Squibb from 19xx to 19xx). She co-ordinated the UK RDS trial in the 1970s [??details??]. On her return to the UK, she moved into medical writing and editing, working as an independent freelance before joining a healthcare communications agency. See, for example, Mullinger (xxxx).

### Professor Colin Normand

FRCP HonFRCPCH (b. 1928) trained in paediatrics at the Hospital for Sick Children, Great Ormond Street, London; Johns Hopkins Hospital, Baltimore; and University College Hospital, London, between 1959 and 1971. He was Professor of Child Health at the University of Southampton from 1971 to 1993 and Dean of Medicine (1990–1993). His many publications in the neonatal field have mainly related to the absorption of lung liquid in the neonatal lung and to the biochemistry of pulmonary surfactant.

### Professor Ann Oakley

PhD (b. 1944) joined the National Perinatal Epidemiology Unit, University of Oxford, as Consultant in 1979, becoming a Wellcome Research Fellow the following year, and was appointed Senior Research Officer in 1983. She moved to the Thomas Coram Research Unit, University of London, in 1985 as


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25 March 2004

Dear Professor Neilson

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

The Wellcome Trust Centre for the History of Medicine at University College London is funded by the Wellcome Trust, which is a registered charity, no. 210183. Histmed logo images courtesy *Wellcome Library*, London.

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

encs.

THE UNIVERSITY
*of* LIVERPOOL

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29 March 2004

Professor James P Neilson thanks Dr Daphne Christie for her kind invitation to the Wellcome Trust's History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth to be held on Tuesday 15 June 2004.

He regrets, however, that owing to a previous business engagement he must decline her kind invitation.

Dr D Christie
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## Wendy Kutner

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 25 May 2004 08:52
**To:** Wendy
**Subject:** FW: Wit Sem 15 June: Smellie & Normand

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 21 May 2004 16:45
To: Daphne
Subject: Wit Sem 15 June: Smellie & Normand

Hi Daphne,
Jean Smellie rang, they (I believe Dr Colin Normand is her husband) are off on hols and won't be back until 3 June. Their telephone is: 01962852550, and Normand would like to attend. She didn't say she wanted a place as well, so perhaps you might ask about that.
Gosh, what a good wife she is.
Hope you had a good weekend, and that both vols are now signed off.
Beset wishes from Lois

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
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(W) spoke to Dr Smellie 7/6/04 – may not be able to attend after all, but will let me know after 8/6/04, before mtg. 9/6/04 no (L)

Professor Ann Oakley
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19th March 2004

Dear Professor Oakley

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004**
**2.00 pm – 6.00 pm**

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is organising a Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1 2BE. Dr Edmund Hey has kindly agreed to chair the meeting and Sir Iain Chalmers is assisting us in the organisation.

Sir Iain Chalmers has recommended that we invite you to this meeting and we would be delighted to have you join us.

These seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history. I enclose a copy of the introduction to the first volume of our published transcripts, which will tell you a little more about these seminars, and a flyer of our recent publications to illustrate the range of topics we cover.

Continued/... Page 2

We are in the process of inviting senior scientists, clinicians, and representatives from relevant organisations to attend the meeting and hope to promote a lively discussion.

We will be providing further details in due course and would particularly appreciate, at this stage, suggestions of possible participants.

I look forward to hearing from you and do hope you will be able to accept this invitation.

Yours sincerely

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

encs.

## Wendy Kutner

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 23 March 2004 09:22
**To:** Wendy
**Subject:** tel message re ann oakley witness seminar 15 June

Note that Professor Oakley is away until mid-April. She will let us know if she is able to attend on her return.
Thanks, Daphne

Dr Daphne Christie
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine at UCL
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London NW1 1AD

Tel 020 7679 8125
Fax 020 7679 8193
Mobile 07810 541812
E-mail d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed

## Wendy Kutner

**From:** Dr Daphne Christie [d.christie@ucl.ac.uk]
**Sent:** 16 April 2004 09:56
**To:** Ann Oakley
**Cc:** Wendy
**Subject:** RE: your letter

Dear Professor Oakley
Definitely - we are pleased that you are able to attend, and will be providing more information shortly before the meeting.
With best wishes
Daphne Christie

-----Original Message-----
From: Ann Oakley [mailto:A.Oakley@ioe.ac.uk]
Sent: 14 April 2004 16:26
To: d.christie
Subject: your letter

Dear Dr Christie
Thank you for your letter about the 15 June witness seminar. I am flattered to have been asked, and am not entirely sure why (though I was working at the NPEU at the time). If you're convinced I'm an appropriate person, I'd be very pleased to come.
Ann Oakley

Professor Ann Oakley
Director
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# The Wellcome Trust Centre for the History of Medicine at University College London

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26 April 2004

Dear Professor Oakley

**The Wellcome Trust's History of Twentieth Century Medicine Group**
**Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
**Tuesday 15th June 2004, 2pm–6pm**

We are delighted that you are able to attend the above meeting and are happy to tell you that plans are proceeding well. A copy of our publicity material is enclosed and I will be sending you a draft programme in due course. A full attendance list will be available at the meeting.

We will be asking some participants to "start the ball rolling" by saying a few words on specific subjects, as we like to prime a few people to lead off the discussions, although there will be ample opportunity to contribute throughout the meeting. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, you would like any material to be available to the audience, we could photocopy a diagram or article for you, and leave a copy on every chair.

Please do not hesitate to contact either myself or Mrs Wendy Kutner 020 7679 8106 if you have any queries prior to the meeting.

We very much look forward to seeing you at the meeting.

Yours sincerely

pp **Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**

enc.

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16 June 2004

Dear Professor Oakley

**The Wellcome Trust History of Twentieth Century Medicine Group Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with pretern birth**

May I say on behalf of The History of Twentieth Century Medicine Group and the co-organiser, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers.

