Correspondence. Surnames, 'Fowden' to 'Hawkins'

Contributors

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 13 May 2004 11:58
To: alf1000
Cc: Wendy
Subject: RE: witness seminar draft programme 15 June prenatal corticosteroids

✓ Yes

Dear Professor Fowden
We are pleased that you are able to attend, and look forward to meeting you on the 15th June.
Best wishes
Daphne Christie

-----Original Message-----
From: Abby Fowden [mailto:alf1000@cam.ac.uk]
Sent: 13 May 2004 11:47
To: d.christie
Subject: RE: witness seminar draft programme 15 June prenatal corticosteroids

Dear Dr Christie,

I will be delighted to attend this meeting.
With kind regards,
Abby Fowden

****
Abigail L. Fowden PhD ScD
Professor of Perinatal Physiology,
Department of Physiology,
University of Cambridge,
Cambridge
CB2 3EG
Tel; 44 (0)1223 333855
Fax: 44 (0)1223 333840
****

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 13 May 2004 11:46
To: alf1000@cam.ac.uk
Subject: witness seminar draft programme 15 June prenatal corticosteroids

Dear Professor Fowden
I have attached a draft programme and updated publicity flyer for our meeting on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth'. I do hope that you will be able to join us.
With best wishes
Daphne Christie

Dr Daphne Christie
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine at UCL
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24 Eversholt Street
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Professor Aidan Halligan
University of Leicester
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LEICESTER LE2 7LX

Dr Daphne Christie
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25 March 2004

Dear Professor Halligan

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

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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.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 09:17
To: Aidan.Halligan
Cc: Wendy
Subject: RE: Prenatal corticosteriods for reducing morbidity and mortality associated with preterm birth

Dear Professor Halligan
We are sorry that you are unable to attend. We will keep you informed regarding publication of the subsequent transcript.
With best wishes
Daphne Christie

-----Original Message-----
From: Wendy.Daniel@doh.gsi.gov.uk [mailto:Wendy.Daniel@doh.gsi.gov.uk]On Behalf Of Aidan.Halligan@doh.gsi.gov.uk
Sent: 02 April 2004 17:07
To: d.christie@ucl.ac.uk
Subject: Prenatal corticosteriods for reducing morbidity and mortality associated with preterm birth

Dear Dr Christie

Thank you for your kind invitaion to Professor Halligan to attend the Prenatal corticosteriods for reducing morbidity and mortality associated with preterm birth seminar.

Professor Halligan appreciates being asked to attend this event on 15 June at the Wellcome Building. Unfortunately, on this occasion, due to a prior long standing diary commitment, Professor Halligan is unable to accept and he has therefore asked me to pass on his apologies.

With best wishes.

Wendy
Senior Personal Secretary to
Professor Aidan Halligan
Deputy Chief Medical Officer
Department of Health
Richmond House
79 Whitehall
London SW1A 2NS
Tel: 0207 210 5017

Wendy Kutner

To: Hall ,Dr Lesley
Subject: RE: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesday 15 June 2004

Dear Lesley
Thank you for your email. We have added your name to the list of attendees.
With best wishes
Daphne

(Wendy is on leave until 3 June)

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
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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: Hall ,Dr Lesley [mailto:l.hall@wellcome.ac.uk]
Sent: 12 May 2004 17:10
To: w.kutner
Subject: RE: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesday 15 June 2004

I should like to attend

Dr Lesley A Hall
Archives and Manuscripts
Wellcome Library for the History and Understanding of Medicine
183 Euston Road, London NW1 2BE, England UK
Tel 0207 611 8483 Fax 0207 611 8703
email l.hall@wellcome.ac.uk
http://library.wellcome.ac.uk

-----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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Dr Steve Hanney
Health Economics Research Group
Brunel University
Uxbridge UB8 3PH

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11 March 2004

Dr Hannay

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: 23 March 2004 13:34
To: Stephen Hanney
Cc: Wendy
Subject: RE: witness seminar

Dear Dr Hanney
We are delighted that you are able to attend the witness seminar on prenatal corticosteroids on 15 June and will be sending further details in due course.
We look forward to meeting you on the 15th.
Yours sincerely
Daphne Christie

-----Original Message-----
From: Stephen Hanney [mailto:Stephen.Hanney@brunel.ac.uk]
Sent: 23 March 2004 13:12
To: d.christie
Subject: witness seminar

Dear Dr Christie,

Many thanks for the kind invitation to the Witness Seminar on prenatal corticosteroids on 15 June. I shall be pleased to attend what should be a most interesting seminar.

I look forward to meeting you,
Best wishes
Steve

Steve Hanney
Research Fellow
Health Economics Research Group (HERG)
Brunel University
Uxbridge
Middlesex, UB8 3PH, UK

Email: stephen.hanney@brunel.ac.uk
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26 April 2004

Dear Dr Hannay

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-5pm

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 Dr Hanney

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 'Assessing payback from research'. 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.

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: stephen.hanney@brunel.ac.uk
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Dr Hanney, 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

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

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Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 26 May 2004 12:16
To: 'Stephen Hanney'
Cc: Edmund Hey (E-mail); Daphne Christie (E-mail)
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Thanks, Steve. Iain

-----Original Message-----
From: Stephen Hanney [mailto:Stephen.Hanney@brunel.ac.uk]
Sent: 26 May 2004 11:02
To: Iain Chalmers
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Dear Iain

Thanks for your email and, just to let you know how things are proceeding, we have just heard that the relevant editor is recommending that the paper be accepted, but it now has to go to the editor-in -chief for final acceptance.

I'll let you know as soon as we hear more.

Best wishes
Steve

Steve Hanney
Research Fellow
Health Economics Research Group (HERG)
Brunel University
Uxbridge
Middlesex, UB8 3PH, UK

Email: stephen.hanney@brunel.ac.uk
Tel: +44 (0)1895 265444
Fax: +44 (0)1895 203330

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 17 May 2004 15:24
To: Stephen Hanney; Iain Chalmers
Cc: Patricia Crowley (E-mail); Edmund Hey (E-mail); Mugford Miranda Prof (MED) w241; Jonathan Grant (E-mail); Martin Buxton
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Thanks for your response to my moanings, Steve.

Given that it's in the section entitled 'Reasons for delays in implementation' I suggest the following:

"The nature of the debate in the editorial, and the subsequent letters, support the conclusion promulgated from 1992 onwards by the Cochrane Collaboration that the picture would have been clear a decade earlier had a meta-analysis such as that featured in the organisation's logo been published (www.cochrane.org/logo/logoexplanation.htm). Sinclair reinforced the Collaboration's conclusion dramatically using the cumulative meta-analysis he presented at the NIH Consensus Conference (Reference

needed)."

You may be right about pages 15/16. I hope that you'll be able to deal with the other points I raised.

See you on 15 June!

Iain

-----Original Message-----
From: Stephen Hanney [mailto:Stephen.Hanney@brunel.ac.uk]
Sent: 17 May 2004 11:58
To: Iain Chalmers
Cc: Patricia Crowley (E-mail); Edmund Hey (E-mail); Mugford Miranda Prof (MED) w241; Jonathan Grant (E-mail); Martin Buxton
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Dear Iain,

Thanks for your email and I'm grateful for you picking up the mistake I made in the sentence related to the logo, and apologise for it. That particular sentence was perhaps the most frustrating to prepare in the entire text. First, I was trying to balance: the point about how the importance of steroids should have been recognised earlier; the point in the Cochrane brochure about the logo illustrating what a systematic review would have looked like in the early 80s had it been published; the reference to a meta-analysis having been conducted in the early 1980s; and the pressure to reduce words wherever possible. Second, I had intended to reference the original Cochrane Centre brochure that we have, but found that it seems to be undated and thus difficult to reference in an article. Therefore I checked on the web and found the only version there was the 2002 one and when I phoned the Cochrane Collaboration they could not help put a date on our original version and as I recall I discussed with them the idea of using the web version. The organisation of that version gives greater prominence to the logo than did the original, but I apologies again for exaggerating what it said and not realising the implications of using the available date of 2002.
I would be pleased to attempt to get a corrected version into the journal and would suggest the following: The nature of the debate in the editorial, and subsequent letters, perhaps substantiates claims made by the Cochrane Centre (1992-IS THIS CORRECT OR SHOULD SOME OTHER DATE OR REFERENCE BE USED) that the earlier availability of a review, such as that illustrated by the Cochrane logo of the seven randomised trials published by the early 1980s, might have increased obstetricians awareness of the effectiveness of corticosteroids.

This is clearly potentially tricky ground, are you happy with this version?

I'm afraid I do not agree that the paragraph on pages 15/16 implies that 'the benefits should be considered solely in terms of their effects on mortality'. True, mortality is given emphasis in specific sentences, but the paragraph explicitly also refers to cases of RDS and to morbidity.

I think some of your detailed points underline the importance of the seminar as an opportunity to explore the whole issue in greater depth than proved possible in an article, but I'll see if there is an opportunity to add a reference to Cochrane and explanations of the logo in Table 1.

Best wishes
Steve

Steve Hanney
Research Fellow
Health Economics Research Group (HERG)
Brunel University
Uxbridge

Middlesex, UB8 3PH, UK

Email: stephen.hanney@brunel.ac.uk
Tel: +44 (0)1895 265444
Fax: +44 (0)1895 203330

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 16 May 2004 14:40
To: Stephen Hanney
Cc: Patricia Crowley (E-mail); Edmund Hey (E-mail); Mugford Miranda Prof (MED) w241; Jonathan Grant (E-mail); Martin Buxton
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Thanks for this, Steve. It promises to be a useful paper, and I am glad that you have taken some of my earlier comments into account. However, I still feel bound to press you on a few points pre-publication in the hope that I won't be forced to do so in the correspondence columns post-publication, particularly as my name is one of those you have listed in the Acknowledgements. I've attached comments on the things that trouble me most.

Best wishes, Iain

-----Original Message-----
From: Stephen Hanney [mailto:Stephen.Hanney@brunel.ac.uk]
Sent: 14 May 2004 16:37
To: Iain Chalmers
Cc: Patricia Crowley (E-mail); Edmund Hey (E-mail); Mugford Miranda Prof (MED) w241; Jonathan Grant (E-mail); Martin Buxton
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Dear Iain and colleagues

Thanks for your email and I'm attaching the version of the paper re-submitted this week to Soc Sci Med. I thought it might be best not to have too many different versions going around, but to take account of your point about it being useful to have the fuller version, I'm also sending as a separate attachment what was Table 2 of the original version. This is the table that collates the findings from various studies about uptake levels in the UK. Even though it is no longer referred to in the text, it is fairly self-explanatory but the points on page 10 of the text about the difficulties with making comparisons between different datasets are relevant. Although at present we would be grateful for these attachments to be treated as confidential, we fully agree with your point about hoping to have copies of the article available for the seminar on 15 June and will be approaching the relevant editor of the journal about this.

In relation to the invitation to be ready to speak at the seminar for about 5 minutes on the payback assessment, I'll obviously plan to base what I say on the relevant section of the paper; the way the agenda has been set up should help facilitate this.

Best wishes and thanks for your helpful comments on the first version.
Steve

Steve Hanney

Research Fellow
Health Economics Research Group (HERG)
Brunel University
Uxbridge
Middlesex, UB8 3PH, UK

Email: stephen.hanney@brunel.ac.uk
Tel: +44 (0)1895 265444
Fax: +44 (0)1895 203330

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 11 May 2004 14:52
To: Stephen Hanney
Cc: Patricia Crowley (E-mail); Edmund Hey (E-mail); Mugford Miranda Prof (MED) w241; Jonathan Grant (E-mail); Martin Buxton
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Thanks for bringing me up to date. I think it would be useful for Ed, Patricia and me to have copies of the unshortened version. Which journal are you dealing with? It might be worth telling the journal now about next month's seminar and that, if they want to have some promotion of the journal, it's an opportunity for them to get that. Best wishes, Iain

-----Original Message-----
From: Stephen Hanney [mailto:Stephen.Hanney@brunel.ac.uk]
Sent: 11 May 2004 13:13
To: Iain Chalmers
Cc: Patricia Crowley (E-mail); Edmund Hey (E-mail); Mugford Miranda Prof (MED) w241; Jonathan Grant (E-mail); Martin Buxton
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Dear Iain,

Many thanks for your email which arrived as I was making the final revisions to the article before re-re-submitting it. Apologies for the delays, but the review process, and our response to the quite substantial revisions requested, took longer than expected. The content was then reported to be fine but we were next asked to cut the length considerably, including the various tables and many references.

Thanks also for the invitation to the Witness Seminar and I'm looking forward to it. We too thought it would perhaps be useful to have the article available for that, but would it be best to wait until we hear about publication? As we are hopefully close to having a version agreed for publication, should I wait before sending it to you, or would you like copies for yourself, Ed and Patricia, it as it is now?

best wishes
Steve

Steve Hanney
Research Fellow
Health Economics Research Group (HERG)
Brunel University
Uxbridge
Middlesex, UB8 3PH, UK

Email: stephen.hanney@brunel.ac.uk
Tel: +44 (0)1895 265444
Fax: +44 (0)1895 203330

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 11 May 2004 10:52
To: Stephen Hanney
Cc: 'Patricia Crowley (E-mail)'; Edmund Hey (E-mail); 'Mugford Miranda Prof (MED) w241'; Jonathan Grant (E-mail); Martin Buxton
Subject: RE: Draft paper on predicting and measuring benefits from antenat al steroid research

Dear Stephen

I am glad that both you, Miranda and Martin will be contributing to the Witness Seminar next month. Has the paper on which you invited me to comment last summer been published? As far as I can see, I haven't received any information from you about it since 23 August last year. I think that copies of the published article (or the current draft) should be available for people attending the seminar; but in the meantime, please would you send one each to me, Ed Hey and Patricia Crowley (contact details below).

Yours, Iain Chalmers

Sir Iain Chalmers
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Professor Patricia Crowley
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Eire
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patc@indigo.ie

-----Original Message-----
From: Iain Chalmers
Sent: 23 August 2003 01:49
To: 'Stephen Hanney'; Iain Chalmers; Mugford Miranda Prof (MED) w241
Cc: Patricia Crowley (E-mail)
Subject: RE: Draft paper on predicting and measuring benefits from antenat al s teroid research

Dear Stephen

Thanks for your message, and for drawing my attention to the information in the Acknowledgements section of Patricia Crowley's Cochrane review.

As far as 'Health Research Systems' is concerned, it probably would be sensible to refer to Tikki Pang's work, but I would drop the initial capitals of the three words. They leave the impression that whatever it is a recognised concept, and I can't imagine that many readers will have heard of it.

I'd like to receive a copy of Jonathan's report in time for me to read it before I meet with him and Grant Lewison on 22 September, so if the published version will be available in time, I would be happy to have that.

Best wishes, Iain

-----Original Message-----
From: Stephen Hanney [mailto:Stephen.Hanney@brunel.ac.uk]
Sent: 21 August 2003 14:55
To: Iain Chalmers; Mugford Miranda Prof (MED) w241
Cc: Patricia Crowley (E-mail)
Subject: RE: Draft paper on predicting and measuring benefits from antenat al s teroid research

Dear Sir Iain,

I'm replying on my return from holiday to thank you for your most helpful and interesting comments on our draft article. We shall look to include as many as points as possible when revising the paper. I particularly liked your comment about randomising the first patient and your suggested phraseology about systematic reviews being crucially important but not sufficient is helpful. The reference to Health Research Systems comes from the concept being developed at WHO by Tikki Pang, but your comment leads me to think it would be helpful briefly to describe the point.

You asked about Patricia Crowley's first review being as early as 1981. This information comes from her acknowledgements in the revised Cochrane review (last downloaded by me on 31/3/03). Your point makes me realise I should add this reference at that point as well and not just have it at the end of the paragraph.

Finally, Jonathan Grant is happy to send you a copy of his report on Comroe and Dripps, but we're just in the process of arranging to publish it simultaneously with a related HERG report which is being finalised. Therefore there has been a little delay because ideally Jonathan would like to give you a copy of the published report.

Best wishes
Steve

Steve Hanney
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-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]

Sent: 07 August 2003 12:47
To: 'Mugford Miranda Prof (MED) w241'; Iain Chalmers
Cc: Stephen Hanney; Patricia Crowley (E-mail)
Subject: RE: Draft paper on predicting and measuring benefits from antenat al s teroid research

Dear Miranda

I have used Track Changes to indicate suggestions.

Best wishes, Iain

-----Original Message-----
From: Mugford Miranda Prof (MED) w241 [mailto:M.Mugford@uea.ac.uk]
Sent: 24 July 2003 08:48
To: 'Iain Chalmers'
Cc: 'Stephen.Hanney@brunel.ac.uk'
Subject: RE: Draft paper on predicting and measuring benefits from antenat al s teroid research

Dear Iain

Have a lovely holiday. We look forward to comments when you have time and renewed energy.

Steve has sent the paper to Mont Liggins. I don't seem to have Jonathan's email, so will ask Stephen to send this message on.

Best, Miranda

>-----Original Message-----
>From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
>Sent: 24 July 2003 08:07
>To: 'Mugford Miranda Prof (MED) w241'; Iain Chalmers (RCT);
>'Dr Patricia Crowley (Trinity)'
>Cc: 'Stephen.Hanney@brunel.ac.uk'
>Subject: RE: Draft paper on predicting and measuring benefits
>from antenat al s teroid research
>
>
>Dear Miranda
>
>I've now read and enjoyed this, but I set off in a couple of hours on
>holiday. There are some things that need fixing, and some additional
>information that I think is relevant. I'll get back to you
>with comments by
>mid-August. Meanwhile, if you haven't already sent it to Mont
>Liggins, you
>might want to do so. His contact details are shown below.
>I'm meeting with
>Jonathan Grant (and Grant Lewison) in September. Please would
>you ask him
>to send me a copy of his In Press paper.
>
>Best wishes, Iain
>
>Prof Sir Graham Liggins
>Department of Obstetrics & Gynaecology
>University of Auckland
>National Women's Hospital
>Claude Road, Epsom, Auckland 3
>New Zealand

>Tel. +64 9 638 9919
>Fax. +64 9 630 9858
>
>
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>
>This e-mail contains information intended for the addressee
>only. If you
>receive this e-mail in error, please contact the sender and delete the
>original from your system. There is no guarantee that any
>attachments to
>this e-mail are free of software viruses, and you are
>recommended to check
>for viruses before opening any attachments.
>
>-----Original Message-----
>From: Mugford Miranda Prof (MED) w241 [mailto:M.Mugford@uea.ac.uk]
>Sent: 17 July 2003 18:02
>To: 'Iain Chalmers (ichalmers@rct-registration.org)'; 'Dr
>Patricia Crowley
>(Trinity)'
>Cc: 'Stephen.Hanney@brunel.ac.uk'
>Subject: Draft paper on predicting and measuring benefits from
>antenatal s
>teroid research
>
>Dear Iain and Patricia
>
>It may interest you to see this paper, which has been drafted
>by Stephen
>Hanney, with co-authorship from Martin Buxton, Jonathan Grant
>and myself.
>It has been submitted to Social Science and Medicine.
>
>I don't want to spoil your summer holidays, or compete with
>all the other
>pressures you have, but any comments and corrections you have
>would be very
>gratefully received by all of us. We've also sent a copy to Peter
>Brocklehurst.
>
>I hope all is well with you both
>
>Best wishes,
>
>Miranda
>
>-----Original Message-----
>From: Stephen R Hanney [mailto:Stephen.Hanney@brunel.ac.uk]
>Sent: 16 June 2003 11:58
>To: M.Mugford@uea.ac.uk; jgrant@rand.org; martin.buxton@brunel.ac.uk
>Subject: ARTICLE submitted
>
>
>Dear all,
>Many thanks for your patience: the article has now been
>submitted. If we
>get a negative response from Soc. Sci Med, I'm sure the
>WHO/BioMed central
>e-journal on health research would be pleased to accept it. On
>the attached
>copy I've added a note on the cover asking for it not to be
>copied or cited
>because I think we agreed it would be useful to send it to a
>few people.
>I'm sending a copy to Phil Green at Wellcome who was interested.
>
>Miranda, I don't know if you would like to send copies to Iain
>Chalmers,
>Peter Brocklehurst, and/or Patricia Crowley inviting comments

>that could be
>taken on board when we asked to incorporate reviewers
>comments, or would
>you prefer me to do it? In either case it might be relevant to
>explain that
>I had been delayed in producing the article but then in the
>end we wanted
>to submit it quickly because of the forthcoming conference.
>Therefore we
>are sending to them at the same time as it goes to the journal.
>
>Best wishes
>Steve
>
>Stephen R Hanney
>Brunel University, UK
>hesrsrh@brunel.ac.uk
>
>Tel: +44 (0)1895 274000 ext 3709
>Fax: +44 (0)1895 203330
>Email: stephen.hanney@brunel.ac.uk
>

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 03 June 2004 16:36
To: Wendy
Subject: FW: RDS article/seminar

RDS-mayrerev.doc

Please add a copy to the files. Thanks, Daphne

-----Original Message-----
From: Stephen Hanney (hesr) [mailto:Stephen.Hanney@brunel.ac.uk]
Sent: 03 June 2004 14:58
To: Iain Chalmers; d.christie
Cc: Patricia Crowley (E-mail); Edmund Hey (E-mail); Mugford Miranda Prof (MED) w241; Jonathan Grant (E-mail); Martin Buxton (hesr)
Subject: RDS article/seminar

Dear Iain, Daphne and colleagues

I'm pleased to attach a copy of our RDS article that has just been accepted by Soc Sci Med and the editor is happy for us to make it available for participants at the Wellcome seminar as a paper 'in press'. You will see that we have tried to make its status clear on the covering page and, because it is likely to be subject to final editorial changes, we would prefer at this stage for it not to be copied any wider than to the seminar participants. Given the journal's policy of putting 'in press' papers on its web site once the proofs have been agreed, it should not be long, however, before the final version is publicly available and I'll let you know when this happens.

I look forward to seeing you at what promises to be a most interesting seminar.
Best wishes
Steve

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Assessing the Benefits of Health Research: Lessons from Research into the Use of Antenatal Corticosteroids for the Prevention of Neonatal Respiratory Distress Syndrome

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[3] RAND Europe, Cambridge

Correspondence to: Dr Steve Hanney, Health Economics Research Group, Brunel University, Uxbridge, Middlesex UB8 3PH.
Email: stephen.hanney@brunel.ac.uk

ASSESSING THE BENEFITS OF HEALTH RESEARCH: LESSONS FROM RESEARCH INTO THE USE OF ANTENATAL CORTICOSTEROIDS FOR THE PREVENTION OF NEONATAL RESPIRATORY DISTRESS SYNDROME

ABSTRACT

Do the benefits from health research justify the resources devoted to it? Addressing this should not only meet increasing accountability demands, but could also enhance understanding of research utilisation and how best to organise health research systems to increase the benefits. The process from basic research to eventual application and patient benefit is usually complex. The use of antenatal corticosteroids when preterm delivery is expected has featured large in the debates about research utilisation and provides an insight into these complexities. Based on an analysis of previous modelling of research utilisation and payback assessment, a framework is developed in which the existing literature on the use of corticosteroids, combined with new material developed by the authors, can be reviewed and synthesised. The move from animal studies to human trials was undertaken by the same individual. Some early clinical application of the findings occurred concurrently with a series of further trials. Nevertheless, the implementation of these findings stalled rather than accelerated as is predicted by some models. The eventual systematic review of the trials played a part in the development of the Cochrane Collaboration and increased the impact on practice. Further implementation approaches were used in various countries, including clinical guidelines, a National Institutes of Health Consensus Conference, and various implementation projects within the UK. This paper shows how an assessment of the benefits from this stream of research and utilisation projects can be constructed. It concludes that the application of a model for assessing payback can help to demonstrate the benefits from the research in this field and enhance our understanding of research utilisation.

Keywords: Assessing research benefits; Research payback; Research utilisation; Respiratory Distress Syndrome; Corticosteroids.

INTRODUCTION

Do the benefits from health research justify the resources devoted to it? This question is increasingly asked, especially when the funding could otherwise be spent directly on providing health care. Various approaches to, and reasons for, assessing the benefits from health research have been advanced (Drummond, Davies, & Ferris, 1992; National Institutes of Health (NIH), 1993; Buxton & Hanney, 1996; Grant, Cottrell, Cluzeau, & Fawcett, 2000; Smith, 2001; Croxson, Hanney, & Buxton, 2001). Some reasons revolve around the increasing demands for accountability for existing research funds, the desire to provide justification for current levels of expenditure and advocacy for extended funding. Others relate to the potential use of assessments in helping both to increase understanding of the processes involved and assist identification of how research systems can best be organised to enhance utilisation and benefits, especially for patients. Finally, it is claimed that assessment of utilisation could provide incentives for greater attention to be given to activities aimed at enhancing utilisation.

Previous modelling of research utilisation and payback assessment recognises that only sometimes do flows of health research knowledge make a direct impact on policy and practice: more often they simply add to the pool of knowledge (Kogan & Henkel, 1983; Hanney, Packwood, & Buxton, 2000). This increases the difficulties of assessing the benefits from research. Not only do the types of benefits that can flow from research have to be clarified, and methods selected for assessing whether these paybacks are accruing, but it is also important to consider how to identify which research is responsible for any payback achieved.

Few topics have figured so prominently in the research utilisation debate as the use of antenatal corticosteroids to prevent neonatal Respiratory Distress Syndrome (RDS) when preterm delivery is expected. Indeed, this issue became a *cause celebre* among those concerned with encouraging greater research utilisation (Department of Health, 1993; Haines & Jones, 1994).

MODELS OF RESEARCH UTILISATION AND PAYBACK ASSESSMENT

We draw on models of research utilisation and frameworks for payback analysis in order to present and organise a wide range of available evidence. Theories of diffusion of innovations generally

examine patterns of adoption of new findings. For example, Rogers (1995) developed the concept of the S-shaped adoption curve which helps inform analysis of how far uptake of research findings will occur 'spontaneously' and how far specific steps are necessary to encourage implementation. Rogers' S-shaped curve shows the number of adopters rising slowly at first, then accelerating and finally increasing at a gradually slower rate as fewer and fewer remaining individuals adopt the innovation. The part of the diffusion curve from about 10% adoption to 20% adoption, he states: 'is the heart of the diffusion process. After that point, it is often impossible to stop the diffusion of a new idea, even if one wished to do so' (Rogers, 1995, p.259). Haynes and Haines (1998) describe a path from evidence generation to clinical application that can involve a series of stages, including synthesising the evidence through systematic reviews and formulating clinical policies. Such models of research utilisation adopt the approach of working forwards from the production of new evidence and examine its implementation. Not all models of payback assessment work in this direction. In an attempt to develop a more systematic approach than evidenced by previous anecdotes, Comroe and Dripps (1976) identified key aspects of then current clinical practice in the cardiovascular field and attempted to work backwards to locate the crucial bodies of knowledge behind them. They showed that much of the key research was not clinically oriented when it was undertaken, although the replicability of Comroe and Dripps' work has been challenged (Smith, 1987).

Most models of payback assessment from the health economics literature focus primarily on providing a quantitative ex-ante assessment of the likely magnitude or value of the payback from research that is being considered for funding. Townsend, Buxton & Harper (2003) reviewed the various models designed to be used in this way. Economic evaluations can be undertaken at various times in the development of a stream of research and play various roles (Sculpher, Drummond, & Buxton, 1997), sometimes forming a key part of payback assessments. In an ex-post assessment of payback linked to the NIH (1993), Drummond et al. (1992) assessed the payback once a body of research on diabetic retinopathy had been completed but on the basis of expert opinion about likely levels of utilisation rather than data on actual uptake.

Our approach, though informed by various quantitative models, was developed to focus on actual take-up levels and aims to enhance understanding of the processes and linkages that connect

payback to the original research. Our framework for assessing payback consists of two elements: a multidimensional categorisation of benefits (ranging from knowledge production, through an improved information base for policymaking, to the final outcomes of health gain and broader economic benefits) and a model of how to apply this categorisation (Buxton & Hanney, 1996; Hanney et al., 2000).

The model contains a series of stages, but key features are the interfaces, and associated levels of permeability, between research and the wider professional and political environments that constitute the context. The initial interface involves the specification of research to meet identified needs. The inputs into research projects, and the subsequent processes, lead to the primary outputs: the production of knowledge in the form of publications and, quite often, capacity building for future research. Then there is the dissemination interface, at which point the research findings usually enter the pool of knowledge—from where they often feedback into further research. The findings might also be disseminated to the wider society of industry, policy-makers, practitioners, and members of the public—especially relevant patient groups (Hanney, Gonzalez-Block, Buxton & Kogan 2003a).

The next stage for the assessment of benefits focuses on the generation of 'secondary outputs' in the form of research informed policies and products. Such policies can range from national public policies to local administrative decisions and clinical guidelines developed by professional groups (Hanney et al., 2003a). Policies are based on many factors, sometimes including systematic reviews of all relevant, rigorous research. There are various ways in which practitioners can be encouraged to adopt or apply research findings and/or research informed policies (Grimshaw, Shirran, Thomas, Mowatt, Fraser, Bero et al., 2001). Application of the research findings by practitioners should lead to the final outcomes, in the form of the benefits to the health and economic sectors, including health gains, cost savings and a healthy workforce.

This model was originally developed for health services research (Buxton & Hanney, 1996). When the focus is on more basic research it is likely that greater emphasis will be given to the various phases of knowledge production. With some adjustments, however, the framework set out in the preceding paragraphs seemed appropriate for the current study.

METHODS FOR STUDYING PAYBACK

For the analysis described here we were able to draw on the considerable existing literature about the use of antenatal corticosteroids. Some of this had been undertaken, in previous studies, by the authors of this article: detailed economic and payback analysis (Mugford, Piercy, & Chalmers, 1991; Mugford, 1993); key informant interviews (Hanney, 1994); surveys of potential users (Hanney, Soper, & Buxton, 2003b); and bibliometric analysis (Grant, Green, & Mason, 2003). The latter analysis involved an attempted replication of Comroe and Dripps' study in which the Wellcome Trust's Policy Unit worked backwards from major clinical advances in neonatology, including the use of corticosteroids when preterm delivery is expected (Grant et al., 2003). Therefore, even though difficulties with replicating the methods used by Comroe and Dripps mean that the approach of working backwards seems unlikely to be applicable on a regular basis, some key background findings from the Policy Unit's study are relevant here.

For the current exercise, the main methods included: a literature review to identify additional and recent accounts, desk analysis of the collated literature, citation analysis, and, following Antman, Lau, Kupelnick, Mosteller, and Chalmers (1992) and Graham (1997), a review of textbooks—in this case those series of obstetrics textbooks from the 1970s onwards that were available from the London library of the Royal College of Obstetrics and Gynaecology (RCOG). The key feature for our study is the application of the framework described above to the large amount of material gathered and the organisation of that material to produce a comprehensive analysis of payback and the reasons for it, which had not previously been attempted.

This article organises key elements from the existing literature on RDS, plus the new data we gathered, in two ways. First, the material is presented in the chronology of selected principal events displayed in Table 1. Second, the analytical sections below broadly reflect the various steps in the models of research utilisation and payback assessment: primary research; secondary research; recommendations for use including development of policy guidelines and other secondary outputs; attempts to encourage adoption of the research findings and assessments of the degree of research use; and assessment of the benefits from implementation, including the final outcomes.

Overall, while the focus, especially in the early part of the paper, is about the international development of the science, much of our account of the implementation and payback assessment concentrates on developments affecting the use of corticosteroids in two contrasting healthcare systems: UK and USA.

THE DEVELOPMENT OF THE PRIMARY SCIENCE

The identification of a specific starting point for an exercise such as this is often problematic but here there are strong arguments for starting with the work of Liggins (Liggins, 1969; Liggins & Howie, 1972). At the end of the 1960s he examined how, when glucocorticoids triggered the onset of labour in pregnant sheep, the lambs born prematurely had well aerated lungs, while many of the control animals died of RDS (Liggins,1969). Further experiments using a range of animals were continued by others in the early 1970s (Avery, 1975).

Human prematurity was a problem gaining increased attention in the 1960s and the sheep model was being researched by various teams. In relation to the use of corticosteroids, however, the contribution of Liggins was particularly important because he also conducted the first trials in humans. Just three years after the influential animal study he published a randomised controlled trial (RCT) of betamethasome therapy involving 282 mothers in whom premature delivery was expected. The aim was to reduce 'the incidence of neonatal respiratory distress syndrome by accelerating functional maturation of the fetal lung' (Liggins & Howie, 1972, p.515) and the results provided 'sufficient evidence of beneficial effects on lung function and of absence of adverse effects to justify further trials' (p.524). Their studies continued and expanded; the eventual numbers (1070) in their trial made it the largest in the systematic review described below, accounting for about one third of the cases in the 12 trials (Crowley, Chalmers, & Keirse, 1990).

In the 1970s further RCTs were initiated. Following an NIH workshop in 1974 a large-scale collaborative study, including long-term follow-ups, started in 1976 and reported in the 1980s (Collaborative Group on Antenatal Steroid Therapy, 1981 and 1984). The 1981 paper, according to an editorial in the same edition of the *American Journal of Obstetrics and Gynecology*, proved the efficacy 'under certain conditions; however, corticosteroids should be used with caution' (Little, 1981,

p.287). In the 1984 account of the Collaborative Group's follow-up studies the evidence in favour of using corticosteroids was even stronger.

SECONDARY RESEARCH

As early as 1981 Crowley undertook a meta-analysis of these trials but this review was first published in a structured form in the *Oxford Database of Perinatal Trials* and *Effective Care in Pregnancy and Childbirth* in 1989 and published in a journal a year later (Crowley et al., 1990). Just 12 trials, out of 23 examined, met the predefined criteria of research quality necessary for inclusion in the systematic review. The results were clear:

> 'Data from 12 controlled trials, involving over 3,000 participants, show that corticosteroids reduce the occurrence of respiratory distress syndrome overall and in all the subgroups of trial participants that we examined.... There is no strong evidence suggesting adverse effects of corticosteroids' (Crowley et al., 1990, p.11).

Overall, the review showed that the reduction in the odds of neonatal respiratory morbidity is about 40-60% and the reduction in early neonatal deaths in babies at risk of RDS is between 25-50%. Having reviewed the trials, Crowley et al went on in the article to report claims that application of the therapy should reduce the costs of hospital neonatal care; they quoted an estimate suggesting possible savings of $35 million per year in intensive care costs in the USA (Avery, 1984). Following a suggestion from Chalmers, one of the authors of the systematic review, Mugford and colleagues assessed the economic impact that would result from implementation of the findings of the systematic review in England and Wales (Mugford et al., 1991). This indicated a potential reduction in NHS neonatal costs of around £8 million.

Concern about limited implementation of the findings in the USA, despite the strength of the evidence, led the NIH and its affiliate, the National Institute of Child Health and Human Development, to develop a Consensus Conference for which Crowley was invited to update the systematic review. It was subsequently published (Crowley, 1995). Her systematic review on the Cochrane Database was substantially updated in 1996 and amended in 1999 (Crowley, 2002).

RECOMMENDATIONS FOR USE

Recommendations for the use of corticosteroids, for that small proportion of women for whom preterm delivery is expected, were made in a variety of documents with differing degrees of authority. These include reviews, editorials and textbooks. As early as 1979, a review article in *The Lancet* referenced Liggins and Howie (1972) and stated that 'Corticosteroids should be given to the mother intramuscularly over 48 hours: they reduce the incidence and severity of Idiopathic Respiratory Distress Syndrome (IRDS) without substantial risk to mother or fetus' (Ritchie & McClure, 1979, p.1228). In an editorial statement accompanying the publication of the findings of the NIH's Collaborative Group in the *Journal of Pediatrics* in 1984, Avery's endorsement was particularly strong: she suggested that failure to act on the evidence 'constitutes poor practice' (Avery, 1984, p.240). Four series of textbooks in the library of the RCOG that had editions from the 1970s through to recent times were examined. Three included some mention of the use of antenatal corticosteroids in the first edition to be published after Liggins and Howie's 1972 paper: in the USA, the third edition of *Danforth's Obstetrics and Gynecology* (Benson, 1977, p.624); and, in the UK, the second edition of what became *Dewhurst's Textbook of Obstetrics and Gynaecology* (Dewhurst, 1976) and the 13th edition of *Obstetrics by Ten Teachers* (Clayton, Lewis, & Pinker, 1980).

Generally, it was not until the publication in the systematic review of clear conclusions in favour of the use of corticosteroids that more authoritative endorsements in the form of policy recommendations or clinical guidelines were produced. Such statements are important secondary outputs in terms of Buxton and Hanney's framework. In the UK, the use of corticosteroids was recommended in two sets of guidelines produced in 1992 (Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians, 1992; Royal College of Obstetricians and Gynaecologists (RCOG), 1992). These guidelines were among a small number subsequently included in a policy statement by the National Health Service Management Executive (1993) that took the form of an Executive Letter advocating the greater use of research-based evidence.

In the USA, the 1994 Consensus Conference produced recommendations for use following a year of study and preparation (NIH Consensus Conference, 1995). These recommendations were generally endorsed by the American College of Obstetricians and Gynecologists (Leviton, Goldenberg, Baker,

Schwartz, Freda, Fish et al., 1999). The conference statement also suggested there could be cost savings of 'more than $3000 per treated neonate' (NIH Consensus Conference, 1995, p. 416).

ASSESSING AND ENCOURAGING ADOPTION/APPLICATION RATES

The Buxton and Hanney model suggests there can be a flow of research impacts. This goes from the primary outputs such as publications containing research findings, to the secondary outputs such as clinical policies and guidelines and then into adoption or application by practitioners. The model recognises, however, that the reality is rarely a simple linear sequence. Assessments of use in relation to corticosteroids show a somewhat curious pattern: in at least some countries there was quite a high early adoption of the use of corticosteroids. A survey in 1987 by the Royal Australian College of Obstetricians and Gynaecologists showed that 76% would prescribe antenatal steroids in uncomplicated preterm labour, and a decade later the figure was 97% (Quinlivan, Evans, Dunlop, Beazley, & Newham, 1998). There are problems when making comparisons between countries, and over time. For example, some surveys of use refer to the percentage of clinicians using it, which in itself can involve self-reporting bias, and others to the percentage of relevant mothers to whom it was administered. And even for those in the latter category there are different interpretations of boundaries for the eligibility criteria. Nevertheless, the analysis below shows that in the UK and USA, even after the evidence for its use had become much firmer, there was considerable resistance to the approach.

Application of the findings in the UK

In 1980 (after Liggins and Howie and only a few other trials) a survey in the UK revealed that as many as 42% of RCOG Members and Fellows claimed to use the treatment frequently and 40% sometimes (Lewis, de Swiet, Boylan, & Bulpitt, 1980). Despite the 51% response rate, the survey was seen as the best evidence at the time and preceded any national clinical policies. Figures gathered from several exercises suggest there is little evidence of much, if any, increase in use during the 1980s in the UK (Mugford, 1993) and the low levels of application revealed in some of these exercises stimulated various reactions. The Getting Research into Practice (GRiP) project in Oxford Regional Health authority in the UK attempted to encourage implementation of four pieces of research evidence, of which the use of corticosteroids was one. That project found that implementation at one

hospital, the John Radcliffe Hospital in Oxford, had in fact already increased considerably in 1992 (Dopson, Mant, & Hicks, 1994).

The use of corticosteroids was also included as one of a number of procedures examined in a project conducted in the late 1990s as part of NHS R&D Implementation Methods Programme. This particular study (Wilson, Thornton, Hewison, Lilford, Watt, Braunholtz et al., 2002) examined changes in levels of compliance with evidence-based recommendations in obstetrics. The study reviewed records to reveal that levels of compliance with the various procedures were very low in 1988; ranging from 0% - 23% for RDS in the 20 units studied. The figures rose considerably by 1996, to a median of 82% for RDS. Wilson et al.'s implementation project, in turn, had high media coverage and is already making some impact on midwives (Hanney, et al., 2003b). These figures are broadly consistent with a survey in 1997 of 210 obstetric units in the UK that indicated almost all units administered prophylactic antenatal corticosteroids when there was a risk of preterm delivery (Brocklehurst, Gates, McKenzie-McHarg, Alfirevic, & Chamberlain, 1999).