As mentioned in previous correspondence and at the meeting, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send you in about six months time for your comments. Ultimately we intend to publish an edited version of the proceedings, and you will be sent a copyright assignment form and final proof before publication.

Yours sincerely

Daphne Christie

**Dr Daphne Christie**
**Senior Research Assistant to Dr Tilli Tansey**


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ack

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Please find attached
1/ amendments to report
2/ copyright form
3/ biographical note

*with compliments* Ann O.

Social Science Research Unit
*Director of Unit* Professor Ann Oakley

indeed before surviving, and the anxiety that goes with that, those things haven't been made explicit and I suspect that if, we had hoped that there would be a woman here who had received corticosteroids, now I don't know what her history was at all, but I was certainly quite impressed by Barbara Stocking, who is now chief executive of OXFAM, saying that in her first pregnancy she delivered prematurely and her son went through a really rough time, she read Patricia's systematic review and in her second pregnancy she insisted that she should have steroids if she went into preterm labour again. She became a big advocate, and I have come across more than one mother, maybe Gill Gyte can enlighten us here, they have lobbied to have this, because they as parents actually think this is important, obviously because they are worried about their children, but so that they can perhaps have less to worry about themselves.

Gyte: I don't have any personal experience of antenatal classes, but I do not NTT does lobby very much to implement evidence, generally in terms to implement evidence-based care.

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

projects that I worked on in 1974 involved an observational study of an antenatal clinic at a hospital in London which has of course got to be nameless, and I hung around this clinic for about a year observing what the doctors were doing, ~~and~~ I was absolutely astonished. In my second week, ~~I think~~ there was a changeover ~~the most~~ in junior doctors, and two of them came to me and they asked me what consultant X would recommend in a particular case, because they didn't know what they were supposed to be doing because they hadn't met their consultant yet. I didn't realize that the eight different consultants who ran this clinic all had different policies. ~~I mean what~~ I was ~~doing was~~ learning what those policies were, ~~but~~ and then I was passing on this information to the junior members of their team, so that they could also practice non-evidence-based medicine. That was a long time ago, but I think it is still the case that many people believe that doctors and other experts know what they are doing. So another issue in all of this is about the ~~epidemiological~~ epistemological shift in ~~people in general in~~ society understanding that experts (including those in other fields, and I spend a lot of my time at the moment with professors of education who don't believe in systematic reviews of the evidence. ~~But it~~ This is about the role of the expert, and the relationship between research, evidence and ~~the evidence and form of~~ policy across a whole lot of different sectors.

They don't engage in evidence-based practice

**Crowley:** In 1985 as an obstetric senior registrar, I inherited a woman who was having an anti..... haemorrhage at 37 weeks as we thought, and we thought she was 37 weeks because the registrar who did her first antenatal visit had made a mistake about her dates. She was in fact 33 weeks and I delivered the baby in consultation with the

## Biographical note

Ann Oakley is Professor of Sociology and Social Policy and Director of the Social Science Research Unit at the University of London Institute of Education. She has been involved in health services research for many years, and has a particular interest in the evaluation of social interventions, methodology, and the experiences of health service users.

**Date of birth** 17 January 1944
**Major appointments**

| | |
|---|---|
| 1974-1979 | Research Officer, Department of Sociology, Bedford College, University of London. |
| 1979-1980 | Consultant to the National Perinatal Epidemiology Unit, University of Oxford. |
| 1980-1983 | Wellcome Research Fellow, National Perinatal Epidemiology Unit, University of Oxford. |
| 1983-1984 | Senior Research Officer, National Perinatal Epidemiology Unit, University of Oxford. |
| 1985-1990 | Deputy Director, Thomas Coram Research Unit, University of London Institute of Education. |
| 1990- | Director, Social Science Research Unit, University of London Institute of Education. |
| 1991- | Professor of Sociology and Social Policy, University of London. |
| 1996- | Honorary Professor in Social Sciences, Division of Public Health Medicine, Institute of Child Health, University College, London. |
| 2001- | Honorary Fellow, Somerville College, University of Oxford. |

THE WELLCOME TRUST

WITNESS SEMINARS

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**********

1. NAME Professor Ann Oakley

2. ADDRESS
   Director, Social Science Research Unit,
   Institute of Education
   University of London
   20 Bedford Way
   London WC1H 0AL

3. WITNESS SEMINAR: Prenatal Corticosteroids for Reducing Morbidity and Mortality
   15 June 2004

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Signed A Oakley Date 10/01/05

OAKLEY

## Lois Reynolds

**From:** Ann Oakley [A.Oakley@ioe.ac.uk]
**Sent:** 22 August 2005 15:34
**To:** l.reynolds@ucl.ac.uk
**Subject:** wellcome trust report

wtrepbit.doc

Dear Lois Reynolds
thanks for the proof copy of this report. The bits about me are fine. You suggested an additional note for pp 18-19: I attach some text you could use. Please let me know if you need anything else.
Ann Oakley

OAKLEY

edited 21/6/05.

From the late 1960s for some 20 years staff at the National Women's Hospital carried out an uncontrolled experiment examining the natural history of untreated cervical cancer. Some women with abnormal smears were left untreated, and outcomes in this group were compared with those in treated women. Smears were also taken from newborn babies. The experiment lacked a scientific research design since there was no proper control group, and there was no provision for informed consent. The scandal of the experiment was exposed by two journalists (Coney 1988) and there was a public inquiry (Cartwright Report 1988).

Coney S (1988) *The Unfortunate Experiment*. Auckland: Penguin Books

Cartwright Report (1988) *The Report of the Committee of Inquiry into Allegations Concerning the Treatment of Cervical Cancer at National Women's Hospital and Into other Related Matters*. Auckland: Government Printing Office.

Dedicated to Health Professionals in New Zealand

THE NEW ZEALAND MEDICAL JOURNAL

NZ & Overseas Vacancies

Journal of the New Zealand Medical Association, 24-September-2004, Vol 117 No 1202

# Looking back at the 1987 Cervical Cancer Inquiry

The Auckland Women's Health Council (AWHC) would like to respond to the article by Barbara Heslop entitled *'All about research'—looking back at the 1987 Cervical Cancer Inquiry*, which appeared in the NZMJ on 6 August 2004 (http://www.nzma.org.nz/journal/117-1199/1000/).

The article is of considerable concern to AWHC members as it represents a misguided attempt to rewrite history and casts doubt on a significant event in the history of the medical profession and the development of patient rights. The AWHC has among its members women who sat through the whole Inquiry into the Treatment of Cervical Cancer at National Women's Hospital as well as others who gave evidence or attended some of the sessions. The AWHC was formed at the beginning of 1988 and has always had a special interest in the issues that arose during what has become known as the Cartwright Inquiry.

Over the past 16 years, the Council has been actively involved in the implementation of the recommendations contained in the Report of the Cervical Cancer Inquiry including actively supporting the establishment and ongoing development of the National Cervical Screening Programme, the establishment of the office of the Health and Disability Commissioner, the development of the Code of Rights, and the nationwide patient advocacy system.

It is simply not possible to respond in the form of a letter to the editor to the number of unsubstantiated claims in Barbara Heslop's article. Most of the claims made in the article are in fact refuted in both the Cartwright Report and Sandra Coney's book, *The Unfortunate Experiment*. The AWHC would also draw attention to the fact that the 5000 pages of evidence contained in the transcripts of the Inquiry are also publicly available and prove that the issues Ms Heslop raised were all thoroughly canvassed during the Inquiry.

For example, it was irrefutably demonstrated at the Inquiry that there were medical researchers both here in New Zealand and throughout the world who not only knew about "the unfortunate experiment" that was underway at National Women's Hospital but that during the 1960s and 1970s some of them actually visited the hospital and met with Herbert Green. Many in the medical research community were horrified by their observations during their visits, and word of what was going on spread far and wide among the research community. People like Ralph Richart openly challenged Green at international symposia.

It simply isn't true that Professor Green worked in isolation. The evidence presented during the Inquiry revealed that he was in fact supported in his views by other senior doctors at the hospital—Bonham, Jamieson, and Liggins.

The AWHC would also point out that Bill McIndoe and Jock McLean were not as ignorant as Ms Heslop attempts to make them. It was demonstrated very clearly at the Inquiry that, contrary to Ms Heslop's assertion that neither man "had given much serious thought to scientific hypotheses," both knew exactly what they were doing and had spent decades fighting Green and attempting to protect women whom they knew to be in serious danger of developing cervical cancer because they were not being treated. The families of these two men believe that the stress they were under contributed to their early deaths. This is why a decade ago the Auckland Women's Health Council and Women's Health Action held a special ceremony

during which a pohutukawa tree was planted and a plaque referring to their work placed at the foot of the tree. So their efforts would not be forgotten—or misinterpreted and maligned by those who come after.

We must not forget that over 30 women died as a result of being part of "the unfortunate experiment at National Women's Hospital" and their untimely deaths were entirely avoidable. The 1960s and 1970s were not the Middle Ages of medical research that Ms Heslop's article would make them out to be. There was in fact an international framework arising from the Nazi experiments during World War 2 that set a clear standard for ethics of research that 50 years later meets the test of today.

Lynda Williams
Director
Auckland Women's Health Council

## Response

I fail to see why I was "misguided" in recording my perception of medical research over the half century during which I was involved with it. Nor do I delude myself that I, or anybody else, can "re-write history". Because I am not quite sure what it means, I make no comment on the assertion that I "cast doubt on a significant event...". I should perhaps point out that medical scientists, among whom I number myself, are apt to see life as long on doubts and short on certainties.

It is also difficult to comment on the "number of unsubstantiated claims" that I am said to have made, since the single example cited by Ms Williams was not a claim that I had made. I certainly did not maintain that doctors and researchers in NZ during the 1960s and 70s did not know that Herb Green held unorthodox views about cervical pathology. I was well aware of it, as were many of my colleagues. What many of the NWH staff lacked was the scientific "know how" that might have prompted them, when presented with a hypothesis, to ask "Is this hypothesis testable? What sort of evidence will it take to falsify it? Will the evidence be easy to get? How long will it take? Is this the best way of getting the evidence? Are there other ways in which the hypothesis could be falsified? How feasible are they?" and so on. Those with service commitments—clinical or laboratory—usually have neither the time nor the need to ponder on the best ways of dealing with research problems.

There is nothing wrong with holding unorthodox scientific views as long as one can justify them. Much productive research, after all, involves disagreeing with somebody or something. This is the way the scientific world operates—disagreement and questioning are its lifeblood. Trouble arises not because of differences of opinion per se, but when the accuracy of the data on which the opinions are based becomes suspect. There is little doubt that the NWH hierarchy took far too long to take a hard look at the quality of Herb Green's data. Nevertheless the main point of my article, which I reiterate, is that had the scientific "know how" of the main protagonists been more sophisticated than it was, Green's hypothesis could have been disproved (falsified) in a few months, if not by Green himself, then by McLean. I don't for a moment doubt that McIndoe and McLean knew exactly what they were doing (most of us do). It is unfortunate that they (and especially pathologist McLean) missed seeing that they were almost certainly sitting on archival hospital material that would have allowed them not only to disprove Green's hypothesis quite quickly, but also to publish the relevant findings without reference to Green. My tentative answer to the question "Why didn't they do it?" (because they were not researchers and it did not occur to them) is rather more charitable than Ms Williams' assessment (that they did indeed know, but chose to take a longer and incomparably more stressful route to their destination).