Application of the findings in the USA

The NIH organised a Consensus Conference in 1994 to produce recommendations because of concerns that the rate of adoption was then only 15% (NIH Consensus Conference, 1995). The Agency for Health Care Policy and Research funded an RCT to compare the dissemination of these recommendations in the usual, passive, way with active dissemination consisting of a year long education effort led by an influential physician and a nurse co-ordinator at each facility. The results reveal the comparatively low use in the USA even in the mid-1990s; the perhaps surprising success of passive dissemination -- adoption rates up from 33% to 58%; and the even greater success of active dissemination – up from 33% to 68% (Leviton et al., 1999).

Reasons for delays in implementation

The reasons for the apparent stalling of the uptake of the use of corticosteroids could be related to various factors, including a critical editorial in the *British Medical Journal* by Roberton (1982). The nature of the debate in the editorial, and the subsequent letters, support the conclusion promulgated from 1992 onwards by the Cochrane Collaboration that the picture would have been clear a decade

earlier had a meta-analysis such as that featured in the organisation's logo been published (www.cochrane.org/logo/logoexplanation.htm). Considerable variation between hospitals has been noted, with evidence that it is larger centres at the forefront of medical research that are more likely to have seen an early introduction of corticosteroids (Donaldson, 1992; Leviton et al., 1999).

In an analysis that raised issues that were then addressed by the NIH Conference, Leviton, Baker, Hassol, & Goldenberg (1995) described some of the reasons for the low uptake in the USA. They claimed that 'many clinicians may overestimate the probability of negative outcomes resulting from corticosteroid use and underestimate the probability of positive outcomes' (Leviton et al., 1995, p. 315). A key conclusion was that neonatologists were much more supportive of the use of corticosteroids than were obstetricians.

Van Someren (1998) compared the comparatively slow introduction of corticosteroids, which are administered by obstetricians, with the much more rapid introduction of another way of addressing RDS: administration of exogenous surfactant by paediatricians to neonates suffering from RDS. Many factors were thought to account for this, including the fact that the pharmaceutical companies' interest in surfactant also meant the industry had been prepared to fund much larger trials than had occurred with steroids and, therefore, more clinicians had been involved and felt ownership of the trial results.

ASSESSMENTS OF PAYBACK

Assessing benefits from Liggins' research

Applying some elements of the multidimensional categorisation and an historical perspective, we start by looking at the benefits from the original work from Liggins, initially funded by a small grant of less than £20000 from the Wellcome Trust (Grant et al., 2003). In terms of knowledge production, the original work on sheep resulted in Liggins' 1969 paper that has been cited over 500 times. By itself such basic work is most unlikely to result in applications; instead, it is more likely to inform further research.

This was spectacularly done in this case with Liggins himself making the vital jump from the animal science to the human trial. In this case, therefore, the findings were not only fed into the pool of

knowledge and used by many others, but also fed back directly to the work of the original scientist. Indeed, one of the great achievements of Liggins could be said to be that he conducted 'randomisation of the first patient', as advocated by Tom Chalmers (Chalmers, 1975). The 1972 paper from Liggins and Howie has been cited over 1200 times, and the analysis from the Wellcome Trust confirms the importance of Liggins' work on subsequent research (Grant, et al., 2003).

Somewhat unusually, the 1972 paper began to have an impact not only on subsequent trials, as it proposed should happen, but also on practice. It is possible that the 1980 survey in the UK overstated the degree of use of corticosteroids because, for example, it was likely to be the most research-aware who had formed the majority of the 51% of the Fellows and Members of the RCOG who responded to the questionnaire. Nevertheless, even taking such bias into account, the figures from that survey (42% used it frequently and 40% sometimes) suggest an overall figure that would be in the range of the numbers that should, according to the S-curve, have automatically led to an accelerated adoption rate. It is not entirely clear why there was this disjunction between the initial adoption and the subsequent stalling, if not actual decline, in the 1980s. It is possible that in 1980 some respondents were influenced by the recommendation in the article in *The Lancet* (Ritchie & McClure, 1979), but that after that use trailed off because there was no real follow-up activity until later and there was the negative editorial by Roberton (1982).

Despite the delays, the benefits from Liggins' work were clearly significant in terms of lives saved. A key difference between our payback model and others discussed earlier is that we attempt to explore actual rates of application of research findings and, by addressing issues of what might have caused the uptake, are able to give some indications as to which pieces of research, or implementation activities, played a part in achieving this. Mugford's 1993 analysis estimated the number of neonatal deaths that might be averted at various percentage levels of uptake. It estimated an uptake level at the start of the 1990s of no higher than 20%. Nevertheless, such a figure would translate to an annual averting of over 150 neonatal deaths in England and Wales.

Assessing the benefits from subsequent studies

Identifying the work of Liggins as the starting point is reasonably clear-cut, despite the fact that he was building on a great deal of earlier research from others. Within the assessment of the impact from the whole stream of research that started with the 1969 paper, it is more difficult to estimate the benefits from specific projects that followed the work of Liggins and colleagues. The NIH-funded trial was second only to Liggins and Howie in terms of the numbers included in their study and in this sense it was significant. A 1986 NIH assessment of the benefits did so in terms of cost savings. Based on the NIH-funded trial it claimed, somewhat unfairly, that the National Heart, Lung and Blood Institute 'developed antenatal steroid therapy to prevent neonatal respiratory distress syndrome' (NIH, 1993). The cost of the research between 1976-1983 was $7.4 million and, with the analysis partly based on speculation about take-up rates, the potential reduction in treatment costs was claimed to be between $16.5 million and $145.0 million. This analysis can be criticised on methodological grounds because no attempt was made to assess actual levels of implementation--either before the findings of the NIH study were produced, or sometime afterwards—but it did usefully highlight the potential benefits from full implementation.

The next major development on which payback analysis could focus is the systematic review. The original review article has been cited on about 370 occasions. In terms of impact, the major expansion in the use of corticosteroids occurred after the systematic review. The impact, however, took some time and, at least in the UK and USA, also involved further activities by parts of the health research system.

In this context it seemed appropriate to Chalmers and Mugford that Mugford should produce a brief paper for the Department of Health based on her economic evaluation (Mugford et al., 1991). This appears to have been used in various official documents, a key one being from the R&D Division of the Department of Health (DH, 1993). This document, like the whole new NHS R&D strategy, stressed the importance of the utilisation of research findings, but the use of corticosteroids was the only research application for which it gave a calculation. It described the systematic review but claimed the then take-up rate was only 15-20%. Based on the calculations of the proportion of lives saved by use of corticosteroids, and figures about cost savings, it stated that if the information 'on

antenatal steroids in premature babies were to be fully utilised, it is estimated that resources equivalent to up to 5% of current spending on neonatal hospital care might be made available for use elsewhere in that field of health care' (DH, 1993, p.35).

The benefits from the economic evaluation by Mugford et al. (1991) were assessed as one of Buxton and Hanney's payback case studies (Hanney, 1994). The cost effectiveness study itself cost very little, but was an advance because none of the antenatal steroid trials had included formal economic evaluation even though some reported hospital charges. Applying the payback analysis just to Mugford's cost effectiveness study highlights the difficulty of attempting to separate out the benefits of one item from the wider stream of work. In general, the documentary review and interviews with key informants established that the systematic review was the evidence that was having the most impact on the production of secondary outputs in the form of decisions by professional groups and administrators to produce their guidelines. Furthermore, the analysis in the payback study demonstrated the difficulties of realising the cost savings in contracts: such savings would mostly be absorbed by providing better or alternative care to other babies (Hanney, 1994).

Guidelines and additional studies such as GRiP will have contributed to increasing usage throughout the 1990s but, as noted by Wilson et al. (2002), it is difficult to identify precise factors leading to the increased uptake. Mugford's (1993) analysis indicated that if uptake in England and Wales rose from a possible 20% figure to 75% of eligible cases, this could result in over 400 additional deaths being averted annually. Data described earlier suggest that adoption rates are now above 75%, therefore there has clearly been substantial benefit in terms of lives saved and release of resources for other uses. Analysis by Mugford et al. (1991) was also used by Wilson et al., but related to the whole UK, to suggest that even the 1996 uptake figures of about 80% still implied 'approximately 500 avoidable cases of RDS and 200 avoidable deaths from prematurity each year in the UK' (Wilson et al., 2002, p.180). Evidence from the way in which uptake increased in the 1990s implies further movement towards 100% adoption rate and, therefore, even more neonatal deaths averted each year. There is, however, a complication. The much greater use of surfactant in the 1990s, and improved neonatal intensive care services, mean that even without corticosteroids many of the deaths that would previously have occurred might now be averted. This makes it difficult to state that without

corticosteroids there would be a specific number of neonatal deaths. Nevertheless, not all the mortality and morbidity would be avoided by relying on surfactant and the NIH Consensus Conference stated: 'The benefits of antenatal corticosteroids are additive to those derived from surfactant therapy' (1995, p.417). Furthermore, the use of corticosteroids as a preventative therapy is still recommended in the most recent editions of textbooks (Edmonds, 1999; Scott, Gibbs, Karlan, & Haney, 2003).

DISCUSSION AND CONCLUSION

This analysis shows that the body of research examined led to important knowledge production, or primary outputs, and resulted in a string of significant secondary outputs in the form of guidelines. But above all, and key to providing 'good stories' to assist with justifying research funds, this example provides an account of how health research can lead to health gains in terms of reduced mortality and morbidity.

The analysis presented here has limitations. It is based on a single case study of a topic that is exceptional in various ways including: a rapid move from animal to human studies; an involvement in the development of the Cochrane Collaboration; a gain both in terms of health and cost reduction; and many existing studies on which to draw. Furthermore, the type of issue involved, ie a clinical intervention that can be studied by traditional RCTs, is one where this type of payback analysis should be most feasible, and yet even here it proved very difficult to give precise figures about the level of payback achieved. Nevertheless, we would argue that the very difficulties involved show how in practice a detailed analysis of actual adoption rates and the factors behind them is likely to be necessary for a realistic analysis of the payback achieved from the various elements in any line of research and its implementation.

In terms of how to conduct assessments, this analysis shows it is sometimes possible to follow through a series of stages from basic to clinical science and on to some implementation in clinical practice. As a case study it also demonstrates that a multidimensional approach to assessing benefits has advantages, in terms of its flexibility, in dealing with what can become complex situations. Limiting the analysis to one category of benefits reduces the scope of the analysis as when, for example, it becomes difficult to demonstrate features such as actual cost savings. By considering a

series of stages, the assessment of benefits can also help illustrate points in an holistic way that complements, and builds upon, some of the more detailed analyses undertaken by other researchers of specific aspects of the utilisation processes. It allows the more diffuse and very important contextual issues to be considered. This case suggests that there can be periods when the implementation appears to stall rather than automatically accelerate as would be indicated by the S-curve. This illustrates that those running health research systems need carefully to consider how they can best contribute to encouraging implementation.

The material described here could help to build a counterfactual scenario. It is possible to imagine that without follow-on activities after the RCTs there would have been a moderate amount of implementation of the research findings, but less than the desirable levels now being achieved. The role of the systematic review was shown to be particularly important in moving application rates to higher levels. The timing of this therapy's introduction complicates the analysis as it straddles the development of meta-analytic approaches. Nevertheless, this study usefully illustrates the crucial importance of such methods but at the same time highlights, as noted repeatedly by those preparing such reviews, that they are not sufficient. Some appropriate implementation is always likely to occur prior to systematic reviews, and there is still resistance to implementation after systematic reviews. Other approaches are also required.

Economic evaluations have various roles to play. Given the rather unusual finding that this therapy offered both potential cost savings as well as health gains, economic evaluations therefore played the role of assisting promotion of the introduction of corticosteroids. The production of guidelines, policies, consensus conference statements and active implementation strategies also all played a part and illustrate the frequent need for multiple approaches towards research implementation (Haines & Jones, 1994). Indeed, our case study suggests some of these approaches can be more successful in certain circumstances than is often thought. This, in turn, reinforces the need for a multidimensional approach to the *assessment* of benefits over a long time-scale.

Finally, therefore, this case study shows how assessments of the benefits from health research can fulfil the roles described in the introduction, including contributing towards greater understanding of

the processes of research utilisation. An advantage of payback assessment approaches, compared with some other utilisation studies, is that they can, as here, provide a rather more positive message in that their focus is primarily on what has been achieved, even if full utilisation is still awaited. Hence, their potential usefulness in providing justification for current levels of expenditure on health research and perhaps in advocacy for extended funding. In this case we have shown that an often quoted example of underutilisation of research findings can, nevertheless, be used to demonstrate the considerable benefits that can arise from various aspects of a stream of research.

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Table 1: A Chronological Table of Selected Events

YEAR (S)	EVENT
1969	Publication of Liggins' animal research (Liggins,1969)
1970-1973	Continuing research on acceleration of animal lung maturation by glucocorticoids-reviewed by Avery (1975)
1972	Publication of first trial on humans (Liggins & Howie, 1972)
1974-1984	NIH conference leads to Collaborative Group research (Collaborative Group, 1981 and 1984)
1977-1979	Publication of the initial subsequent five clinical trials on humans included in Crowley's 1989 systematic review
1979	Strong recommendation for use in a review in *The Lancet* (Ritchie & McClure, 1979)
1980	UK survey suggests 82% of Member or Fellows of the RCOG use it frequently or sometimes (Lewis et al., 1980).
1980-1989	Publication of six further RCTs included in the original systematic review
1984	Editorial in *The Journal of Pediatrics* advocates use (Avery, 1984) following publication of Collaborative Group's findings
1986	Attempt by NIH to show the payback from their trial (NIH, 1993)
1987	Royal Australian College of Obstetricians and Gynaecologists: 76% would use it (Quinlivan et al, 1998)
1989	Systematic review published (Crowley 1989 – also 1990)
1988-1995	Six further RCTs published and included in later systematic reviews
1991	Publication in the UK of economic evaluation of benefits to UK of implementing findings from systematic review (Mugford et al., 1991)
Early 1990s	Level of uptake in England and Wales between 15% - 20% (DH, 1993). At the 20% level about 150 neonatal deaths averted annually (Mugford, 1993)
From 1992	Cochrane Collaboration: explanation of its logo that illustrates a review of steroid trials
1992-1993	Publication of guidelines and other recommendations: BAPM/RCP (1992); RCOG (1992); Executive Letter from the NHS Management Executive (1993)
1994	Low uptake in USA results in: NIH Consensus Conference (1995); a further systematic review (Crowley, 1995); and a project implementing conference recommendations (Leviton et al., 1999)
1996	Last major update of Cochrane systematic review (Crowley, 2002)
1997	Virtually all units in the UK would give corticosteroids to women at risk of preterm delivery (Brocklehurst et al., 1999)
1999	Implementation trial in USA shows increased use from 33% to 58% following traditional dissemination of NIH recommendations and from 33% to 68% following active dissemination (Leviton et al., 1999)

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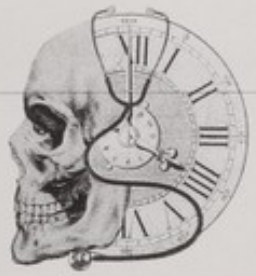

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16 June 2004

Dear Dr Hanney

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.

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

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Corticosteroids

Dr Daphne Christie

From: Stephen Hanney [Stephen.Hanney@brunel.ac.uk]
Sent: 18 January 2005 21:06
To: d.christie
Subject: RE: witness seminar

RDS-final.pdf

Dear Daphne,

My comments on the transcription are in the post, but I'm attaching a pdf version of the now published article on which I based my presentation. I've added this reference as one of my footnotes, but thought you might like a copy of this final version.

I found it fascinating to go through the transcript of the seminar, with so many interesting points having been made by a range of participants.

Best wishes
Steve

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-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 11 January 2005 12:06
To: Stephen Hanney
Subject: RE: witness seminar

Dear Steve
Thank you for your e-mail. Our mail is being forwarded to the new address so it should be okay to use the reply envelope. Others have arrived safely.
With best wishes
Daphne Christie

-----Original Message-----
From: Stephen Hanney [mailto:Stephen.Hanney@brunel.ac.uk]
Sent: 10 January 2005 21:19
To: d.christie@ucl.ac.uk
Subject: witness seminar

Dear Daphne,

I'm just going over the draft transcript for the Corticosteroids seminar, and apologise for being a few days late, but I was wondering whether I need to put the new address on the reply envelope.

Best wishes
Steve

Steve Hanney
Research Fellow
Health Economics Research Group (HERG)
Brunel University
Uxbridge
Middlesex, UB8 3PH, UK

Email: stephen.hanney@brunel.ac.uk
Tel: +44 (0)1895 265444
Fax: +44 (0)1895 269708

Dear Daphne,
Many thanks for the chance to check my contributions to this most interesting seminar. Please contact me if any of my points are unclear.
I've added biographical details at the end.
Best wishes
Steve Hanney

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WEST LONDON

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Director: Professor M J Buxton

With compliments

HANNEY

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

Corrected 2/6/05

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

that as time went on and ventilation techniques and so on got better, that the controversy about steroids seemed to be reduced and then surfactants came along and so on, so that there wasn't a controversy about whether one should use steroids or not.

Hanney: The point was raised by Jane about the attitude that Ross Howie felt that there was in the UK, and I don't know whether people here were at the earlier Witness Seminar on neonatal care that was undertaken a few years ago, but exactly that point was made by somebody who felt that in the UK there was this attitude and that was one of the reasons why there had been a lower uptake. I am very interested Patricia when you raised the issue of the role of the NIH collaborative trial because we were trying to trace ~~schools~~ through uptake levels and it did seem to us that in the seventies there had been some increase in uptake and there was a ~~supported~~ supportive review in the *Lancet* for example in 1979, and there had been the survey of use by members and fellows of the Royal College which showed that quite a lot of them were using it in 1980. It then seemed that things happened in the 1980s, as I think you were saying, that did seem if anything to increase the opposition, and there ~~were~~ was for example the editorial in the BMJ written by Cliff Robertson*, based on the NIH collaborative sub-group analysis that's got criticised. So I would just like to ask you how far you think that sub-group analysis perhaps did reduce usage.

Crowley: I think first the results of the US collaborative trial set things back, because this was the first of the randomized trials

* FOOTNOTE: Roberton, NRC. (1982) Advances in respiratory distress syndrome. British Medical Journal, 284: 917-918.

published which didn't show any difference in neonatal mortality even though it showed a difference in referred distress and in particular the duration on the cost of neonatal care and this was the first trial that looked at economic outcomes. But nonetheless, the lack of difference in neonatal mortality seemed to get a lot of press and then the excessive performance of sub-group analysis was given undue emphasis, sub-groups that had been specified at the start of the trial, they were produced following data dredging after the trial had concluded, and these were emphasized, for instance in that editorial by Cliff Robertson. You referred to the survey of members and fellows of the Royal College of Obstetricians. That was asking obstetricians about their practice and what they said they do, or what we say we do, is not the same as what we actually do, and so I think at the same time as people were saying that 44 per cent, 'often' trials involving surfactant. 12 per cent exposed to steroids antenatally [sense?]

TAPE TWO: SIDE ONE:

Hey: .....and that was a huge trial wasn't it? Forty or 50 hospitals, it was the first time any paediatrician in the UK had been able to get their hands on surfactants. And it was free, so everybody joined the trial. And the analysis of that study when it came out showed that nationally in 1990–91, which was when that trial ran less than 12 per cent of British babies were potentially eligible for surfactant treatment, getting any surfactant, any serum at all.

do something that they don't think is save to be done, regardless of what the evidence says. So what happened was that after about six months they went through a series of educational events at this particular hospital and eventually decided to start introducing ECV and as far as I know it's now common policy. But we couldn't make them do it, they had to do it themselves, and they had to take their own clinicians with them, and I think it was a painful and difficult process for them. Can I just mention, main conclusions from this particular piece of work. Don't expect to get it into the *British Medical Journal* it won't go in. Secondly, advocates are really important when it comes to getting guidelines happening and I think opinion leaders are really important within institutions, but the important thing is that the guidelines have got to be written to be usable, and understandable and accessible to the person who is going to have to implement it, and that means clear inclusion and exclusion criteria. Another important agent for change are users, and if you have women asking these questions, after a while people do get a bit embarrassed by coming up with the same answer which clearly won't get supported by evidence or by your colleagues and 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 in Richard's study that there was no sign of managers actually implementing any change. 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, who's been a GP, and are not afraid of consultants, that we will hold the line if necessary. Managers cannot do that, and I don't think one 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 decisions. We can encourage people when new interventions are being rolled out to be at the centre of it, so they get feedback of positive results. It's much easier then to get change implemented.