Pointing this out does not entail "misinterpreting or maligning" anybody living or dead, nor does it detract from the significance of what they eventually did. It is no more derogatory than commenting that my parents' generation could have communicated more effectively had they been familiar with today's information technology, or that I could have approached yesterday's immunogenetic problems more effectively had I used today's molecular biological techniques. It merely serves as a reminder that yesterday's research is apt to have obvious shortcomings

when viewed from the vantage point of today's knowledge.

Being challenged by the leaders in the field on one's home ground or at conferences does not necessarily mean that one's opinions are wrong, a point well illustrated by Bryan Sykes in *The Seven Daughters of Eve* (Corgi Books 2001, pp 190–193). What it does mean is that one's evidence had better be pretty good, and freely available to anybody who wants to scrutinise it minutely. Those who present material at international conferences—from plenary sessions to posters—expect to be challenged. For heaven's sake, why would anybody go to a conference if this were not going to happen?

Finally, the assertion "The 1960s and 1970s were not the Middle Ages of medical research that Ms Heslop's article would make them out to be". Actually I specified those years as occupying the dawn of the current golden age of biology, and noted the shortcomings of "a lot of medical research and especially clinical research" at that time. Those who are familiar with the allocation of money for medical research will know that for the last 30 years or so, clinical research has experienced difficulty attracting funds in competition with scientifically more sophisticated biomedical research projects. This has been a world-wide phenomenon, and has prompted various solutions, including the establishment of multidisciplinary collaborative research groups whose members have complementary skills. Whatever label one chooses to attach to Green's working years, today's clinical research is hugely different from most of that practised in the 1960s and 1970s. It is not too hard to see why the change had to happen.

Barbara Heslop
Emeritus Professor
Dunedin

## SANDRA CONEY

Sandra Coney was until 2003 the executive director of Women's Health Action, a women's health consumer advocacy organisation that she founded in 1984 with Phillida Bunkle. She was co-author of the *Metro* article on 'the unfortunate experiment' at National Women's Hospital that led to the Cartwright Inquiry (1987) and was a party to that Inquiry. She has continued to work on issues of health consumers' rights, consumer participation and. screening. She was on the Expert Group that established the National Cervical Screening Programme and co-wrote the first policy for the programme. She is currently a member of the Consumer Reference Group for screening programmes. In her role at WHA, she oversaw the redevelopment of consumer resources for the NCSP and the development of other resources based on evidence, most recently on HRT. She has served on a large number of health committees and is currently a board member of the National Centre for Health and Social Ethics, chair of the PHARMAC Consumer Advisory Committee and a women's health adviser to the Cervical Cancer Audit. She has recently written a report for the New Zealand Guidelines Group on consumer participation in the health sector. A writer, she has published a number of books on health, including *The Menopause Industry* and *Hysterectomy* (co-written with Lyn Potter). She is an elected Auckland Regional Councillor

## CONSUMER VOICE: AN IDEA WHOSE TIME HAS COME

**Presenter:** Sandra Coney

### Abstract

A number of countries are taking steps to enhance consumer participation in the health sector; the UK is even legislating for it. The roots of this trend lie in the social movements of the 1960s and 1970s but concerns about the 'democratic deficit' and the need for consumer-centred services have provided new impetus. The paper will discuss the evidence for the benefits of participation, what consumers hope to achieve from it, and its limitations. The current status of participation in New Zealand will be described, and models from other countries will be outlined. The paper is based on a recent report on effective consumer networks to the New Zealand Guidelines Group.

cited.

# EDITORIAL

## Will Exercising Informed Consent Stop "Unfortunate Experiments"?

> Not one of the women was warned of the peril she was in. While the medical profession at the largest women's hospital in the country maintained closed ranks and kept an unbroken silence, the women continued to come to the hospital like lambs to the slaughter.
>
> *Sandra Coney*, The Unfortunate Experiment, *1988, p 253*

Twenty-one years ago an article appeared in the medical literature about a shocking experiment that had taken place in New Zealand. Events were exposed 3 years later, driving home to people everywhere that informed consent needed to be an essential component of lawful and ethical human research. I am a New Zealander, and I lived in Auckland for a time while "the unfortunate experiment," as it became known, was going on, so the story was even more painful. My interest in informed consent, particularly as it applied to practice and studies involving women, was aroused and grew as obstetrical technologies, procedures, and research proliferated.

What happened? In 1984 the well-respected *Obstetrics and Gynecology* had published the results of a disastrous research project on women that began in 1955 and was conducted until 1976 without their consent at National Women's Hospital in Auckland (1). The purpose of the study was to examine the natural history of carcinoma in situ of the cervix in 948 women who had abnormal (positive) cells found in a cervical smear. One group of 817 was treated and the other group of 131 was not treated, even though the risk of progression to invasive cancer was known. The untreated women developed potentially fatal cervical cancer at 25 times the rate of the treated women and had a 12 times greater chance of dying.

Allegations about treatment of cervical cancer at the hospital, the largest women's hospital in the country, were made by two courageous women in a magazine article, titled "The Unfortunate Experiment" (2), later expanded into a book by Sandra Coney, a feminist and consumer advocate (3). The article opened up a "can of worms," in the words of some involved doctors, precipitating a national outcry and the appointment of a Committee of Inquiry in June 1987 to investigate (4). The Cartright Inquiry, as it was known, attracted worldwide attention, generating a scrutiny of research practices, patients' rights, teaching methods, issues of power between physicians and patients, informed consent, and ethics, and leading to a major reform of health care ethics and practice in New Zealand. Women themselves became more assertive, asking more questions about their care and wanting to see their medical records (3).

Other countries, too, have had their unethical and "unfortunate" experiments. One all-too-similar study that was conducted in the United States, the "Tuskegee study," began in Alabama in 1932, also without the consent of participants. So that the natural course of syphilis could be studied, effective treatment was withheld from a group of 400 poor rural black men. Even though new drugs such as penicillin had been discovered, the U.S. Public Health Service failed to make treatment available to the men. The study was finally exposed 40 years later, in 1972, in a Washington, DC, newspaper, but it was not until 1972 that federal hearings finally prompted the U.S. government to establish rigorous regulations for conducting human research.