Hey: Thank you very much. That rings true to lots 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. But Harold, after the steroid trial you were involved in, we did hear but you were out of the room at the time, is that people, 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 nationally that less than six per cent were using it. But 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 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 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 [Hayward], we at least read your work. There is a paper that set out most of the detail, in this list of the in press, and it is going to be published in *Social Science and Medicine*. So I will just highlight all the key points for now. Apologies, perhaps

* FOOTNOTE: 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: 937-947.

it's just worth spending a minute, going over our pay-back framework so you can see how we tried to drop this stream of work into a frame that we had already developed. Apologies to those who have already heard this many times before. Basically, we have two aspects to our pay-back framework, there's 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, thirdly better informing policies with a long term view of what the policies are being widely interpreted, fourthly, health gain and benefits to the health sector, and fifthly the broad economic benefits. And 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, included the links with previous discussions. There's always a problem when doing this type of analysis as to where you start. Various initial presentations today showed clearly that the research builds on previous research etc. and so whenever one makes a start point, it's always artificial, but on the other hand I do think the nature of the discussions, and what Mary Ellen has to say, does provide a realistic basis for saying we will start by looking at the work, or at least start looking at the work, or we started by looking at the work of Liggins and Howie. And in terms of knowledge production clearly the 1969 paper from Liggins, 1972 paper from Liggins and Howie, were very important. There are lots of weaknesses in citation analysis, but for all that 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 12 000 times. Then there has been some bibliometric analysis undertaken in this

field undertaken by the ~~Foster~~ Policy Unit here at the Wellcome Trust* and they trailed back through various generations of papers and showed ~~that~~ again that this ~~worked and how it~~ was the most important work in this field in several generations. Clearly knowledge production definitely very high. In terms of affecting future research, again citations indicate that it has influenced much subsequent work. But 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 ~~the fact~~ 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. ~~And okay~~ In the UK the figures in the 1980s, are somewhat unclear, but it was definitely higher in Australia and New Zealand. By the 1990s there seemed to be this consensus that the ~~pick~~ take up rate was between perhaps 10 and 20 per cent, and ~~a somewhat~~ Miranda's ~~random~~ analysis shows that at 20 per cent take up level that could be said to lead to at least 150 deaths annually being averted in England and Wales. So it is clear that even in the 1970s, and 1980s, that there were substantial health gains primarily from this Liggins and Howie work with obviously the other trials providing a bit more evidence. There were also not only deaths averted, ~~probably~~ and less morbidity due to the reduced incidence of RDS, ~~and~~ but also there were the cost savings, even if these were cost savings in terms of the resources being available to treat other babies.

* FOOTNOTE: Grant J, Green L, Mason B (2003) Basic research and health: a reassessment of the scientific basis for the support of biomedical science. Research Evaluation 12: 217-224.

TAPE THREE:

…Richard raised the interesting analysis from Rogers' work on the diffusion of innovations. I agree with you, ~~that~~ the analysis that I have that on the whole the profession is much more now receptive. One of the things that ~~Richard~~ Rogers did say was that often when an innovation gets to between 10 and 20 per cent, ~~that~~ in fact diffusion becomes almost impossible to stop, it just tends to escalate. What I find interesting in this case is that it is clear that ~~there is a sort of~~ bottom level of where take-off should be impossible to stop was achieved and then it just didn't take off for quite a long time. There was a stalling at exactly the point when Rogers suggested usually that there would be this take-off. So what was it that gave it the nudge to start going again, and this is where the systematic review comes in as being very important. It was published in 1989–90, we have heard, and perhaps particular attention was focused on this systematic review for several reasons. The ~~[illegible] of~~ the logo Cochrane collaboration, the fact that ~~[illegible]~~ cost-effective studies showed that this was one of the few areas where there had been economic cost savings as well as health gain. So a few years later there were several policy statements advocating the use of clinical guidelines from professional bodies and ~~if you read what it~~ said in the paper, ~~that~~ these did cite systematic reviews, again emphasizing the importance of this ~~point of view~~. I hadn't realized until he spoke quite how explicitly ~~how she~~ looked through systematic reviews and ~~then through~~ the clinical guideline on that, ~~but~~ clearly the systematic review there influenced the policy guideline. There were also these important implementation initiatives. There's one that's mentioned. All these factors seem to have resulted in quite a dramatic increase in uptake during the 1990s. There's the

figures from your study Richard, ~~including~~ and figures in 1977, from 9 your survey, Peter, which shows a very large uptake by the end of the ~~1980s to~~ 1990s. ~~Random~~ Miranda's analysis suggested that with 75 per cent uptake there would be more than 400 deaths averted annually in England and Wales. So clearly, there has been quite a big health gain. The problem though, as has already been mentioned, without putting a precise figure on this, is that with the use of surfactant and the improvement of the neonatal care, it is not clear of course that all these deaths would have actually happened if there hadn't been ~~for~~ the use of steroids. But nevertheless as has been said there is also evidence that even if some of them would never have happened, surfactant wouldn't have stopped all of them. What I think is unclear, is whether there is an actual measure of how many. So definitely this has had substantial health gain as well as impact on policy, knowledge gain, impact on further research. In the USA mention has been made of ~~in census~~ an NIH consensus conference. This was broadly endorsed by the American College* Footnote and it claimed, that this consensus statement, and the college statement, had more impact than most of them. An implementation project found that after a year of just passive dissemination, in fact implementation of the ~~college~~ guidelines went up from 33 to 58 per cent, which is quite substantial. But after active dissemination it went up from 33 to 68 per cent. So it does seem that there are many elements of this whole stream of research that have produced benefits and perhaps the key thing from our work ~~use of ...~~ on this stream of research, that is different from some other perspectives in the debate about research utilization, is that our work has been concentrated on showing that benefits have been achieved even when ~~though~~ the uptake level has been less than optimum.

* FOOTNOTE: American College of Obstetricians and Gynecologists. Committee Opinion 147: Antenal Corticosteroid Therapy for Fetal Maturation. Danvers, Mass: American College of Obstetricians and Gynecologists, 1994.

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

Crowley: Probably a very important one is the reduction in the risk of intraventricular haemorrhage, bleeding into the ..... in the brain in premature babies and that's a particular benefit for the most premature babies and a reduced number of days on a ventilator for babies who do get respiratory distress syndrome, that's the number of days spent on a ventilator reduced the number of time spent in neonatal intensive care probably necrotizing enterocolitis, they would be I suppose from that enterprise the most important.

Harding: Yes, reduction in patient doctors and the new systematic review will also suggest benefits in terms of childhood developmental outcome.

Chalmers: We keep on talking about benefits in terms of the baby, but what about the parents? The reduced exposure to these terrible courses that babies would go through before death, and perhaps

in 1965, then Senior Lecturer, Reader in Paediatrics and Director of the Neonatal Unit, 1979, and in 1994 Professor of Neonatology, later Emeritus. He established the London Perinatal Group in the 1970s, later known as the Thames Regional Perinatal Group.

Dr Gino Giussani

Mrs Gill Gyte

Dr Stephen Hanney

P.T.O. for biographical details

Professor Jane Harding

Dr John Hayward

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

Professor Richard Lilford

Professor Sir Graham (Mont) Liggins

Professor Miranda Mugford

Mrs Brenda Mullinger

Professor Ann Oakley

Dr Sam Richmond

Dr Roger Verrier Jones

Professor Dafydd Walters

Mr John Williams

Dr Stephen Harney

PhD (b. 1951) trained as a political scientist but has specialised in examining evaluation and policy-making in the higher education and research fields. For over 10 years he has worked with Martin Buxton at the Health Economics Research Group, Brunel University, developing and applying ways of assessing the payback, or benefits, from health research.

Glossary

Note the use of bold for items in glossary

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 L A Reynolds and E M Tansey

Dr Stephen Hanney: We have been looking at the payback or benefits from this whole stream of work, and I will be talking later. Just on this specific thing, we did have a figure of £20 000 at one stage from the Wellcome Trust for one of these pieces of work, I think for the original animal trial.[1] I am not quite sure how that fitted in, how long a period that was, but that is a figure that was quoted. It was obviously a very small grant even in those days.

...

Hanney: The point was raised by Jane about the attitude that Ross Howie felt that there was in the UK, and I don't know whether people here were at the earlier Witness Seminar on neonatal care that was undertaken a few years ago [If you want to add a reference it is the Witness Seminar volume 9, 2000], but exactly that point was made by somebody who felt that in the UK there was this attitude and that was one of the reasons why there had been a lower uptake. I am very interested Patricia when you raised the issue of the role of the NIH collaborative trial because we were trying to trace through uptake levels and it did seem to us that in the 1970s there had been some increase in uptake and there was a supportive review in the *Lancet* for example in 1979,[2] and there had been the survey of use by members and fellows of the Royal College which showed that quite a lot of them were using it in 1980. It then seemed that things happened in the 1980s, as I think you were saying, that did seem if anything to increase the opposition, and there was for example the editorial in the *British Medical Journal* (*BMJ*) written by Cliff Roberton, based on the NIH collaborative sub-group analysis that's got criticised.[3] So I would just like to ask you how far you think that sub-group analysis perhaps did reduce usage.

...

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[1] Hanney and Wellcome funding [I'm not sure what this refereence means]

[2] Which supportive review in 1979? Ritchie K, McClure G. (1979) Prematurity. *The Lancet*, **2**: 1227-1229.

[3] Roberton N R C. (1982) Editorial: Advances is respiratory distress syndrome. *British Medical Journal* **284**: 917–18.

Feedback: 12/7/05

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 I have worked on it with Miranda and Martin Buxton and Jonathan Grant. I apologize 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 [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*.[4] 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 that we had already developed. Apologies to those who have already heard this many times before. Basically, we have two aspects to our payback framework, there's 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; the broad economic benefits. And there's a series of stages in the model in which we think these various benefits can be identified. A key feature of our model is to attempt to identify actual levels of uptake so that we can then say what the benefit has been, and this, of course, links with previous discussions. There's always a problem when doing this type of analysis as to where you start. Various initial presentations today showed clearly that the research builds on previous research etc. and so whenever one makes a start point, it's always artificial, but on the other hand I do think the nature of the discussions, and what Mary Ellen says, does provide 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, the 1972 paper from Liggins and Howie, were very important.[5] 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.[6]

There has been some bibliometric analysis in this field undertaken by the Policy Unit here at the Wellcome Trust.[7] 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

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[4] Hanney *et al.* (2005).

[5] Liggins (1969); Liggins and Howie (1972).

[6] *Citation Classics*, webpage address to check 1200 citations? [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, and a reference for this calculation would be the Hanney et al, 2005 paper. Mont Liggins had an article in the Citation Classics series in March 1982 and by then the number of cites for the 1972 paper was already 565: is there a web site where the current total figure could be checked?].

[7] Grant J, Green L, Mason B. (2003) ~~Basic research and health: a reassessment of the scientific basis for the support of biomedical science. *Research Evaluation* 12: 217–24. OR~~ *From Bedside to Bench: Comroe and Dripps Revisited*. HERG Research Report No. 30. Uxbridge: Brunel University. [which 2003 citation??]

citations indicate that it has influenced much subsequent work. ~~But i~~It's also interesting that many of the other pieces of work, trials etc., actually start with a reference to the work of Liggins and Howie, which again I think emphasizes their importance for further work. And it's also been mentioned that Ross Howie felt that further trials should be undertaken rather than necessarily saying that people should act on the findings. Nevertheless, there was quite an uptake in some places, on the basis of this very important trial and the ensuing publications from it. In the UK the figures in the 1980s are somewhat unclear, but it was definitely higher in Australia and New Zealand. By the early 1990s there seemed to be this consensus that the takeup rate in the UK was between perhaps 10 and 20 per cent, and Miranda's analysis shows that at a 20 per cent takeup level it could be said to lead to at least 150 deaths annually being averted in England and Wales. So it is clear that even in the 1970s, and 1980s there were substantial health gains primarily from the Liggins and Howie work with obviously the other trials providing a bit more evidence. There were also not only deaths averted and less morbidity due to the reduced incidence of RDS, but also there were the cost savings, even if these were in terms of ~~the~~more resources being available to treat other babies.

Richard [Lilford] raised the interesting analysis from Rogers' work on the diffusion of innovations.[8] I agree with you, from the analysis that I have, that on the whole the profession is much more now receptive. One of the things that Everett Rogers did say [??is this the S-shaped curve and if so is the quote on page 259 , your 2005 paper, p 938??-Yes] was that often when an innovation gets to between 10 and 20 per cent uptake, in fact diffusion becomes almost impossible to stop, it tends to escalate. What I find interesting in this case is that it is clear that the bottom level of where take-off should be impossible to stop, was achieved and then it just didn't take off for quite a long time. There was ~~a~~ stalling ~~[??point??]~~ at exactly the point when Rogers suggested ~~usually~~ that usually there would be this take-off. So what was it that gave it the nudge to start going again, and this is where the systematic review comes in as being very important. It was published in 1989–90, we have heard, and perhaps particular attention was focused on this systematic review for several reasons.[9] The link, as explained earlier, with the logo of the Cochrane Collaboration and Miranda's subsequent cost-effective studies, showed that this was one of the few areas where there had been economic cost savings as well as health gain.

A few years later there were several policy statements advocating the use, in the form of clinical guidelines from professional bodies and, as is said in the paper, these did cite the systematic review, again emphasizing the importance of this particular~~ly~~ review.[10] I hadn't

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[8] Rogers E. (1995) *Diffusions of Innovations*, 4th edn. New York, NY: The Free Press.

[9] Crowley P, Chalmers I, Keirse M J. (1990) The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *British Journal of Obstetrics and Gynaecology* 97: 11–25.

[10] Which Guidelines had you in mind? Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians. (1992). Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome. *Archives of Disease in Childhood*, **67**, 1221-1227.

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

Mention has been made of the US NIH concensus conference and statement.[11] This was broadly endorsed by the American College of Obstetricians and ~~g~~Gynecologists[12] and it is claimed that this consensus statement ~~and the college statement,~~ had more impact than most of them ~~[??other college statements??guidelines??]~~.[13] An implementation project[14] found that after a year of passive dissemination, implementation of the guidelines went

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Royal College of Obstetricians and Gynaecologists. (1992). *Antenatal corticosteroid administration reduces the incidence of neonatal respiratory distress syndrome*. London: Scientific Advisory Committee, Royal College Of Gynaecologists.~~British Association of Perinatal Medicine. (1998) *Guidelines for good practice in the management of neonatal respiratory distress syndrome.* Report of the second working group. Guideline produced in November 1998. Not valid beyond 2002. Freely available at: www.bapm.org/documents/publications/rds.pdf (visited 2 June 2005).~~

[11] US NIH concensus conference, ??reference??.National Institute of Child Health and Human Development. (1994) Effect of corticosteroids for fetal maturation on Perinatal outcomes. *NIH Consensus Statement* 12: 1-24.

[12] American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. (1995) Antenatal corticosteroid therapy for fetal maturation. ACOG committee opinion no. 147, December 1994. *International Journal of Gynaecology and Obstetrics* 48: 340–2. American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. (1999) Antenatal corticosteroid therapy for fetal maturation. ACOG committee opinion no. 210, October 1998 (replaces Number 147, December 1994). *International Journal of Gynaecology and Obstetrics* 64: 334–5.

~~[13] American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. (1995) Antenatal corticosteroid therapy for fetal maturation. ACOG committee opinion no. 147, December 1994. *International Journal of Gynaecology and Obstetrics* 48: 340–2. American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. (1999) Antenatal corticosteroid therapy for fetal maturation. ACOG committee opinion no. 210, October 1998 (replaces Number 147, December 1994). *International Journal of Gynaecology and Obstetrics* 64: 334–5.~~

[14] Reference?[will be reference 13 not 14] Leviton, L.C., Goldenberg, R.L., Baker, C.S., Schwartz, R.M., Freda, M.C., Fish, L.J., Cliver, S.P., Rouse, D.J., Chazotte, C., Merkatz, I.R., Raczynski, J.M. (1999). Methods to encourage the use of antenatal corticosteroid therapy for fetal maturation. A randomized controlled trial. *Journal of American Medical Association*, **281**: 46-52.

up from 33 to 58 per cent, which is quite substantial. But after active dissemination it went up from 33 to 68 per cent. So it does seem that there are many elements of this whole stream of research that have produced benefits and perhaps the key thing from our work on this stream of research ~~is~~ that is ~~[although]~~ different from some other perspectives in the debate about research utilization, is that ~~is that~~ our work has been concentrated on showing that benefits have been achieved even when the uptake level has been less than optimum.

Dr Stephen Hanney

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

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 L A Reynolds and E M Tansey

Dr Stephen Hanney: We have been looking at the payback or benefits from this whole stream of work, and I will be talking later. Just on this specific thing, we did have a figure of £20 000 at one stage from the Wellcome Trust for one of these pieces of work, I think for the original animal trial.[1] I am not quite sure how that fitted in, how long a period that was, but that is a figure that was quoted. It was obviously a very small grant even in those days.

...

Hanney: The point was raised by Jane about the attitude that Ross Howie felt that there was in the UK, and I don't know whether people here were at the earlier Witness Seminar on neonatal care that was undertaken a few years ago [If you want to add a reference it is the Witness Seminar volume 9, 2000], but exactly that point was made by somebody who felt that in the UK there was this attitude and that was one of the reasons why there had been a lower uptake. I am very interested Patricia when you raised the issue of the role of the NIH collaborative trial because we were trying to trace through uptake levels and it did seem to us that in the 1970s there had been some increase in uptake and there was a supportive review in the *Lancet* for example in 1979,[2] and there had been the survey of use by members and fellows of the Royal College which showed that quite a lot of them were using it in 1980. It then seemed that things happened in the 1980s, as I think you were saying, that did seem if anything to increase the opposition, and there was for example the editorial in the *British Medical Journal* (*BMJ*) written by Cliff Roberton, based on the NIH collaborative sub-group analysis that's got criticised.[3] So I would just like to ask you how far you think that sub-group analysis perhaps did reduce usage.

...

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[1] Hanney and Wellcome funding [I'm not sure what this refereence means]

[2] Which supportive review in 1979? Ritchie K, McClure G. (1979) Prematurity. *The Lancet*, **2**: 1227-1229.

[3] Roberton N R C. (1982) Editorial: Advances is respiratory distress syndrome. *British Medical Journal* **284**: 917–18.

Corrections added 18/7/05

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 I have worked on it with Miranda and Martin Buxton and Jonathan Grant. I apologize 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 [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*.[4] 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 that we had already developed. Apologies to those who have already heard this many times before. Basically, we have two aspects to our payback framework, there's 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; the broad economic benefits. And there's a series of stages in the model in which we think these various benefits can be identified. A key feature of our model is to attempt to identify actual levels of uptake so that we can then say what the benefit has been, and this, of course, links with previous discussions. There's always a problem when doing this type of analysis as to where you start. Various initial presentations today showed clearly that the research builds on previous research etc. and so whenever one makes a start point, it's always artificial, but on the other hand I do think the nature of the discussions, and what Mary Ellen says, does provide 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, the 1972 paper from Liggins and Howie, were very important.[5] 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.[6]

There has been some bibliometric analysis in this field undertaken by the Policy Unit here at the Wellcome Trust.[7] 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

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[4] Hanney *et al.* (2005).

[5] Liggins (1969); Liggins and Howie (1972).

[6] *Citation Classics*, webpage address to check 1200 citations? [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, and a reference for this calculation would be the Hanney et al, 2005 paper. Mont Liggins had an article in the Citation Classics series in March 1982 and by then the number of cites for the 1972 paper was already 565: is there a web site where the current total figure could be checked?].

[7] Grant J, Green L, Mason B. (2003) ~~Basic research and health: a reassessment of the scientific basis for the support of biomedical science. *Research Evaluation* 12: 217–24. OR~~ *From Bedside to Bench: Comroe and Dripps Revisited*. HERG Research Report No. 30. Uxbridge: Brunel University. [which 2003 citation??]

citations indicate that it has influenced much subsequent work. ~~But i~~It's also interesting that many of the other pieces of work, trials etc., actually start with a reference to the work of Liggins and Howie, which again I think emphasizes their importance for further work. And it's also been mentioned that Ross Howie felt that further trials should be undertaken rather than necessarily saying that people should act on the findings. Nevertheless, there was quite an uptake in some places, on the basis of this very important trial and the ensuing publications from it. In the UK the figures in the 1980s are somewhat unclear, but it was definitely higher in Australia and New Zealand. By the early 1990s there seemed to be this consensus that the takeup rate in the UK was between perhaps 10 and 20 per cent, and Miranda's analysis shows that at a 20 per cent takeup level it could be said to lead to at least 150 deaths annually being averted in England and Wales. So it is clear that even in the 1970s, and 1980s there were substantial health gains primarily from the Liggins and Howie work with obviously the other trials providing a bit more evidence. There were also not only deaths averted and less morbidity due to the reduced incidence of RDS, but also there were the cost savings, even if these were in terms of ~~the~~more resources being available to treat other babies.

Richard [Lilford] raised the interesting analysis from Rogers' work on the diffusion of innovations.[8] I agree with you, from the analysis that I have, that on the whole the profession is much more now receptive. One of the things that Everett Rogers did say [??is this the S-shaped curve and if so is the quote on page 259 , your 2005 paper, p 938??-Yes] was that often when an innovation gets to between 10 and 20 per cent uptake, in fact diffusion becomes almost impossible to stop, it tends to escalate. What I find interesting in this case is that it is clear that the bottom level of where take-off should be impossible to stop, was achieved and then it just didn't take off for quite a long time. There was ~~a~~ stalling ~~[??point??]~~ at exactly the point when Rogers suggested ~~usually~~ that usually there would be this take-off. So what was it that gave it the nudge to start going again, and this is where the systematic review comes in as being very important. It was published in 1989–90, we have heard, and perhaps particular attention was focused on this systematic review for several reasons.[9] The link, as explained earlier, with the logo of the Cochrane Collaboration and Miranda's subsequent cost-effective studies, showed that this was one of the few areas where there had been economic cost savings as well as health gain.

A few years later there were several policy statements advocating the use, in the form of clinical guidelines from professional bodies and, as is said in the paper, these did cite the systematic review, again emphasizing the importance of this particular~~ly~~ review.[10] I hadn't

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[8] Rogers E. (1995) *Diffusions of Innovations*, 4th edn. New York, NY: The Free Press.

[9] Crowley P, Chalmers I, Keirse M J. (1990) The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *British Journal of Obstetrics and Gynaecology* **97**: 11–25.

[10] Which Guidelines had you in mind? Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians. (1992). Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome. *Archives of Disease in Childhood*, **67**, 1221-1227.

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

Mention has been made of the US NIH concensus conference and statement.[11] This was broadly endorsed by the American College of Obstetricians and ~~g~~Gynecologists[12] and it is claimed that this consensus statement ~~and the college statement,~~ had more impact than most of them ~~[??other college statements??guidelines??]~~.[13] An implementation project[14] found that after a year of passive dissemination, implementation of the guidelines went

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Royal College of Obstetricians and Gynaecologists. (1992). *Antenatal corticosteroid administration reduces the incidence of neonatal respiratory distress syndrome.* London: Scientific Advisory Committee, Royal College Of Gynaecologists.~~British Association of Perinatal Medicine. (1998) *Guidelines for good practice in the management of neonatal respiratory distress syndrome.* Report of the second working group. Guideline produced in November 1998, Not valid beyond 2002. Freely available at: www.bapm.org/documents/publications/rds.pdf (visited 2 June 2005).~~

[11] US NIH concensus conference, ??reference??.National Institute of Child Health and Human Development. (1994) Effect of corticosteroids for fetal maturation on Perinatal outcomes. *NIH Consensus Statement* 12: 1-24.

[12] American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. (1995) Antenatal corticosteroid therapy for fetal maturation. ACOG committee opinion no. 147, December 1994. *International Journal of Gynaecology and Obstetrics* 48: 340–2. American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. (1999) Antenatal corticosteroid therapy for fetal maturation. ACOG committee opinion no. 210, October 1998 (replaces Number 147, December 1994). *International Journal of Gynaecology and Obstetrics* 64: 334–5.

~~[13] American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. (1995) Antenatal corticosteroid therapy for fetal maturation. ACOG committee opinion no. 147, December 1994. *International Journal of Gynaecology and Obstetrics* 48: 340–2. American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. (1999) Antenatal corticosteroid therapy for fetal maturation. ACOG committee opinion no. 210, October 1998 (replaces Number 147, December 1994). *International Journal of Gynaecology and Obstetrics* 64: 334–5.~~

[14] Reference?[will be reference 13 not 14] Leviton, L.C., Goldenberg, R.L., Baker, C.S., Schwartz, R.M., Freda, M.C., Fish, L.J., Cliver, S.P., Rouse, D.J., Chazotte, C., Merkatz, I.R., Raczynski, J.M. (1999). Methods to encourage the use of antenatal corticosteroid therapy for fetal maturation. A randomized controlled trial. *Journal of American Medical Association*, **281**: 46-52.

up from 33 to 58 per cent, which is quite substantial. But after active dissemination it went up from 33 to 68 per cent. So it does seem that there are many elements of this whole stream of research that have produced benefits and perhaps the key thing from our work on this stream of research ~~is~~ that is ~~[although]~~ different from some other perspectives in the debate about research utilization, is that ~~is that~~ our work has been concentrated on showing that benefits have been achieved even when the uptake level has been less than optimum.

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Dear Lois,

Returned with apologies for the slight delay.

I have checked the pages as requested and responded to your highlighted points and made a few other points using standard proof correction marks. I hope this is OK and very much look forward to the final version. Best wishes Steve Hanney

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With compliments

Hanney

please see pages 24-25, 42-43, 85-89
biographical note : 114
– all these pages checked and comments made on the text. Steve Hanney

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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corrected 27/9/05

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feedback 9/9/05.
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

expected. And the difference turned out to have been that some of the animals got steroids and some didn't, and the ones that were advanced had received the steroids. There was a concern that that would be a permanent effect if they were treated *in utero*, but injured in some way by the steroid; that they would grow up with small lungs or the lung would fail to perform in some way, and so he needed all the information he could get about safety. I think we published our first paper on six sets of twins. That wasn't a very big series, but six out of six showed the same result. It meant that the data were pretty secure, but the next question was, 'What happens when they are ten years old?'

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

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

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

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

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

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, but I could go back and ask him. He commented about who gave him the money and I think probably he simply asked for research funding to look at preterm labour.[33] 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.

Dr Daphne Christie: Dr Tilli Tansey has tried to find out some information about this, so we might be able to get back to you later on this.[34]

Dr Stephen Hanney: We have been looking at the 'payback' or benefits from this whole stream of work, and I will be talking later. On this specific question,

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[33] See Appendix xx, pages xx –xx, for details of the eight years of funding for research assistance from the Wellcome Trust, 1969–76.

[34] See Tansey???Appendix???

at one stage we did have a figure of £20 000 from the Wellcome Trust for one of these pieces of work, I think it was for the original animal trial.[35] I am not quite sure how that fitted in, how long a period that was, but that is a figure that was quoted. It was obviously a very small grant even in those days.

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

Hey: That included his going to America and learning how to hypophysectomize fetal sheep.[36]

Harding: He did all that before he came back [?to New Zealand from ??California?], and when he came back was when he had the Wellcome funding to start his own lab.[37]

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

Harding: That's correct. He had presumed that that would be the case. When he was on sabbatical at UC-Davies he devised a way of doing the hypophysectomy and did the initial experiments there and then came back to set up a sheep lab in New Zealand with Wellcome Trust funding at that time.

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[35] Hanney and Wellcome funding

[36] Surgical removal of the hypophysis, or pituitary gland, in the pregnant ewe.

[37] See Appendix xx, page xx.

So I think that was probably the one and only grant and a very large one at that time for working expenses.

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

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

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

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

their toes. It was actually paediatric versus obstetric issues in many centres that discouraged its use.

Mr John Williams: I am a humble obstetrician, who is a recipient of the literature rather than a contributor, but I was developing [working??] during the era of these publications, and here are some of the things that struck me. The first was an oration by Sir Stanley Clayton [President of the Royal College of Obstetricians and Gynaecologists, 1972–75] in 1975 at the American Congress [??College??] of Obstetrics and Oncologists[??Obstetricians and Gynecologists??], where he said that in his experience as the editor of the grey journal, the *Commonwealth Journal* as it was then, how much rubbish was submitted for publication.[40] He wished that registrars didn't have to do research to get jobs, and it was time it was all stopped. That was the first thing that hit me. And I was then at a meeting in Cardiff where Cliff Roberton spoke, and he seemed to be of the opinion that obstetricians shouldn't be treading on the toes of paediatricians, and that they were very good at looking after babies and we didn't need to interfere. He went on to pour scorn on quite e uncontrolled and poor publications, and again this struck me. I were these published if they were such bad studies?', and he said, w, people having a glass of whisky and refereeing a paper, if it's they know they will put it in, if it's not they won't'. He was fairly of the poor quality publications, and it gave the impression certainly ff that we shouldn't be using steroids. And that set me back a little way.

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The poor publications continued to come out and were very confusing. In fact I wrote to Iain [Chalmers] asking what was going on: 'I want to carry out best practice.' Paediatricians where I was then working in Chester were very keen that we should be using steroids based on the original work, and I said that everyone else says it's rubbish. And it wasn't until the systematic reviews and

[40] Was this published?

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[60] Was this published?

the guidelines came out that we actually introduced it as an overall practice, we gave it to certain selected patients, but not overall. I think that was a common view among obstetricians in this country in the non-academic world.

Dr Roger Verrier Jones: There are two hospitals in Cardiff, two maternity hospitals, and John worked in the other one. The reason I am here is that Iain kindly asked me because he reminded me of a letter that I wrote to him in 1980, saying that we had done a retrospective study using steroids in St David's Hospital in Cardiff, and that the results seemed to be quite startling. Now we had started using steroids in the late 1970s, I think, I am not 100 per cent certain, based on the work that Liggins and Avery and others had done. We were using steroids, although our obstetricians, in particular Joan Andrews, were relatively conservative, but we were using them. I did a retrospective study, which I sent up to Iain, who by then had moved from Cardiff to the National Perinatal Epidemiology Unit (NPEU) in Oxford, and the third figure seemed to be quite striking, in that we looked at 47 babies of which 11 had steroids and 36 didn't. The mortality rate was zero in the steroid group and 28 per cent in the control group. When you looked at the incidence of RDS, the incidence in the steroid group was 18 per cent and in the control group 59 per cent. So on the basis of that certainly in St Davids Hospital, John [?Williams?] you worked in the [?University Hospital of Wales??] UHW, the University Hospital, we were using steroids, and continued to use them, but my memory is that as time went on and ventilation techniques got better, that the controversy about steroids seemed to be reduced and then surfactants came along, so that there wasn't a controversy about whether one should use steroids or not.

Hanney: The point was raised by Jane that Ross Howie felt about the attitude that there was in the UK. I don't know whether people here were at the earlier Witness Seminar on 'Neonatal Intensive Care' that was undertaken a few years ago, but exactly that point was made by somebody who felt that in the UK

there was this attitude and that was one of the reasons why there had been a ~~lower~~ [slower] [prenatal/antenatal steroid] uptake.[61] I am very interested, Patricia, when you raised the issue of the role of the NIH Collaborative Group trial because we were trying to trace through uptake levels and it did seem to us that in the 1970s there had been some increase in uptake: there was a supportive review in the *Lancet* for example in 1979,[62] and there had been the survey of use by Members and Fellows of the Royal College [??RCOG??] which showed that quite a lot of them were using it in 1980.[63] It then seemed that things happened in the 1980s, as I think you were saying, that did seem if anything to increase the opposition, and there was, for example, the editorial in the *British Medical Journal (BMJ)* written by Cliff Roberton, based on the NIH Collaborative Group sub-group analysis that's got criticized.[64] So I would just like to ask you how far you think that sub-group analysis perhaps did reduce usage?

Crowley: I think first the results of the US Collaborative Group trial set things back, because this was the first of the randomized trials published which didn't show any difference in neonatal mortality even though it showed a difference in respiratory distress and in particular the duration and the cost of neonatal care. This was the first trial that looked at economic outcomes. But nonetheless, the lack of difference in neonatal mortality seemed to get a lot of press and then the excessive performance of sub-group analyses was given undue emphasis even though these sub-groups had not been specified at the start of the trial. They were produced following data dredging after the trial had concluded, and these were emphasized, for instance, in that editorial by

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[61] Christie and Tansey (eds) (2001): 55–60.

[62] Ritchie and McClure (1979).

[63] Lewis *et al.* (1980).

[64] Roberton (1982). Dr Crowley, could you elaborate on the sub-group analysis? Is there a table that could illustrate this point?

Cliff Roberton.[65] You referred to the survey of Members and Fellows of the Royal College of Obstetricians and Gynaecologists, which asked obstetricians about their practice and what they said they did, which is not the same as what we actually do.[66] While 44 per cent of obstetricians surveyed in 1979 said that they used antenatal corticosteroids 'often',[67] only 12 per cent of preterm babies recruited to the UK Ten Centre Study of artificial surfactant had been exposed to steroids antenatally.[68]

Hey: That was a huge trial in 40 or 50 hospitals, wasn't it?[69] It was the first time any paediatrician in the UK had been able to get their hands on surfactants. And it was free, so everybody joined the trial. The analysis of that study when it came out showed that nationally in 1990/1 – which was when that trial ran – less than 12 per cent of British babies who were potentially eligible for treatment were being treated.

Dr Sam Richmond: That's absolutely true. We did a sub-analysis of the regional data. The whole of the northern region entered this study and we published results looking back at steroid usage and found very similar results.[70]

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[65] See note 64.

[66] Lewis *et al.* (1980).

[67] Lewis *et al.* (1980).

[68] Ten Centre Study Group (1987).

[69] Open Study of Infants at High Risk of or with Respiratory Insufficiency – the Role of Surfactant (OSIRIS) Collaborative Group (1992). In 1990–91, 6774 babies were recruited to an international multicentre trial to assess when administration of Exosurf, a synthetic surfactant, should be started and how often it should be given.

[70] Khanna and Richmond (1993). Dr Sam Richmond wrote: 'I would point out that the price difference between steroids and surfactant mentioned in the last paragraph of this letter [Khanna and Richmond (1993)] contains a basic arithmetical error – the price of surfactant being nearly 100 times that of steroids rather than 10 times.' Letter to Mrs Lois Reynolds, 26 June 2005.

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.

[147] Hanney *et al.* (2005).

I Agree your suggestions.

I agree with your suggestions

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).

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

Richard [Lilford] raised the interesting analysis from Rogers' work on the diffusion of innovations.[151] From the analysis that I have, I agree with you that on the whole the profession is much more now receptive. One of the things that Everett Rogers did say was that often when an innovation gets to between 10 and 20 per cent uptake, in fact diffusion becomes almost impossible to stop, it tends to escalate.[152] What I find interesting in this case is that it is clear that the bottom level of where take-off should be impossible to stop, was achieved and then it just didn't take off for quite a long time. There was stalling at exactly the point when Rogers suggested that usually there would be this take-off. So what was it that gave it the nudge to start going again? This is where the systematic review comes in as being very important. It was published in 1989–90, we have heard, and perhaps particular attention was focused on this systematic review for several reasons.[153] The link, as explained earlier with the logo of the Cochrane Collaboration and Miranda's subsequent cost-effectiveness ~~[cost-benefit??]~~ studies, showed that this was one of the few areas where there had been economic cost savings as well as health gains.

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[151] Rogers E. (1995) *Diffusions of Innovations*, 4th edn. New York, NY: The Free Press. See page 259 for the S-shaped curve.

[152] Hanney *et al.* (2005): 938.

[153] Crowley *et al.* (1990).

Yes – Hanney et al 2005

A few years later there were several policy statements advocating the use, in the form of clinical guidelines from professional bodies and, as is said in the paper [??which paper?? Hanney *et al.* 2005??], these did cite the systematic review, again emphasizing the importance of this particularly review.[154] I hadn't realized until he spoke quite how explicitly Richard [Lilford] looked through systematic reviews to produce the clinical guideline on that, and clearly the systematic review there influenced the policy guidelines. There were also these important implementation initiatives. There's one that's been mentioned. All these factors seem to have resulted in quite a dramatic increase in uptake during the 1990s. There's the figures from your study, Richard, and figures in 1997, from your survey, Peter [Brocklehurst], which shows a very large uptake by the end of the 1990s. Miranda's analysis suggested that with 75 per cent uptake there would be more than 400 deaths averted annually in England and Wales. So clearly, there has been quite a big health gain. The problem though, as has already been mentioned, without putting a precise figure on this, is that with the use of surfactant and the improvement of the neonatal care, it is not clear of course that all these deaths would have actually happened if there hadn't been the use of steroids. But nevertheless as has been said there is also evidence that even if some of them would never have happened, surfactant wouldn't have stopped all of them. What I think is unclear, is whether there is an actual measure of how many. So definitely this has had substantial health gain as well as impact on policy, knowledge gain, impact on further research.

Mention has been made of the US NIH concensus conference.[155] This was broadly endorsed by the American College of Obstetricians and Gynecologists and it is claimed that this consensus statement had more impact than most of them.[156] An implementation project found that after a year of passive

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

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

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

dissemination, implementation of the guidelines went up to 58 per cent, which is quite substantial.[157] But following active dissemination it went up from 33 to 68 per cent. So it does seem that there are many elements of this whole stream of research that have produced benefits. Perhaps the key thing from our work on this stream of research that is different from some other perspectives in the debate about research utilization, is that our work has been concentrated on showing that benefits have been achieved even when the uptake level has been less than optimum.

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

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

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

Chalmers: We keep on talking about benefits in terms of the baby, but what about the parents? The reduced exposure to the terrible courses that babies would go through before death, and indeed before surviving – and the accompanying anxiety –those things haven't been made explicit. We had hoped that there would be a woman here who had received prenatal

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[157] Leviton *et al.* (1999).

corticosteroids.[158] I was impressed by Barbara Stocking, now chief executive of OXFAM, saying that in her first pregnancy she had delivered prematurely and her son went through a really rough time. After she read Patricia's systematic review before her second pregnancy, she insisted that she should have steroids if she went into preterm labour again. She became a big advocate of prenatal steroids when she was a senior manager in the NHS. I have come across more than one mother – maybe Gill Gyte can enlighten us here – who has lobbied to have this. Obviously, as parents, they think this is important, because they are worried about their children. But possibly also so that they have less to worry about themselves.

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

Oakley: This is slightly beside the point, or perhaps not, because I think this issue of the role of the users of health services and the extent to which they are demanding evidence is a very important one and it's something that we need to know more about. But of course one of the problems with that, or one of the issues in that area, is that first of all the user needs to be dissuaded from the belief that experts know what they are doing. I remember one of the early projects that I worked on in 1974 involved an observational study of an antenatal clinic at a hospital in London that, of course, has got to be nameless, and I hung around this clinic for about a year observing what the doctors were doing. I was absolutely astonished. In my second week, there was a changeover in junior doctors, and two of them came to me and they asked me what Consultant X would recommend in a particular case, because they didn't know what they were supposed to be doing because they hadn't met their consultant yet. I didn't realize that the eight different consultants who ran this clinic all

[158] More about patient???

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.