What was so shocking, in addition to the suffering of these study women and men and the cover-up by medical professionals for years about what was going on, was that the "subjects" were never told that they were being used, essentially as "guinea pigs," in medical research. They were denied the right to two basic tenets of informed consent in human research—promotion of individual autonomy and rational decision-making (5). Even worse, two legal documents, the Nuremberg Code in 1948 and the World Medical Association's Declaration of Helsinki in 1964, had identified ethical restrictions for medical research on humans and been accepted throughout the world many years earlier. According to the Nuremberg Code, the consent of an experimental subject must be competent,

voluntary, informed, and comprehending, but also, before a person is even asked to participate in research, a careful review of the science must determine if the study or experiment should be done at all (5).

To try to protect research participants even further, the most comprehensive study of informed consent for medical procedures to date was undertaken in the United States by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (6). It concluded that informed consent for medical procedures was founded on both ethics and law, and that "ethically valid consent is a process of shared decision making based on mutual respect and participation, not a ritual to be equated with reciting the contents of a form that details the risks of particular treatments" (6, pp 2,3).

The American College of Obstetricians and Gynecologists (ACOG), in a 1980 policy statement, "Ethical Considerations Associated with Informed Consent," acknowledged the importance of patients' exercising their rights under the doctrine of informed consent. This document, subsequently revised in 1992 and 2004 (7), moved away from the medical paternalism of the past in an endeavor to safeguard patients' autonomy when making medical decisions about treatment and participating in research and teaching exercises. Nevertheless, I was still jarred by wording in one passage in the 2004 version of the statement: "The 1980s and 1990s exhibited a growing sense of the need for shared decision-making as a corrective to the exaggerated individualism that patient autonomy had sometimes produced" (7). "Exaggerated individualism"? No examples are given, but do I detect some anger toward women who write a birth plan, are "noncompliant," or make choices at odds with or deemed inadvisable by caregivers?

The two primary components of the ethical concept of "informed consent" are comprehension (or understanding) and free consent, the policy statement notes. It also notes, however, that fully achieving informed consent is not easy. Difficulties include the social imbalance of power in the provider-patient relationship, and gender, race, and class bias in attitudes and actions of individuals and institutions toward patients (7). Some groups are especially vulnerable in terms of medical research and practice —the very young and the very old, the poor, the ignorant, the handicapped, ethnic minorities, women who speak a different language ... oh yes, and women in labor. Emergency situations, time constraints, tradition, and scarcity of personnel, equipment, and services (e.g., interpreters) are other well-known barriers to achieving informed consent in maternity care.

Another more rare limitation is "therapeutic privilege," the withholding of information from a patient by a physician in the belief that the knowledge will seriously harm the patient. This "privilege" comes close to paternalism, and can conflict with and override respect for patient autonomy. Legal expert George Annas notes, "no court has ever held a doctor liable for giving his patient too much accurate information" (5, p 92). Nevertheless, it is not just *what* information is given, it is *how* it is worded or presented that can bias a person's decision for consent or refusal. Consent forms—an example is a form for vaginal birth after a previous cesarean (VBAC) used at some U.S. hospitals—can be written with more intent to protect the physician from a lawsuit than safeguard women from harm.

Despite good intentions, what ACOG's policy statement on informed consent preaches is often not what is practiced. For example, episiotomy, a frequently performed surgery, has been scientifically proved not to benefit women's health (8), yet consent for it is seldom obtained. Has "familiarity bred contempt"? So, too, women are often routinely hooked up to electronic fetal monitors, again without giving informed consent for what is not an evidence-based beneficial procedure. Also, formal consent is frequently not obtained for use of some types and dosages of obstetrical medications, the benefits of which may be scientifically questionable and unproved.

A small study in this issue of *Birth* explores women's perceptions about participating in research (9). Among other findings, women expressed a sense of vulnerability and disempowerment, often using the term "guinea pig." Unethical practices and experiments on women still happen, even in institutions with ethics committees and institutional review boards. Only when women have accurate information and support from their caregivers and experience the proper process for exercising informed consent, will their rights be protected. The words of one "unfortunate experiment" participant, when she learned with horror from the magazine article what had been done to her, speak for many and underscore the simple right to self-determination that she was denied: "I am the guardian of my own body, and I believe it is an invasion of my rights to have something done to me without being told about it" (4, p 154).

*Diony Young*

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| Publisher: | Auckland, N.Z ; New York, N.Y : Penguin Books, 1988 |
| Physical desc.: | 287 p : ill ; 20 cm |
| ISBN/ISSN: | 0140116710 |
| Note: | "A Penguin original."-- P. [4] of cover<br>Includes bibliographical references (p. 277-281)<br>Includes index<br>Subtitle on cover: The full story behind the inquiry into cervical cancer treatment |
| Subject: | National Women's Hospital (Auckland, N.Z)<br>Cervix uteri - Cancer - Treatment - New Zealand - Auckland<br><br>Human experimentation in medicine - New Zealand - Auckland<br>Physicians - Malpractice - New Zealand - Auckland |

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| Publisher: | Auckland : Government Printing Office, 1988 |
| Physical desc.: | 288p |
| ISBN/ISSN: | 0473006642 |
| Note: | Cover title: Report of the Cervical Cancer Inquiry |
| Subject: | Neoplasms - therapy |
| Other Names: | Cartwright, Silvia Rose<br>Mackay, Eric V. (Eric Vincent) |

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# "The Hidden Bits": Understanding Cervical Screening.

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This paper could also be called 'Speaking about the Unspeakable' because it deals with the topic of cervical screening from two perspectives: that of naming the 'hidden bits' with words that are difficult to speak out loud as well as words imposed on the hidden bits of women, and because it deals with research and information gathering which had unspeakable consequences.

It is based on three very different episodes of collecting information about cervical screening in New Zealand over the last thirty years. In 1992 I carried out some qualitative research on women's knowledge of and attitudes to cervical screening for the Waikato Area Health Board. However, this research was bracketed by two major medical disasters to do with cervical screening. The first, in the 1980s, was what has come to be called 'the unfortunate experiment at National Women's Hospital'. It resulted in a governmental inquiry. The second disaster arose out of inadequate cytological laboratory practices in Gisborne which were revealed in the late 1990s. It also resulted in a governmental inquiry.

## The Unfortunate Experiment at National Women's Hospital

National Women's Hospital (NWH) was built in 1964. There was some opposition to combining obstetrics, which deals with childbirth, and gynaecology, which deals with problems in women's reproductive area. It was suggested by Dr Doris Gordon, then head of NWH, that putting the two together pathologised women's reproductive role. This was not an idle suggestion. The history of the medical treatment of women has been one which defined anything to do with female reproduction as problematical, dirty, likely to cause mental upsets and demonstrated the need to control women who had a tendency to be peculiar or childish because of their hormones. However, the two specialisations were put together and the hospital also became a teaching hospital with links to the University of Auckland. This entailed a research function

The initial occurrence that led to this first inquiry was purely accidental. In the mid 1980s, a woman who worked at the Auckland School of Community Medicine read a piece of research a statistician colleague was working on for some doctors at National Women's. She mentioned it to a friend, feminist freelance journalist Sandra Coney and gave her a copy. The paper was, like a lot of medical research designed for journal publication, a summary of the findings with little on the methodology. It appeared to be the outcome of an experiment on women who had had abnormal cervical smears that had not been treated. It

appeared that the figures suggested outcomes of the research that were very poor and included the deaths of some of the women involved. Coney spoke to the doctors who had written the paper and to some women who had had gynaecological problems referred to NWH and decided that some extremely unethical research had been carried on for years at NWH.Those few sentences disguise months of detective work, obfuscation from doctors at the hospital, incomprehension from patients and some lucky breaks in finding people willing to talk about what had been going on. Finally, the two women published a long article in Metro magazine in 1987 entitled "The Unfortunate Experiment". The article won several journalism awards and unleashed a scandal so large that a government inquiry was launched.

The inquiry was centred around Professor Herbert Green, a professor of medicine who taught and did research into cervical cancer from the time of his appointment to NWH in 1956. A year later the Pap smear was introduced to NZ and overseas studies showed that it could identify cell changes at an early stage, which allowed successful intervention. Studies also showed that if there was no intervention, while not all pre-cancerous cells developed into full-blown cancer, at least a third did. Therefore diagnosis was an important preventative measure.

The treatment for pre-cancerous cells in the 1950s was hysterectomy – total removal of the uterus and therefore of a woman's ability to have children. By the 1960s cone biopsy was used but this could also reduce chances of conception. Herb Green was a strong opponent of abortion and very concerned by anything that reduced a woman's fertility. Green told one of his patients that a woman would throw away her unique possession if she lessened her chances of conception and he said it was a woman's heritage to keep her uterus. This was not uncommon discourse for the time; women's magazines ran articles on how a man should be particularly nice to his wife if she had a hysterectomy even though she was no longer real woman. And a gynaecologist was on record saying, "I think of menopause as a deficiency disease like diabetes". The discourse of the time located female identity in the uterus.

Green developed a missionary zeal to save women's fertility. At first he suspected that CIS (carcinoma in situ – the precursor stage) did not always develop into cancer and eventually he persuaded himself that this was true. To test his belief he personally saw every woman who came to NWH for colposcopy (microscopic examination of a cervix which had shown some cell abnormality) for more than 20 years. He followed the progress of these women, recalling them often, taking cell samples but never treating them because he wanted to show the natural history of the disease and prove that cervical screening was a waste of time. At the inquiry stories were told of women who had been recalled for more than 20 years, many of whom had developed cancer and some of whom had died. One woman had had eleven smears taken, ten of which showed malignancy, she had had small bits of her cervix removed for analysis but had had no treatment and was told she was being recalled because, "she was a bit

of an odd bod" and Professor Green found her very interesting. This of course persuaded her she was being carefully monitored and no harm could come to her so for 23 years she returned to NWH until she developed full-blown cancer and the Professor was no longer interested in her. It was the figures from this research that came to the attention of Coney and led to her writing the Metro article, which provoked the inquiry.

At the inquiry experts were flown in from all over the world to testify that Green's ideas were contrary to all evidence, that his presentations at international conferences were greeted with disbelief and that reputable journals refused to take his papers. This raised the question of why doctors in NZ had not questioned his experiments. It turned out that some had but the power of his position and his personality had over-ridden their objections. He was also responsible for educating student doctors and his rejection of the utility of screening programmes persuaded many GPs not to give smear tests to their patients. This was despite material published both by WHO and health departments of other countries, which showed significant reduction of deaths from cervical cancer when adequate screening programmes were introduced.

Several things came out of the inquiry: questions about informed consent were raised and problems to do with research ethics identified. There was also a clear indication that part of the Hippocratic oath – 'I will treat other doctors as my brothers' – was being interpreted as a familial binding akin to the Mafia and few brother doctors were prepared to publicly question Green's ideas. This was all in the 1980s and caused reforms in obtaining patient consent, monitoring the ethics of research, patient advocates were appointed at NWH and there was a general raising of consciousness about women's rights to information and kinder treatment. The government also had to take on board recommendations from the inquiry (headed by lawyer Silvia Cartwright, now Governor General of New Zealand) that there were benefits from screening programmes and a National Screening Register should be set up in NZ. This is where my study comes in.

In 1988 the government decided to set up a national cervical screening programme. Initially, a pilot programme was set up in Dunedin in the South Island and in 1990 the government decided to set up another trial programme in the North Island in the Waikato Area Health Board (WAHB) area and I was contracted to construct a telephone questionnaire on the topic.