Wendy Kutner

To: m.hanson@soton.ac.uk
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

CortiHANSONltr.doc

Dear Professor Hanson, Your name and e-mail address have been sent to us by Professor Marelyn Wintour-Coghlan (Australia) in connection with the above meeting. Please see the attached letter. Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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Euston House
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Professor Mark Hanson
Southampton University

m.hanson@soton.ac.uk

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

31 March 2004

Dear Professor Hanson

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 15 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.

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.

We have drawn up a list of possible participants, including clinicians and representatives from relevant organisations, and would like to include physiologists/endocrinologists from the 1960s and early 70s. Sir Graham Liggins is unable to attend but Dr Mary Ellen Avery has agreed to introduce his work. Professor Marelyn Wintour-Coghlan in Australia has suggested I contact you to see whether you would be able to help with names of scientists, (preferably based in England, as we don't have the means to fund overseas travel) particularly those who were involved in the work on sheep during the 1960s.

I look forward to hearing from you and do hope you will be able to help.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

Wendy Kutner

From: Professor Mark Hanson [m.hanson@soton.ac.uk]
Sent: 31 March 2004 17:21
To: w.kutner
Subject: Re: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Hi

I would suggest that Prof Daffyd Walters and Prof Sir Robert Boyd (St Georges) would be good people. Prof Osmond Reynolds would also be good, but I don't know how much he attends meetings these days. Dr Paul Johnson (Oxford) would be another possibility. I was not sure if you wanted me to attend - I did not really commence work in this area until 1979!

regards

Mark Hanson

----- Original Message -----
From: "Wendy Kutner" <w.kutner@ucl.ac.uk>
To: <m.hanson@soton.ac.uk>
Cc: "Daphne Christie" <ucgachr@ucl.ac.uk>
Sent: Wednesday, March 31, 2004 2:16 PM
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

> Dear Professor Hanson, Your name and e-mail address have been sent to us by
> Professor Marelyn Wintour-Coghlan (Australia) in connection with the above
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> w.kutner@ucl.ac.uk
> www.ucl.ac.uk/histmed
>
>

Wendy Kutner

To: Professor Mark Hanson
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Professor Hanson, Thank you very much for your reply. I have today sent invitations to Professor Walters and Sir Robert Boyd. We would be delighted to have you at the meeting if you would like to attend as all interested parties are welcome. We will be sending out further details prior to the meeting, so will await your reply then. Yours sincerely, Wendy Kutner

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Wendy Kutner

To: Deborah Peach
Cc: Daphne
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Deborah, Thank you for your e-mail. We are sorry that Professor Hanson is unable to attend. We will keep his details on our database and will send him details of the transcript when it is published in 18 months to 2 years time. Wendy Kutner

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-----Original Message-----
From: Deborah Peach [mailto:D.J.Peach@soton.ac.uk]
Sent: 27 April 2004 13:13
To: w.kutner
Subject: Re: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Wendy

Many thanks for the invitation for Professor Hanson to attend the Witness Seminar on 15 June. He was planning to attend but unfortunately now he will be abroad on this date. Our apologies and we hope this had not caused too much trouble!

Many thanks

Deborah
PA to Professor Mark Hanson

> ----- Original Message -----
> From: "Wendy Kutner" <w.kutner@ucl.ac.uk>
> To: "Professor Mark Hanson" <m.hanson@soton.ac.uk>
> Sent: Thursday, April 01, 2004 4:35 PM
> Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004
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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 10:25
To: Wendy
Subject: FW: Wellcome Meeting

wendy - we need to deal with this asap. Daphne

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 14 April 2004 23:14
To: 'shey@easynet.co.uk'; 'ichalmers@jameslindlibrary.org'
Cc: 'd.christie@ucl.ac.uk'; Stuart Dalziel
Subject: Wellcome Meeting

Dear Iain and Ed,

Thank you both for your kind and enthusiastic words about our latest 'little' project. I must say I am quite excited about it, having been initially trained in Auckland with Mont Liggins and Ross Howie amongst my teachers. In fact, the office from which I write now used to belong to Ross Howie, and the original trial data sheets from which we traced the subjects 30 years later have lived in the cupboard in this office for many years (and still do).

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I shall look forward to hearing more about the seminar. I do hope we will be able to make some arrangements for a 'down under' contingent to be present.

Best wishes

Jane

Jane Harding
Professor of Neonatology
University of Auckland
Private Bag 92019
Auckland, New Zealand
Ph +649 3737599 Ext 86439
Fax +649 3737497

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

TRANSMISSION OK

TX/RX NO	2093
CONNECTION TEL	9006493737497
SUBADDRESS	
CONNECTION ID	
ST. TIME	22/04 13:48
USAGE T	04'10
PGS.	10
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 Jane Harding
Department of Neonatology
University of Auckland
Private Bag 91029
Auckland
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

20 April 2004

Fax: 00 649 373 7497

Dear Professor Harding

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

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

TRANSMISSION OK

TX/RX NO	2090
CONNECTION TEL	9006493737497
SUBADDRESS	
CONNECTION ID	
ST. TIME	21/04 10:01
USAGE T	04'29
PGS.	9
RESULT	OK

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

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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.

As one of the members of the team who are working on the long-term follow up of the patients from the seminal Liggins and Howie trial Sir Iain Chalmers and Dr Edmund Hey feel that your attendance would greatly enhance the success of the meeting. I am writing, therefore, to enquire whether, in principle, you would be able to travel to England to participate as a main witness on Tuesday 15th June 2004. Unfortunately, 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 and will reserve an extra night's accommodation if you require it.

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: Wendy Kutner [w.kutner@ucl.ac.uk]
Sent: 22 April 2004 14:49
To: j.harding@auckland.ac.nz
Subject: Witness Seminar: Prenatal corticosteriods - 15th June 2004

WHATIS--april2004revdc.DOC

Apologies, I didn't attach 'What is a Witness Seminar', attached herewith.
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

Wendy Kutner

To: j.harding@auckland.ac.nz
Subject: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth


CORTIHardingSEASinvltr.doc... OVERDRAFTcorticoFLYER 190404.doc

Dear Professor Harding, I attach an invitation letter with attachments, inviting you to the above meeting and apologise that you have not received our fax of yesterday, which I will send once again after I have sent you this e-mail. We very much hope you will be able to attend this meeting. Yours sincerely, Wendy Kutner pp Dr 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

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 06 May 2004 16:19
To: Jane Harding
Cc: Wendy
Subject: RE: Wellcome Meeting

Dear Professor Harding
I do hope that you have received our invitation to attend the Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth', on Tuesday 15 June 2004. It would be wonderful if you were able to join us.
We have now drafted a programme which I attach for your information. If you are able to attend, we would be grateful if you could start the proceedings, with a brief presentation (5–10 minutes) to include a description of how the work by Liggins and Howie came to be done as well as a brief summary of the 30 year follow up study that you are doing. Mel Avery would then follow you (see item 4 on the agenda, >From ewes and lambs to women and babies). 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.
If you would like to include a brief recorded message (up to 5 minutes) from either Liggins and/or Howie specially for the seminar, we would be happy to make necessary arrangements for this to be played at the meeting.
I look forward to hearing from you.
With best wishes
Daphne Christie

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 14 April 2004 23:14
To: 'shey@easynet.co.uk'; 'ichalmers@jameslindlibrary.org'
Cc: 'd.christie@ucl.ac.uk'; Stuart Dalziel
Subject: Wellcome Meeting

Dear Iain and Ed,

Thank you both for your kind and enthusiastic words about our latest 'little' project. I must say I am quite excited about it, having been initially trained in Auckland with Mont Liggins and Ross Howie amongst my teachers. In fact, the office from which I write now used to belong to Ross Howie, and the original trial data sheets from which we traced the subjects 30 years later have lived in the cupboard in this office for many years (and still do).

I am delighted to hear that some of the fantastic work of this remarkable pair of people might be recorded and acknowledged in some way (and I agree with the sentiment that the importance of the Paediatric component has not always been recognised). However forgive my ignorance, but I have no knowledge of the seminar to which you refer. Is it possible to get some more details? One or both of us might be tempted by the opportunity to 'represent' in some way how the original study happened and all the subsequent ramifications, but you will understand that travel

from NZ to UK is tedious and expensive and we will need to think further about it once we have some more information. Even a small financial contribution is also likely to help!

I shall look forward to hearing more about the seminar. I do hope we will be able to make some arrangements for a 'down under' contingent to be present.

Best wishes

Jane

Jane Harding
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Private Bag 92019
Auckland, New Zealand
Ph +649 3737599 Ext 86439
Fax +649 3737497

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 11 May 2004 09:14
To: Alan (E-mail)
Cc: Wendy; Tilli Tansey
Subject: FW: Wellcome Meeting
Follow Up Flag: Follow up
Flag Status: Flagged

Dear Alan
Are you happy for me to offer her two nights accommodation and say £100 towards her air fare from New Zealand? Thanks, Daphne

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 10 May 2004 10:37
To: 'd.christie@ucl.ac.uk'
Cc: 'shey@easynet.co.uk'; 'ichalmers@jameslindlibrary.org'
Subject: FW: Wellcome Meeting

Dear Dr Christie,

My apologies for the delay in replying to your invitation and e-mails. I am certainly very interested in coming to the Witness Seminar and have been working on clearing my diary to make this possible. To be honest, the financial issues are also a substantial consideration when travelling from NZ. I wonder if it would be possible for you to fund the minimum of two nights accommodation in London that I would need, and also make at least some small contribution to an airfare, perhaps equivalent to whatever internal fare within the UK you think is reasonable?

On the assumption at least some additional assistance will be forthcoming, I shall aim to join you in London in June. I shall ask Liggins and Howie if they would be prepared to record a few words for the seminar, and also if there is material they would like me to make available to the group.

I shall look forward to hearing further from you in due course, and to meeting in person very soon.

Regards

Jane

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Ph +649 3737599 Ext 86439
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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 11 May 2004 09:52
To: Jane Harding
Cc: Wendy
Subject: RE: Wellcome Meeting

Dear Professor Harding
We are delighted that you are hoping to join us for the Witness Meeting on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' in London in June. We are pleased to say that we are able to fund three nights accommodation in London and also to make a £100 contribution to an airfare.
It would be great if Liggins and Howie would be prepared to record a few words for the seminar.
I do hope that you are able to attend as a key witness and look forward to hearing from you.
With best wishes, Daphne

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 10 May 2004 10:37
To: 'd.christie@ucl.ac.uk'
Cc: 'shey@easynet.co.uk'; 'ichalmers@jameslindlibrary.org'
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Regards

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www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

DC to edit

12 May 2004

Dear Professor Harding

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

We are delighted that you may be 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 already 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. your presentation we would also like to include Also a brief description of the 30 year follow up study.

We would be very grateful if you would be prepared for the Chairman to call upon you to give a short presentation for about 5 minutes, on behalf of Professor Mont Liggins and Professor Ross Howie. 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.

on how their work came to be done

As agreed, we are able to contribute £100 towards the cost of your flight and whilst you are in the UK. The Wellcome Trust Centre for the History of Medicine at University College London will reimburse your return travel costs to the meeting only if supported by suitable receipts. They are inflexible in this matter.

We would also like to arrange three night's accommodation for you at The Hotel Ibis London Euston: for Monday 14th and Tuesday 15th June, and either Sunday 13th or Wednesday 16th June. I would be most grateful if you could contact me upon receipt of this letter, d.christie@ucl.ac.uk or 0044207 679 8125 to confirm your requirements. Again, please note that University College London will only pay for accommodation reserved and authorised by us.

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.

Dr Tilli Tansey and I would like to invite you to join us for an early supper at a local restaurant after the meeting. We should be finished by 9pm ~~to give you ample time to return to the hotel~~. Please let me know whether you are able to attend the supper (d.christie@ucl.ac.uk). You may also contact Mrs Wendy Kutner (w.kutner@ucl.ac.uk) 0044 207679 8106 or myself if you have any queries on the above or would like any further information.

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.

Professor Jane Harding FRACP FRSNZ,
Dept of Neonatology, University of Auckland,
Private Bag 91029, Auckland,
NEW ZEALAND

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Continued/ Page 2 …

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Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 02 June 2004 12:09
To: Wendy
Subject: FW: witness seminar 15 june prenatal corticosteroids

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 18 May 2004 08:48
To: Jane Harding
Cc: Wendy
Subject: RE: witness seminar 15 june prenatal corticosteroids

Dear Professor Harding
Thank you for your e-mail. It really is great news that you will be joining us for the meeting.
We will make the necessary arrangements for your accommodation and let you know if there is any problem with late check-out.
With best wishes,
Daphne Christie

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 16 May 2004 20:54
To: 'd.christie@ucl.ac.uk'
Subject: RE: witness seminar 15 june prenatal corticosteroids

Dear Dr Christie,

Thank you for your letter and the attached programme. I would be pleased to join you for supper after the meeting on the 15th, and shall look forward to meeting you.

+ £50

Regarding accommodation, I will only need this for the nights on Monday 14th and Tuesday 15th, though I would be very grateful if late check-out could be arranged for the Wednesday, ideally until about 7pm. I will need to return to NZ that night, and it is most helpful to be able to use the room during the day before leaving. Can I presume that you will make this booking directly?

I shall talk to Profs Liggins and Howie about how they would like their work presented. I fear they may be less than forthcoming, but perhaps I will be wrong. I shall certainly do what I can.

Regards

Jane Harding
Professor of Neonatology
University of Auckland
Private Bag 92019
Auckland, New Zealand
Ph +649 3737599 Ext 86439

Fax +649 3737497

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 19 May 2004 11:53
To: Wendy
Subject: FW: witness seminar 15 june prenatal corticosteroids

please make necessary arrangements. thanks, daphne

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Regards

Jane Harding
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University of Auckland
Private Bag 92019
Auckland, New Zealand
Ph +649 3737599 Ext 86439
Fax +649 3737497

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 21 May 2004 11:39
To: Wendy
Subject: FW: copy of my letter for Jane

-----Original Message-----
From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 20 May 2004 11:57
To: Jane Harding
Cc: Daphne Christie (E-mail)
Subject: Fw: copy of my letter for Jane

Jane,

I am relieved to hear that you will be able to make the meeting on June 15 and to see that Mont has agreed to help you recount some of this for 'posterity'. Iain and I had not wanted to give you yet more work to do when he first suggested that you might like to put something together with my help after the meeting was over for publication in the new journal Clinical Trials.

Indeed, Iain had originally made that suggestion merely in the belief that your own people might have been able to offer some contribuition towards the cost of the trip if it put you in a position to be able to say that the trip would generate an 'authored' publication afterwards.

I quite realise that the History of Medicine unit here in London does not have unlimited funds. However, given that it was the main Foundation's chief excutive who first suggested the possibility of such a meeting I had thought that some way might have been found of covering more of the cost you have incurred in helping us out in this way. It might not have cost quite as much had you been given more than six weeks warning of the invitation coming your way.

I have put something in the post to you today.

Edmund

-----Original Message-----
From: Iain Chalmers
Sent: 20 May 2004 08:05
To: 'g.liggins@auckland.ac.nz'
Subject: RE: copy of my letter for Jane

No problem, Mont. I'll put copies in the post to both of you today. We're very glad that Jane is going to be representing the Auckland team at the seminat, although I'm peeved that the second richest medical research charity in the world is contributing only £100 towards her travel expenses. Best wishes, Iain

-----Original Message-----
From: Graham Liggins [mailto:g.liggins@auckland.ac.nz]
Sent: 18 May 2004 22:44
To: ichalmers@jameslindlibrary.org
Subject: copy of my letter for Jane

Dear Iain,
Could I trouble you to send a copy of the long letter I sent you some time ago containing my account of historical events to Jane. I seem to have mislaid my copy. She would like to use it in preparing her material. She intends perusing an oral history I recorded some months ago to see whether it contains material that would be useful for you.

I have promised to help if it is decided to prepare a manuscript for a journal publication.
Best regards, Mont

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 02 June 2004 09:40
To: Jane Harding
Cc: Wendy
Subject: RE: Witness Seminar on Corticosteroids

Dear Professor Harding
That's great news.We will make the necessary arrangements for a player to be available at the seminar.How long is the recording?
Wendy Kutner will e-mail the contact details of the hotel.
We wish you a safe journey.
With best wishes
Daphne Christie

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 01 June 2004 11:04
To: 'd.christie@ucl.ac.uk'
Subject: Witness Seminar on Corticosteroids

Dear Dr Christie,

I am pleased to tell you that I have obtained a recording of Mont Liggins describing some of his original work, which he has agreed that I can use at the seminar. It is on an ordinary cassette tape, which I can bring with me, If you are able to arrange for a player to be available at the seminar.

On a different topic, please could you confirm the contact details for the hotel that I presume you have booked (address, phone and fax numbers etc). I am travelling in Australia before the meeting and leave NZ this Friday (4th). I expect to be able to look at e-mails occasionally but unpredictably while I am travelling, so it would be helpful to have any last details regarding this and any other arrangments before I leave.

I look forward to hearing from you, and to meeting you soon.

Best wishes

Jane

Jane Harding
Professor of Neonatology
University of Auckland
Private Bag 92019
Auckland, New Zealand
Ph +649 3737599 Ext 86439
Fax +649 3737497

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 02 June 2004 11:09
To: Wendy
Subject: FW: Witness Seminar on Corticosteroids

wendy - for the files

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 02 June 2004 10:52
To: 'd.christie@ucl.ac.uk'
Subject: RE: Witness Seminar on Corticosteroids

Dear Dr Christie,

Thanks for your note. I thought that I would play perhaps 3-5 minutes of the tape, depending on how tight the timing is.

I shall look forward to hearing from Wendy, and seeing you soon.

Best wishes

Jane

Jane Harding
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Wendy Kutner

From: Jane Harding [j.harding@auckland.ac.nz]
Sent: 02 June 2004 19:59
To: 'w.kutner@ucl.ac.uk'
Subject: RE: Witness Seminar - Prenatal corticosteroids - 15 June 2004

Dear Wendy,

Many thanks for that information. It is very helpful.

Regards

Jane Harding
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Wendy Kutner

To: j.harding@auckland.ac.nz
Subject: Witness Seminar - Prenatal corticosteroids - 15 June 2004

Dear Professor Harding, I confirm that your accommodation has been reserved for the nights of Monday 14th and Tuesday 15th June, with late departure up to 7pm on Wednesday 16th June as requested, at the Ibis Hotel Euston, 3 Cardington Street, London NW1 2LW (tel: 00 44 207 388 7777) (fax: 00 44 7388 0001) (e-mail: H0921@accor-hotels.com) www.ibishotel.com. There is a location map at their website, but for your information, Cardington Street runs parallel to the Euston Road, directly behind Euston Station and is also very close to the Wellcome Building (diagonally opposite Euston Station) and to the restaurant where the supper will be held after the meeting in Eversholt Street. There is also a location map on the Wellcome Trust website, where the meeting is being held at www.wellcome.ac.uk I do hope this reaches you before you leave New Zealand. Please contact either Daphne or myself if you have any queries on the above. Wendy

Mrs Wendy Kutner
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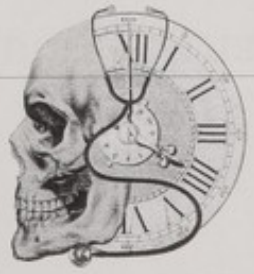

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16 June 2004

Dear Professor Harding

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.

We particularly want to thank you for travelling from New Zealand to attend the meeting. Your personal contribution was much appreciated and added to the success of the meeting.

Yours sincerely

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.

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****

1. NAME Professor Jane Harding FRACP FRSNZ

2. ADDRESS Liggins Institute, Faculty of Medical & Health Sciences,
~~Dept of Neonatology~~, University of Auckland
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3. WITNESS SEMINAR: Prenatal Corticosteroids for Reducing Morbidity and Mortality
15 June 2004

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HARDING ucd 19.1.05 Acc "

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

space pages removed.