To prepare myself for doing the questionnaire I read a lot of material on cervical smears: technological material on brush versus spatula; doctors' recall systems, statistics on smears, cytology, histology, women's experiences and so on. I learned many things but the most significant piece of information was that telephone surveys like the one I was being asked to construct had been carried out in Australia and the number of women who said they had had smears bore no relationship to the numbers of smears read by laboratories – women were massively over-reporting that they'd had a smear. It seemed important to find out

why – were they just saying yes to get rid of the interviewer, were they saying yes because they knew they ought to have had a smear, or did they not know what the interviewer was talking about? I persuaded the WAHB to let me do a series of focus groups to find out women's understandings of the process and the words they used before constructing the questionnaire. They agreed and I set up focus groups old and young, rural and city women to discover if they knew what was inside their bodies, what could go wrong and what interactions they had had with doctors over this process. There was an editorial in the Lancet, which said

> All the necessary scientific facts for saving most of the lost lives have been known for 20 years [i.e. since mid 1960s]…. [But] many with invasive cancer in the older age groups have never been screened at all; some do not know about the test, some do not know where to go for it and *some do not have the vocabulary to ask for it.*
> (1985. Editorial, "Cancer of the Cervix: Death By Incompetence", *The Lancet,* August 17:363-4, emphasis added.)

Therefore I was interested in the words women used about this process.

The third piece of information came from "The Gisborne Inquiry", April – Sep 1999.

The Gisborne inquiry was again triggered by one woman asking questions about why she and others, who had had regular smear tests over the years, been told that their cells were normal, then found themselves with cervical cancer. Where the NWH scandal came from a doctor suppressing the knowledge that some women had abnormal cervical cells, in the Gisborne case one particular laboratory which read the smears was getting them wrong in a huge percentage of cases. Again the fault was attributed to one doctor, Dr Bottrill, but the resulting inquiry raised many more questions about quality control and registration of laboratories, training of cytologists and pathologists and ultimately about the National Screening Register (established between 1990 and 1992). This was set up without building in the required safeguards which could have revealed the poor laboratory work affecting all the women of the East Coast area.

23,000 smears belonging to 12,000 women and read by Dr Bottrill were sent to Sydney for re-reading. 2000 women were advised of abnormalities they had not previously been told about. 616 cases of cancer were identified, 519 of which had not been picked up by Dr Bottrill. Once again there were the testimonies from women to the inquiry which were similar to the submissions to the NWH inquiry – "I knew there was something wrong but my doctor said it was OK because the lab tests were clear" (brother relying on brother again).

The first part of the inquiry showed that laboratory standards were inadequate and steps were put in place for increased quality control. The second part dealt with the inadequacies of the National Cervical Screening Register. WHO and health departments of countries with their own national registers had published

widely on the appropriate way to set up a register. They said it should be centralised and that it should comprise of three sub-registers (cytology, population statistics and histology) which could be cross-tabulated. The process should also be opt-off – that is, women would actually have to ask not to be put on the register.

As it turned out 14 separate regional registers were set up – one for each area health board, they couldn't communicate with one another so if a woman moved from one place to another her records had to be put on paper and posted, histology could not be tied up with cytology so no one could monitor what happened to abnormal smears and it was opt-on so that every single time a woman had a smear she had to sign a release to allow it to be put on the register. Doctors advised very strongly against this configuration but it went ahead, duly proving its inutility and was finally and expensively centralised in 1997 – too late to pick up the misread cases of Dr Bottrill. The advice about setting up the system had come largely from computer companies, not fully aware of the medical requirements of an adequate screening programme. It had also been hampered to a degree by women's groups and Maori groups. They looked at the ethical problems revealed by the first inquiry and put in so many safeguards over women's privacy that the material collected for the register was not even available for statistical purposes. Maori groups went even further, saying that they were sick of being defined as the group with the worst health statistics (Maori women actually get cervical cancer at about 4 times the rate of Pakeha women) and therefore no information was to go out about Maori women.

The whole point of a screening programme is that it is medical and preventative and intended to reduce the number of deaths from cervical cancer. It needs monitoring and it needs to be based on efficient medical practices from surgery to cytology lab. With national statistics it would have been possible to see that fewer than average cases were being reported from the East Coast and further investigations made.

Analysis

This material raises several interesting issues: I will discuss two rather briefly.

DISCOURSE

The most interesting thread that ran through these three investigations was the language, much of it based on unequal power relations. As Fairclough said,

> The ways in which we communicate are constrained by the structure and forces of those social institutions within which we live and function. Language is the primary medium of social control and power. Ideology is pervasively present in language.
> (1989. N. Fairclough.*Language and Power.* London: Longman.)

Dr Peter Davis, at the NWH inquiry, made a submission that said the relationship of woman to doctor brings unacknowledged sexual politics into play. It enormously widens the gap in status that already exists between doctor and patient and extends the stereotype of passive woman and dominant male. Thus the physician may approach the woman with advice, commands and decisions rather than discussion – the relationship takes on the quality of a parent-child relationship. The woman is reluctant to ask questions because of her feeling of ignorance or a reluctance to cause trouble. She feels helpless in the encounter. The infantilisation of women is rooted in the power imbalance between doctor and patient. This was illustrated in Clare Matheson's evidence that when she told Professor Green that she was sick of coming to the hospital for repeated checks, he replied, "You will do what you're told".
(In Coney, Sandra 1988. *The Unfortunate Experiment.* Auckland: Penguin Books, p.243.)

In the NWH affair, there were the testimonies from both doctors and patients to the inquiry and the publicity sparked public debate in newspapers and magazines. The patients all spoke of their helplessness in the face of medical procedures and the medical testimony spoke of patronage. There were two interesting statements by doctors in letters to Metro magazine. One said women were acting like kids who were starting to grow up and were disappointed to find that their parents weren't perfect and another wrote that the inquiry "made poor old Herb into a symbol of medical oppression of the fair sex".

The pathologising of women's reproductive area sets an ideological base for understanding women's health and ill health. As well, the use, both in popular and medical literature about women's prime identity being in her reproductive organs contributes to this idea. Sexuality as well as reproduction comes into this construct and sexuality is equally pathologised in this discourse: because human papilloma virus (genital warts) is implicated in cervical cell change, and it is sexually transmitted, there was a suggestion originally that only promiscuous women needed smear tests. (Promiscuity in this context was initially defined as having more than one sexual partner. Later it was defined as having had four partners.)

The focus groups I conducted produced many interesting ideas from the participants about their bodies and their interactions with doctors. On the whole, while women knew they had a uterus/womb, most did not know about the cervix. Here are some of the statements women made during the focus groups about their understanding of their bodies and the smear process:

***It's very sensitive isn't it? I mean it's our innermost parts and the most sensitive part. On the whole women are not baring it all, they're just not that way inclined, especially not our generation.***

Had they asked a doctor for the smear? On the whole they waited to be offered one it because it seems rude to ask a strange man (or woman) to look at your genitals.

One woman said she had asked her doctor and when I asked her what she said she answered, "***Well, I said I'd been sleeping with a guy who is bit suss – could you have a look at me."*** Another woman said "***But is that a smear?"*** and the first one replied, ***"Oh well, while they're in there they look at everything."***

Very few had the attitude of one woman who said,
***I go once a year. I'm happy with the bits I've got and I don't want to wake up one day and find they're diseased – to me it's preventative medicine. I hate having it done but I'll go along.***

If the doctor calls them up they go but don't like it

***I hate it when the doctor says Whoops it's a bit cold. Sorry.***

***I hate having smears done. It's degrading and it hurts***

***Yeah I hate the way he says flop your legs open like a frog***

***You leave your pride at the door***

Trivial matter loom large

***I'll tell you one thing that always bothers me – what to do with my pants. Do you stuff them in your bag or fold them up. I don't know where to put them and afterwards you are all messy.***

In matters of vocabulary they tended to refer to their genital area as "down there".

***I know the word vagina but I wouldn't use it to a doctor because it's a doctor's word. I wouldn't want to say to a doctor "I've got a sore vagina' but I couldn't say 'sore fanny' either. We need to find a more casual way of talking about it.***

The issues of unequal power were clear and the women felt they had few rights of ownership over their bodies:

***My doctor would say you have thrush and I would say OK but he wouldn't say what caused it.*** She was asked why she hadn't questioned him further and she said ***I felt the whole thing was not my business even though I knew it was, I mean, it's my body but these are professionals.***

Another one had been told she had thrush and she thought it was polite way of saying syphilis.

A older woman showed the complexity of the interaction with her doctor. He took her blood pressure which was a bit elevated before she had her smear. She said,

***He said that might be because of what you're having done. I thought that was a sensitivity by the doctor. At one time doctors didn't think that you might be a bit stewed up yourself about having such things done. You know, I felt a lot better about it and even to the extent that he rang twice for the nurse and she didn't come and he actually went on with the examination even though she wasn't there and I felt that was a feeling of trust in me, you know, that he didn't have to worry that I was one of those people who might kick up a fuss. I sort of came away feeling thoroughly better that he treated me like that.***

However, she went on to say that it was probably a one off and that if she had mentioned the little things that made her feel better he wouldn't have understood.

The evidence given at the Gisborne inquiry contained many similar statements from the women whose smears had been misread. The central theme of their testimony was that they did not feel it was their place to express their unease about continuing physical symptoms and that the doctor must know best.

The second issue arising form these studies is the question of research ethics. Ethical codes are codes for making moral decisions but they are time and culture specific. They are based on four core principles: autonomy, non-maleficence, beneficence and justice. However, there are several metaethical perspectives which underlie codes of ethics and each investigation or inquiry came from a perspective which could be seen as ethical. These approaches are:

1.Teleological ethics and professional purpose. This stance orients actions to ends which have been defined as good and believes in knowledge for knowledge's sake. While Professor Green broke the four core principles of non-maleficence and so on, he acted according to an ethic which believed in a justifiable end and a justifiable pursuit of knowledge.

2. Utilitarian ethics and cost benefit analysis. This approach is results-oriented and is based on the idea of the greatest good for the greatest number. This is more or less what the National Cervical Screening Register achieved although there is a footnote to this outcome.

3. Deontological ethics and categorical duties. This ethical code is based on the idea of categorical imperatives, of absolute right and wrong. It allows no room for change or exception. None of the three studies mentioned above followed this ethic unless a rather fixed idea about women by some of the actors counts in this category

4. Critical philosophy and advocacy research. This recognises self-interest and lack of objectivity in research but endeavours to speak FOR, not ABOUT, the participants with the intention of bringing about change for the better. I tried to do this. However, this can also have unintended consequences.

The NWH inquiry, which coincided with the rise of feminism in New Zealand, raised awareness of women, their right to have a voice in research which affects them and, more broadly, in the medical treatment they receive generally. The result of this consciousness raising was the establishment of patient advocates and the appointment of women to many statutory bodies and committees. Maori women, equally, gained representation and both groups insisted that informed consent and confidentiality be central to all research on women.

The interesting corollary of this was that when the national register was established, women's groups (and Maori even more so) insisted on so many safeguards that the register was virtually useless. This was commented on by the Scottish woman doctor who was brought in to oversee the inquiry. She has recently returned to New Zealand to present her final report and again commented on the barriers raised by women and Maori to the detriment of the medical purpose of the register.

This discussion of language notes the paradoxes: women who had no voice in some 1980s research; women given a voice in the focus groups but being unsure what to say; and, finally, women saying 'we know but we will not say'.