7-8 June 05 corrected

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

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~~ Liley, 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 ..... that the cortisol had accelerated the maturation of enzymes in the lung that caused accelerated maturation. Now at that time ……..facilities were kind of occupying 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 discoveries that surfactant was necessary for the maintenance of lung expansion. So we were going to New Zealand and I was at a meeting in Christchurch and described my findings in this, well it was a series of lambs actually, with expanded lungs. She couldn't ..... get back to Boston fast enough to 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

I do not know what was said here. If nobody else can help, get back to me and I will try to retrieve the original tape again

> 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 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 was 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,

> supervised the collection of data and did all the work in analysing it. I still remember the excitement I felt when he handed me the lungs of twin lambs for pressure volume studies. The lambs had been delivered very early. One had been infused with ~~liquid corticoids~~ glucocorticoids and the other not. Lungs of the infused lamb were perfectly stable after inflation, pink, fluffy and floated in water. In total contrast, the lungs of the other remained solid and liver-like, and sank.

There are a couple of things that interest me about these descriptions. One is the unique pairing of an experimental scientist who was also an obstetrician, with the only paediatrician in the country who was capable of looking at the babies. Another is that whatever the later perceptions became, it's clear that both the authors of the study were involved together from the beginning, in the animal laboratory, as well as in the clinical aspects. Finally, I am entranced with Ross's comments that this lamb trial was simply a sideline for both of them. It's an interesting warning against the narrow and predetermined end points of some research programmes, and highlights the importance of serendipity in ~~progress~~ stet. Ross describes presenting the results of the completed study, not the initial part of the study that was published in 1972, but the completed study, at a symposium hosted by the Royal College of Obstetricians and Gynaecologists of the UK in 1977. He said to me, 'They didn't really want to hear'. He also reported that when he was asked for a recommendation as to what people should be doing, he said that the treatment looked very promising, but that it would be unsafe to initiate a new treatment on the basis of a single trial. He said that he knew what he should do, but

that others should wait for ongoing trials. Other people here can talk about the progress of the treatment after that time. My own involvement began perhaps when I entered medical school in 1973. Both of the principal actors were my tutors. The use of antenatal steroids was routine at that time in our hospital and has remained so ever since. By this time Mont had moved onto other studies. Ross was completing the four- and six-year follow up of the original cohort, funded by the World Health Organization. He always believed very strongly that long-term follow up was essential for anything in neonatal care and set about this with his usual thorough approach. The follow-up studies were published in the early 1980s and the ongoing follow-up studies we will talk about later.

Hey: Thank you very much. Would you like to explain why they chose the steroids that they did, because a lot of people now seem to have noticed, and most people even when they think they are using betamethasone, are not using the product that Ross and Mont did? They think it is betamethasone, full stop.

Harding: I can tell you that story because I specifically asked both of them in recent weeks. To paraphrase the ~~lung~~ long story. Mont had been doing work in human pregnancy on the effects of steroids on the fetus, and he had a reasonable idea of what dose of steroid was required to suppress progesterone production and he presumed that that would be an adequate dose to do something to the fetus. He knew that he wanted something that would be reasonably long-

lasting, so that it didn't have to be given too frequently to pregnant women and decided that something that would last for 24 hours and therefore two doses would give you about a 48-hour effect would be adequate, based on the animal studies. He therefore set about looking for a drug that would be clinically easy to manage, long-lasting, and which had an identically appearing placebo. This is not easy, because all the long-lasting preparations of glucocorticoids are opaque, they are milky substances, and a placebo wasn't easy to find. He wrote to a number of drug companies, asking for help, and in the end Glaxo, which was originally a New Zealand company, and it so happened that the medical director was a mate of Mont's, ~~came up with, they~~ said they would provide an opaque placebo. Their long-acting preparation was the one he used, because that was the one that was available and they were provided with the placebo. So the placebo was cortisone acetate, which had very low potency but looked the same, and the drug that he selected was the Glaxo drug because that's what was available and because the director was a mate who provided it for free. The study was unfunded I might say. Mont said to me "we didn't need funding to do this trial." And of course they didn't need funding, because the drug was provided for free and both Mont and Ross were fully salaried and were able to put in all of their time.

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

Harding: Twelve hundred. I could look up the real number, just over 1200. *

* The actual number was 1218

Hey: Still the biggest trial.

Harding: Still the biggest trial. The original publication that everybody ~~sights~~ cites from 1972 was only the ~~first 418, I think~~ first 282. But they continued to recruit long after that trial. If I could just comment. The other thing that most people aren't aware of is in fact after the first ~~400 and something~~ 717 women were enrolled, and when they did the first analysis, thought the stuff really does work," they doubled the dose. In the rest of the trial, the other ~~800~~ 500 odd actually received twice the dose, to see whether more was better, and they concluded that it was not, and published all of the data as a combined single trial, ~~1200 and something~~.

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

Harding: That's correct.

Hey: Were the fresh patients actually randomized, did they start right from the beginning.

Harding: They truly did start randomizing at the end of 1969 and it really was the beginning of the trial. 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 also 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.

I do not know what was said here but this does not make sense.

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 ~~...~~ Bird ventilator and started using (?) CPAP in the 1970s which was before Gregory's publication on (?) CPAP 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 seepep~~ 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. He also describes I think in that paper, but certainly to me, at the end of the trials, in 1975 he went to Geneva 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 respiratory distress syndrome while he was away, 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 this because I know a little bit about the history of the National Women's Hospital in Auckland and it doesn't have a very good history itself in terms of ethics of trials. 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 will be verbal consent. And like probably you and a

number of other people I wondered how real and how effective that process was at the time, and I can tell you that 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 that we weren't sure how informed the consent was. We have been overwhelmingly impressed with how positive people were about the trial. In the end we traced 75 per cent of the original participants and a number of the children, now 30-year-olds, obviously did not know they were part of this trial, and they went back to their mothers and sometimes we traced the mothers rather than the children, there were a few women who did not recall being part of the trial. I think that's unsurprising given the circumstances. Remember that the (?) for the first three years of the trial was epinol. IV epinol was the tocolytic (?) used until 1970. However, the vast majority of women did recall that they were in the trial and recalled it very positively, and 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 they had a preterm baby who survived as a result of this trial, as they perceived it, and were very positive about it. So 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 30 years later was very positive.

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 coming along were convinced they had had steroids because they survived, and we have done our best not to unblind them, because we think 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 the mothers of the babies who did not survive, we didn't trace.

Professor Dafydd Walters: Could you remind us of the gestation, the youngest gestation of this group of babies.

Harding: Given a moment I could look it up, but from memory the youngest gestation was about 28 or 29 weeks, and the average gestation at delivery was around 35 weeks.

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

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

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

Sir Iain Chalmers: Jane, these mothers and children that you are in touch with, I don't know whether you have tried to do this already, but it would be wonderful if they came to know just how important a contribution they made to the history of perinatal care, and if you haven't planned to do that already, during the contact with them, could you think about doing that.

Harding: We tried very hard to emphasize, this is part of our recruitment process, as you can imagine. Getting 30-year olds, who are busy with family and life and career and everything else, to come along and have fairly extensive testing is not an easy topic, and we did

spend a great deal of time and energy trying to explain to the participants and their mothers how important this trial was and how important it was to know what effect it may have in the long term

TAPE ONE: SIDE TWO: .... But as I think I have already alluded to, people were very, very positive about the whole experience of being involved in the trial, which really reassured me immensely about the consent process and the whole management of the trial.

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

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

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

Avery: At the meeting in Christchurch. Well I had given the most boring paper I ever gave in my life, describing the time of onset of a whole bunch of things we could measure to map out the terrain of the maturation of different organs in the lamb, knowing that we were particularly interested in lambs. Why did we tumble to that, well it was partly that Mont wanted those figures. He needed them, and they were different from what he expected. And the difference turned out to have been that some of them got steroids and some didn't, and the ones that were advanced had the steroids. There was a concern that that would be a permanent effect if they were, 'maybe treated in utero but injured in some way by the steroid, that they would grow up with small lungs or some failure of the lung to perform in some way, and so he needed all the information he could get about safety. And I think published our first paper on six sets of twins. That wasn't a very big series, but six out of six, which showed the same result. But it meant that …[?] data were pretty secure, but the next question was what happens when they are ten years old, and fortunately some of the follow up has been done and it turns out that the lungs play catch-up just as children on steroid therapy for a month for whatever disease, when you withdraw it, you see their growth curves flat while they are on steroids, and then they catch up and hit the very level that was predicted before. Well catch-up growth takes place in these babies. And that's quite remarkable. Maturation at the expense of cell division. Take away the stimulus of the cells, they do more than they would have done otherwise and 'catch up'. I think others in this room might be better students of this phenomenon than I am, and I turn the microphone over.

Gabbay: If I could just pursue that for one second. You have taken us into the science of it. I was interested if you like in the community of scientists who were interacting, and how it was you came to be discussing, 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.

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.

Dr Daphne Christie: Dr Tilli Tansey has tried to find out some information about this, so we might be able to get back to you later on this.

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

Harding: I think at that time it would have been a very large grant in New Zealand, and it was probably the only one, because I am pretty sure Mont only had the one block of funding to work on the sheep

initiation of parturition work. I have already commented that the clinical trial itself was never funded, because they just did it.

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

Harding: He did all that before he came back, and when he came back was when he had the Wellcome funding to start his own lab.

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

Harding: That's correct and he had presumed that that would be the case, ~~and~~ when he was on sabbatical at UCL Davies devised a way of doing the hypo~~the~~physectomy and did the initial experiments there and then came back to set up a sheep lab in New Zealand with Wellcome Trust funding at that time. So I think that was probably the one and only (grant) and very large at that time for working expenses.

Hey: One of the things that we learn is that sometimes, as Maureen Young will tell us, you cannot jump from species to species, and

sometimes you can, and that hypothesectomy doesn't work and steroids do.

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

Hey: We ought to move on and start listening to what happened when people started pulling the many other trials. Ross sounded as though he actually encouraged other people to go ahead and do more trials, mostly of which seemed to have occurred in the USA.

Harding: That's true, Ross was very much, and still is, of the view that even if a treatment did work, and he was convinced that this treatment did work in his hands, that it was unlikely to work all of the time in all groups of patients, under all circumstances, and he was very concerned about the potential long-term risks as were most other people at that time. He remained unapologetic for that in the sense that you know medicine is not simple, biology is not simple, and there's no point in pretending that it is. He was convinced that even if this treatment worked, it may not work in some groups, and it may have adverse effects in some groups. He felt it was important that other people tested this in other places, under other circumstances, in other groups, and he also thought it was critical that the long-term

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~~ NIH trial, which we will no doubt come to, and the follow up was still going on at the time that the Auckland trial follow up was completed. 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 by starting with a little bit of personal recollection. I first heard about antenatal ~~cure steroids~~ corticosteroids 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 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

and if we take all the 1000 babies who received antenatal steroids, in part of randomized trials during the 1980s, and the 1000 babies who received placebo during the 1980s, 130 of the babies who received placebo died, and 70 babies who received antenatal steroids died, during trials performed in the 1980s. But perhaps the people recruiting for the collaborative trials in the NIH were unaware of these results and had they been aware of these results it would have been very difficult to persuade anyone to be randomized to placebos in the late 1970s or early 1980s. As the 1980s progressed, I methodologically updated the list of trials that I had in my possession, and because the papers that ensued from the US collaborative trials, I became interested in sub-group analysis of these outcomes. The US collaborative trials from the NIH gave rise to a huge number of sub-group analyses and it was noted that antenatal steroids worked best between 32 and 34 weeks and didn't work in white males, and did work in black females, and nonsensical sub-group analysis arose, and because they were being produced in the literature, I went back to the collection of trials that I now had and looked at what happened to white males in Auckland and found they benefited from antenatal steroids. And so that was how so many of the sub-group analysis that we produced in the original systematic review of randomized trials, that was how they came into being. It was driven by a need to refute constant output of editorials and reviews questioning the efficacy of antenatal steroids based on these sub-group analysis principally from the .....head collaborative study. So some form of systematic review of antenatal steroids was part of my life in various ways throughout the early 1980s, and at the conference I attended in Italy in 1984, showed that by then I was looking at the outcome of some seven trials, still

only preventing the confidence intervals in terms of P value and then in 1987 to 1988 the technology became available at the National Perinatal Epidemiology Unit to produce a systematic review, to enter the data from trials, and to generate all its residues (?). This review of antenatal steroids was, in fact, the first set of data entered on to the Oxford database of perinatal trials and it was a very exciting time when I .... the results of the review, which showed very attractive graphics and confidence intervals. I thought at that time, in 1988/9 when the results of this international review were published in electronic format and then in the book *Effective Care in Pregnancy and Childbirth*, I thought that this information was out there and acceptable to obstetricians around the world, and I didn't think that any further publications were necessary. However, I was eventually persuaded by Iain Chalmers – persuaded or bullied – into producing a paper version of this dramatic review, which was published with Iain Chalmers, Marc Keirse, and myself in 1990 in the *British Journal of Obstetrics and Gynaecology*, and looking at practise throughout the world with respect to antenatal steroid use, it's only after 1990 that we can see any more than 20 per cent of preterm babies being exposed to antenatal steroids, any further steps in Australia and New Zealand, work from Bob ~~Kitchlin~~ Kitchen in Melbourne in the 1970s, showed 45 per cent of Melbourne babies in the 1970s were treated with antenatal steroids prior to delivery. Anywhere around the world, it fell often under 10 per cent and never higher than 20 per cent, up to 1990. So the publication of this paper in the *British Journal* was a landmark in terms of improving the use of antenatal steroids.

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 ..... 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. 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 update 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.

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 Petra 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

question that there can be white matter problems which she has documented and published, which have to be read and thought about I think. 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 randomized trials we have always kept an eye on intraventricular haemorrhage and periventricular leukomalacia and it's reduced by antenatal steroids across the gestational ages and it's only in babies exposed to postnatal steroids where there is an adverse outcome with use of postnatal steroids, but not with antenatal steroids. Antenatal steroids are protective in terms of neonatal neurology, whether you look at the brain at autopsy or with imaging techniques for periventricular leukomalacia. Would you agree with that Jane?

Harding: If I could come back to briefly address Richard'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 Seventh Ross Conference on Paediatric Research which was I think about 1979, but I don't have a date on the paper. [From the floor: 76]. It was one of the places where ~~Mark~~ Liggins reported outcomes of the Auckland trial, ~~and~~ he also reports the outcomes of L/S ratios ~~and~~ amniotic fluid

before and after steroid treatment, and points out that they don't change consistently, so that amniotic testing ~~on the~~ for fetal lung maturation didn't reflect clinical lung maturation. And his concluding paragraph I was reminded of, and which is why I dragged it out,

> We have not attempted to select patients on the basis of assessment of pulmonary maturation from amniotic fluid analyses. In pregnancies beyond 34 weeks, in which the risk of RDS is low, a strong case can be made for giving glucocorticoids only when the results of amniocentesis 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.

So well back then, they had considered the ~~phenatical (?), we~~ phenomenon, had picked the people to do, and concluded that it wasn't worth doing, except perhaps in people more than 34 weeks. If I could go back to the issue 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 ~~become in~~ come into widespread use, and they have both given me the same two general answers. One is that particularly in the UK they felt, 'Nothing good could come from ~~economies~~ 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 discouraging use, ~~and~~ 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 their toes, and that it was

actually paediatric versus obstetric issues in many centres that discouraged its use.

Mr John Williams: A humble obstetrician who is a recipient of the literature rather than a contributor. But I was developing during the era of these publications, and some of the things that struck me. The first was an oration by Sir Stanley Clayton in 1975 at the American Congress of Obstetrics and Oncologists, where he said that in his experiences the editor of the grey journal, *Commonwealth Journal* as it was then, how much rubbish was submitted for publication and he said that he wished that registrars didn't have to do research to get jobs, and it was time it was all stopped. That was the first thing that hit me. And I was then at a meeting in Cardiff where Cliff Robertson was speaking, and he seemed to be of the opinion that obstetricians shouldn't be treading on the toes of paediatricians, and that they were very good at looking after babies and we didn't need to interfere. And he went on to pour scorn on quite a lot of the uncontrolled and poor publications, and again this struck me. And I said, 'Well, why were these published if they were such bad studies?', and he said, 'Well you know people having a glass of whisky and refereeing a paper, if it's somebody they know they will put it in, if it's not they won't put it in'. He was fairly scornful of the poor quality publications, and it gave the impression certainly in Cardiff that we shouldn't be using steroids. And that set me back a little way. The poor publications continued to come out and were very confusing. In fact I wrote to Iain saying what's going on here, I want to carry out best practice. Paediatricians where I was then working in Chester were very keen,

based on the original work that we should be using steroids, and I said well everyone else says it's rubbish. And it wasn't until the systematic reviews and the guidelines came out that we actually introduced it as an overall …., we gave it to certain selected patients, but not overall. I think that was a common view among obstetricians in this country in a non-academic world.

Dr Roger Verrier Jones: There are two hospitals in Cardiff, two maternity hospitals, and John worked in the other one. The reason I am here is that Iain kindly asked me because he reminded me of a letter that I wrote to him in 1980, saying that we had done a retrospective study using steroids in St Davids Hospital in Cardiff, and that the results seemed to be quite startling. Now we had started using steroids in I think the late 1970s, I am not 100 per cent certain, based on the work that Liggins and Avery and others had done, and we were using steroids, although our obstetricians, in particular Joan Andrews, were relatively conservative, but we were using. I did a retrospective study, which I sent up to Iain and by then he had moved from Cardiff to the National Perinatal Epidemiological Centre in Oxford and the third figure seemed to be quite striking, in that we looked at 47 babies of which 11 had steroids and 36 didn't. The mortality rate was 0 in the steroid group and 28 per cent in the control group. When you looked at the incidence of RDS, the incidence in the steroid group was 18 per cent and in the control group 59 per cent . So on the basis of that certainly in St Davids Hospital, John you worked in the UHW, the University Hospital, we were using steroids, and continued to use them, but my memory is

Chalmers: I just wanted to comment on some themes which have come up about extrapolation from data in animals and if you like physiological data, or physiopathological data in humans and observational data in humans. I think one of the most remarkable things about Auckland was that Mont and Ross went directly from hypotheses they had tested in animals to see whether they were relevant to women. One of the things that gets me really annoyed is people working with animals who generate hypotheses whether it's about brain damage in the long time or some other sorts of things, but then do not exercise the self-discipline which Mont Liggins and Ross Howie did. I am going to give you one example that I came across in Oxford and it may be a little bit improper to speak ill of the dead, but I am going to tell you an anecdote about Geoffrey Dawes. Geoffrey Dawes was one of the hubs of perinatal physiological research in this country, and we often had arguments together along the lines that I have just been complaining about. I had the impression that he was very annoyed that he didn't make the discovery that Mont Liggins and Ross Howie made and I remember him in the 1990s, by which time I had moved to the Cochrane Centre, ringing me up in some glee, saying that he had discovered that steroids, this is an observational study, steroids had an apparent association with the pattern of fetal breathing movements, which he was very interested in. So I said to him, 'So what? You have now a mass of data from women and babies, if you have a hypothesis that's worth testing in terms of the relevance of your observations to human health, then test it, using the data, the mass of data that's now available from human experiments'. But there is this incredible lack of self-discipline where people who know how to design experiments in

animals actually don't know how to design them in human beings. They don't know how to design them or analyse them, as we have been hearing as a consequence of the dangers of sub-group analyses coming from someone faced with a statistically non-significant effect on death as it happened in the US collaborative trial. And it's just an example of very considerable scientific ill-discipline which Ross and Mont showed how well you could avoid. That's all.

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

Mont

Avery: Just a note, ~~Mark~~ 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 Mark was there.

Mont

UK, and then within a very short space of time, we were throwing it around like smarties, and I suppose what nobody has mentioned is that in order to get 90 per cent coverage of babies admitted to the neonatal unit, you have to give an awful lot of women antenatal steroids. I remember a lovely quote from Jacque Alferich (?) at Liverpool Women's Hospital. He said, 'If a woman under 34 weeks goes into Liverpool and burps, then she gets antenatal steroids'. They were giving so much of it, in order to get 95 per cent of babies admitted with steroids. And then the use of multiple courses of steroids, and now of course what's being considered more and more in the literature are the potential adverse effects, not just of multiple courses of steroids, but John Newnam's group which is coming up with evidence about the potential long-term hazardous effect of a single course of antenatal steroids on brain development. It's all very new stuff, but we may find ourselves going in a different direction to an extent. I think a lot of what is difficult about this issue, is that we are not very good at predicting preterm birth, and if we were better at predicting who was going to deliver preterm we would probably feel much more comfortable about using steroids in a much more targeted way. The concern is that currently probably at least 50 per cent of women who get antenatal steroids do not deliver preterm and therefore if there is long-term harm, it will be in those babies that will manifest it, and if we could target it better, we would probably all feel a bit more comfortable. So I just think we are beginning to go the other way, where people are actually being more cautious now with steroids than they were maybe even five years ago.

Crowley: Could I remind you that in the Auckland trial a lot more babies died in the placebo group, and therefore the survivors of prematurity of that time should in fact be neurologically worse? That there should be a disadvantaged group on steroids, because a lot survived prematurity. So if you have those people at 30 years of age, and if there's no difference neurologically at age 30, then it's unlikely that they taking steroids single-dose was doing any harm.

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

To come back to the issue of ruptured membranes, and I think it is fair to say in the mid-1990s there was still confusion about the issue, but the solution was not to do a new trial. The solution was to go back to the old trials. There had been at that time over 4000 women randomized, and the data was present from the original trials, they had just never been analysed, and in fact we in about 1994/5 and I cannot remember the exact date, but we had a debate around a clinical case at a clinical conference at my hospital, after which David Knight, who was the Director of the nursery at the time, said to me isn't that question answered. Surely the data must be there. Now just

parenthetically, David Knight was at the Barcroft Symposium in 1973, at which Mont presented the data, and that was one of the reasons that he came to New Zealand and ended up Director of the nursery. He got all excited about antenatal steroids and thought that he would come to Auckland. That's a slight aside. But it was David discussing this with me that prompted me for the first time to go back to Mont and Ross and say, 'You know all those files in the locked cupboard in the corridor where my office was, how would you feel about us getting them out and doing a new analysis, because I think the data might be there and we need to know the answer and it wasn't a question that you had asked at the time'. With enormous generosity they agreed that I could do that. I would hate somebody to come along 30 years later and ask for my data of any of my studies and reanalyse it, it's a very scary thought, and I think they were very brave. But they said yes, that would be fine, and the original trial data sheets, beautifully handwritten by Ross, were still in the locked cupboard in the corridor. They have lived in my office ever since, under lock and key. And we were able to retrieve from those, there was a code on the coding sheet that said ruptured membranes at trial entry, yes/no, so we were able to retrieve about 400 women who had ruptured membranes at trial, and even more remarkably we were able to go back to the hospital clinical records section and get out 80 per cent of the clinical records, which I think is phenomenal 30 years later, but they were still there. They have also lived in my office under lock and key ever since, and we were able to go back, retrieve the original data, redo the systematic review, and show I think very clearly that there was still of considerable benefit in the presence of ruptured membranes, and that there was no evidence of adverse effects.

Hey: The answer for Gill Gyte was that the data was there but 20 years later, it had still not even been analysed. Who can put their hands up and say that a trial that we did five years ago, and has now been reported, we could find the results. And one of the things, I mean the most amazing thing, that I found in just 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.

Harding: Yes, and 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 come up that trials weren't necessarily designed to answer at the time, but it's terribly important that the data is still there. The third, 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, got it rejected from two journals, got it 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's been a randomized trial, multi-centre randomized trial being run by Caroline

* Reference attached

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?

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.

* Reference attached

Hey: Because people are still asking the question, 'Does it work in twins?' or 'Should you give it in trihypertension?'.

Gamsu: Our numbers of course are very small.

Hey: So are everybody's, but if people have kept their data, there's more that can be analysed that's not yet been done. Would 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 Newnam 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 no, because I heard it presented in Glasgow about six weeks ago, but I haven't seen anything in the press yet. But I think it is largely in animals, and you'll be able to elucidate further. But I think the issue that having tried to do one of the large trials, a multiple course of steroids, one of

to detrimental effects. We all agree that glucocorticoids are life-savers, but we cannot begin to think as to whether some of these more fine-tuned effects may be detrimental in later life. And I was just wondering whether we are going to get to talk about that later on, as to perhaps think of fine-tuning some of the dosing of the glucocorticoid therapy today.

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

Dr John Hayward: I just wonder whether it's an opportunity if we are looking at getting research into practice, which is one of the future topics after we have had our tea break, just to hold in our mind some of the questions that have been raised. Interestingly, when I, and other people in this room, who knew me 40 years ago, one person talked as a medical student, another I applied as a job and didn't get, something went wrong, my fellow applicant got the job that he hadn't applied for, and I got the job that he applied for. It was bizarre. It's

* Reference attached

nice to see Sir Christopher Booth here, who I never did work for eventually. Interestingly, I also worked with Cliff Robertson when he was a paediatrician at Hillingdon Hospital and was having difficulty in getting a job. The thing that strikes me is one of these interesting things as I have hovered in my own career as that of a GP, then getting interested in systematic reviews, training in public health, and coming back to public health, rather a weird career, dotting a lot of the lines, the same issues keep cropping up. There's always a concern: have we looked at the subjects right? What will the long-term detrimental effects be? Everybody's actually influenced by some horror that they have come across. And that's perhaps not so much the case for steroids, but it's certainly true if you look at the extent of the .....[?] breech presentation for example. My statement later will be about how we looked at getting research and practice and values to it. I think the danger is everybody worrying about some rare outcomes some 30 years hence as justification for sitting on your hands and not doing anything. The outcome of interest here was death, compared with survival, and I think that's the critical thing that's held 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 and they actually got the intervention rather than the control, and I would have thought that those adults who are now alive would accept a certain amount of hypertension or some other problem as an alternative to not being here at all.

figures from your study Richard, including figures in 1977, your survey, Peter, which shows a very large uptake by the end of the 1980s to 1990s. Random analysis suggested that with 75 per cent uptake there would be more than 400 deaths averted annually in England and Wales. So clearly, there has been quite a big gain. The problem though, as has already been mentioned, without putting a precise figure on this, is that with the use of surfactant and the improvement of the neonatal case, it is not clear of course that all these deaths would have actually happened if it hadn't been for the use of steroids. But nevertheless as has been said there is also evidence that some of them would never have happened, surfactant wouldn't have stopped all of them. What I think is unclear, is whether there is an actual measure of how many. So definitely this has had substantial health gain as well as impact on policy, knowledge gain, impact on further research. In the USA mention has been made of in census conference. This is broadly endorsed by the USA College and it claimed, that disconsensus statement, the college statement, had more impact than most of them. An implementation project found that after a year just passive dissemination, in fact implementation of college guidelines went up from 33 to 58 per cent, which is quite substantial. But after active dissemination it went up from 33 to 68 per cent. So it does seem that there are many elements of this whole stream of research that have produced benefits and perhaps the key thing from our work, use of .... research, is different from some other perspectives in the debate about research utilization, is that our work has been concentrated on showing that benefits have been achieved even though the uptake level has been less than optimum.

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

Crowley: Probably a very important one is the reduction in the risk of intraventricular haemorrhage, bleeding into the ..... in the brain in premature babies and that's a particular benefit for the most premature babies and a reduced number of days on a ventilator for babies who do get respiratory distress syndrome, that's the number of days spent on a ventilator reduced the number of time spent in neonatal intensive care probably necrotizing enterocolitis, they would be I suppose from that enterprise the most important.

Harding: Yes, reduction in patient doctors and the new systematic review will also suggest benefits in terms of childhood developmental outcome.

Chalmers: We keep on talking about benefits in terms of the baby, but what about the parents? The reduced exposure to these terrible courses that babies would go through before death, and 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.

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 ~~core~~ 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~~ raised, the repeat steroids, which dose, which drug, how often, at what gestation, to which pregnancy,

all of those things were raised by Liggins and Howie in their original publications and said these are the things that need work, including long-term follow up. When Stuart Dalziel, who has been the key person doing the 30-year follow up presents this data, he starts off by saying, 'Why do we do this?' puts up a quotation from the original papers, and said they told us we had to 30 years ago. Incidentally, for what it's worth, to complete that story, Stuart also presented this data recently at a meeting at the National Women's and said, 'I expect that it will be my PhD student in 20 years time who will have to do the 50-year follow up'.

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

Biographical notes

Dr Mary Ellen (Mel) Avery

Sir Christopher Booth

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

Dr Peter Brocklehurst

Sir Iain Chalmers

Kt FRCPE FFPHM FMedSci (b. 1943) has been Director of the UK Cochrane Centre in Oxford, since 1992. With the NHS Centre for Reviews and Dissemination in York, the Centre is part of the information system supporting the NHS Research and Development Programme and a component of the Cochrane Collaboration – an international organization that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. Before taking up his current post, he was Director of the National Perinatal Epidemiology Unit in Oxford (1978–92).

Professor Patricia Crowley

Professor John Gabbay

Professor Harold Gamsu

FRCP FRCPCH (1931–2004) graduated in Johannesburg in 1954. His training in paediatrics commenced there, and continued subsequently in Sheffield and in Cleveland, Ohio. He was appointed as Wates Fellow at King's College Hospital, London,

Harding. Corrections added 27/9/05
Recd 4/9/05.

P 6 Last para. This content of this sentence is muddled - the randomised trial was done in women, not lambs, and the 100 days could not possibly apply to lambs and probably not to women either. I suggest that the reference (8) is omitted here. It is cited elsewhere, and is not clearly relevant here.

email to Avery

P9 Footnote 12. This footnote seems irrelevant. I would have thought that no explanation at all was required for cortisol. It was not being used as a drug, hence the irrelevance of the footnote. If an explanation is considered desirable, then I would suggest the footnote could simply read "Cortisol is the naturally occurring glucocorticoid in humans and sheep".

P12 para 2 last 3 lines. "…who was able to ventilate newborn babies. I would like to quote now from Ross Howie's words.." (delete extra apostrophe after "Ross")

P12 Footnote 17 The recording is held in the University of Auckland library. I am not sure how to cite it, but the catalogue details are:

Author: Liggins, G. C.
Title: Graham (Mont) Liggins [sound recording] / interviewed by Megan Hutching.
Published: [Auckland, N.Z. : University of Auckland], 2003.
Description: 3 sound cassettes (ca. 180 mins.)
Summary: Interview with perinatologist Emeritus Professor Sir Graham Collingwood (Mont) Liggins, Postgraduate School of Obstetrics and Gynaecology, University of Auckland.
LC Subject Heading(s): Liggins, G. C. Interviews.
Obstetricians New Zealand Interviews.
Other Author(s): Hutching, Megan.
University of Auckland.
Location: GENERAL LIBRARY SPECIAL COLLECTIONS Audio Visual
Notes: Ask at Special Collections Reception. For use in Library only
Call Number: CASSETTE SC04-028

P13 para 2 line 3-4. "…who was capable of looking after the premature babies."

P13 Footnote 20. The reference for this presentation to the RCOG is:
Howie R, Liggins G. Clinical trial of antepartum betamethasone therapy for prevention of respiratory distress in pre-term infants. In: Anderson A, Beard R, Brudenell J, Dunn P, eds. Proceedings of the fifth study group of the Royal College of Obstetricians and Gynecologists. London: Royal College of Obstetricians and Gynecologists, 1977:281-289.

P14 para 1 line 9. Should read "Mont had moved on to other studies." (not "onto", which implies on top of).

P14 Footnote 21. The 1987 NZMJ reference is irrelevant and should be deleted. References should be:
MacArthur BA, Howie RN, Dezoete JA, Elkins J. Cognitive and psychosocial development of 4-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* 1981;68(5):638-43.
MacArthur BA, Howie RN, Dezoete JA, Elkins J. School progress and cognitive development of 6-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* 1982;70(1):99-105.

P14 Footnote 22. The follow-up studies referred to in the last sentence of the first paragraph, are those referenced in footnote 21, so a separate footnote (22) is not really

needed for these. The ongoing follow-up studies are referred to later in the programme. I doubt they need referencing here, but if you wish to, they are:

Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, Harding JE. Cardiovascular risk following exposure to antenatal betamethasone: Thirty year follow-up of a randomised controlled trial. Lancet 365: 1856-1862, 2005.

Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A, Harding JE. Psychological functioning and health related quality of life after exposure to antenatal betamethasone: Follow up into adulthood of a randomised controlled trial. British Medical Journal, in press, 2005. (This will be published electronically within the next week, so you should be able to find details very soon).

P15 Footnote 23, line 4. Typo in "intramuscular"

P16 Footnote 24. The results of the entire trial were published in a number of places rather than a single final paper. Some were:

Howie R, Liggins G. Clinical trial of antepartum betamethasone therapy for prevention of respiratory distress in pre-term infants. In: Anderson A, Beard R, Brudenell J, Dunn P, eds. Proceedings of the fifth study group of the Royal College of Obstetricians and Gynecologists. London: Royal College of Obstetricians and Gynecologists, 1977:281-289.

Howie RN, Liggins GC. Lung Development: biological and clinical perspectives, II 1982;Academic Press, London & New York, The New Zealand Study of antepartum glucocorticoid treatment. 255-265Farrell PM.

Liggins GC. Prenatal glucocorticoid treatment: prevention of respiratory distress syndrome. Lung maturation and the prevention of hyaline membrane disease, report of the 70th Ross Conference on Pediatric Research 1976;97-103Moore TD, Ross Laboratories, Columbus.

Howie RN. Respiratory distress syndrome 1986;Academic Press, London & New York, Pharmacological acceleration of lung maturation. 385-396Villee CA, Villee DB, Zuckerman J.

P17 Footnote 25. The San Francisco group included Roberta and Phil Ballard, Jo Kitterman, Bill Tooley, John Clements.

P18 line 5. This date is correct.

P19 Footnote 30. If a reference is desired here the Dalziel one is appropriate. The others are irrelevant and should be deleted.

P21 para 2. The youngest was 20 weeks and the mean gestation at delivery was 34 weeks

P21 Footnote 32. In fact there have been at least 6 trials. References include:

Botet F, Cararach V, Sentis J. Premature rupture of membranes in early pregnancy. Neonatal prognosis. *J Perinat Med* 1994;22:45-52.

A multicenter, prospective randomized study in premature rupture of membranes (PROM). Respiratory and infectious complications in the newborn. 12th European Congress of Perinatal Medicine; 1990; Lyon, France.

A multicenter, prospective randomized study in premature rupture of membranes (PROM). Maternal and perinatal complications. 13th World Congress of Gynaecology and Obstetrics (FIGO); 1991; Singapore.

Carlan SJ, Parsons M, O'Brien WFen. Pharmacologic pulmonary maturation in preterm premature rupture of membranes. *Am J Obstet Gynecol* 1991;164:371.

Garite TJ, Rumney PJ, Briggs GG, Harding JA, Nageotte MP, Towers CV, et al. A randomized, placebo-controlled trial of betamethasone for the prevention of respiratory distress syndrome at 24 to 28 weeks' gestation.[comment]. *American Journal of Obstetrics & Gynecology.* 1992;166(2):646-51.

Kari MA, Hallman M, Eronen M, Teramo K, Virtanen M, Koivisto M, et al. Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: a randomized placebo-controlled multicenter study. *Pediatrics.* 1994;93(5):730-6.

Garite double blind
randomized
placebo cont trial

unable to demonstrate evidence
of benefit → incidence of IRDS

33 beta
38 placebo.
Dec 1984 – May 1990

66%
24 already
discharge on beta
29 on placebo
68%

76 patients eligible,
37 to beta (4 delivered
elsewhere)
39 placebo.

understand now about the lung came from the combination of those interests, didn't it?

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

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

My research fellows at Johns Hopkins set out to map the course of events in the developing fetal lung of the lamb, the animal of choice. I have often wondered why, and I think it's because babies and lambs are about the same

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[3] See, for example, Barclay A E, Barcroft J, Barron D H *et al.* (1939) A radiographic demonstration of the circulation through the heart in the adult and in the fetus, and the identification of the ductus arteriosus. Br. J. Radiol. 12: 505–???. Barclay A R, Franklin K J, Pritchard M M. (1944) *The Foetal Circulation and Cardiovascular System, And the Changes that they Undergo at Birth*. Oxford: Blackwell. Born G V R, Dawes G S, Mott J. C., *et al.* (1954) Changes in the heart and lungs at birth. In *Cold Spring Harbor Symposia on Quantitative Biology*, Vol. XIX. New York. Young M. (19xx) ???? [could you suggest an appropriate article?]

[4] Smith C A. (1945) *The Physiology of the Newborn Infant*. Springfield, IL: C C Thomas. Strang L B. (1977) *Neonatal Respiration: Physiological and clinical studies*. Oxford: Blackwell Scientific. For Professor Sir Robert Boyd's appreciation of Strang's work on the adaptation of the fetal lung to air breathing, see Christie and Tansey (eds) (2001): 16.

size at birth and the equipment you had for one worked for the other. I don't know if that is quite true or not, but those are my thoughts on the matter.

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

That was 1962. Then we said we have to know about the normal appearance of various enzymes and so on in the developing lamb. That's when all the people in the laboratory – which then numbered 15 or 20 – produced a paper about the timing of various enzymes and other events in the normal lamb lungs.[6] I went to New Zealand [in 19xx] as a guest of the Society of Obstetricians and the Paediatric Society. Mont Liggins was there and after I said that lambs were perfectly normal by 147 days gestation, Mont said, 'What if I told you we can identify accelerated maturation in the lambs' lungs at 115 days?' That's too big [a difference] to be an error. Were New Zealand lambs that different from the lambs in the USA? I didn't believe that, neither did he. It appeared that, in fact, glucocorticoids could accelerate lung maturation of lambs.[7]

The story of the glucocorticoids moved ahead when Liggins and Howie proposed a randomized control trial, I think 100 days before the birth of the lamb, and it was obvious that the effect was reproducible.[8] I would also like to pay tribute to Sue Buckingham, a Fellow at the Columbia Presbyterian

queried 1st sentence Answered 27/9/05

[5] Moog F. (1953) The influence of the pituitary–adrenal system on the differentiation of phosphatase in the duodenum of the suckling mouse. *Journal of Experimental Zoology* 124: 329–46.

[6] ??1962 paper from your laboratory??

[7] Liggins (1969).

[8] Liggins and Howie (1972).

> transfusion fame,[11] how to choose a topic. He said to look for a major problem that was potentially solvable. The major problem was easy. Prematurity stood out above everything else. I naively thought that all I had to do was solve the ancient question of what controlled the onset of labour at term and the reason for premature onset would become apparent.

Mont then described how he worked on his idea that the onset of labour was controlled by the fetus not the mother, and how he spent a sabbatical period at the veterinary school at the University of California at Davis, to assess the role of cortisol[12] 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.[13] 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 [2003], as part of a recording of an oral history project undertaken by the place at which I now work, the Liggins Institute. It is named after him, and we asked Mont to record essentially his life story. He agreed that I could play a part of it to you, as it relates to this story.

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[11] Liley A W.(1964) The technique of fetal transfusion in the treatment of severe haemolytic disease. *Australian and New Zealand Journal of Obstetrics and Gynaecology* **30**: 145–8.

[12] Cortisol (hydrocortisone) is a glucocorticoid, whose synthetic derivative is prednisolone for patients who cannot take cortisol orally, used clinically to suppress immune responses. ACTH (adrenocorticotropic hormone) is a polypeptide whose release from the pituitary gland is regulated by corticotrophin-releasing hormone (CRH). At this time cortisol was dervied from xxxx. See Pearson O H, Eliel L P. (1950) Use of primary adrenocorticotropic hormone (ACTH) and cortisone in lymphomas and leukemias. *Journal of the American Medical Association* **144**: 1349–53. See also Vale W, Spiess J, Rivier C, Rivier J. (1981) Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science* **213**: 1394–7.

[13] The Wellcome Trust gave £40 000 in grants for research assistance over eight years from 1969 to 1976. See Appendix xx, pages xx–xx.

Mont Liggins [from a tape recording]: I had always been meticulous in doing a complete autopsy of all the lambs that I delivered, weighed organs, helped I must say by my secretary. 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 I speculated that the cortisol had accelerated the maturation of enzymes in the lung that caused accelerated maturation. Now at that time my facilities were fully occupied in studying the question of parturition and I didn't have time to pursue this problem.[14] But it so happened that Mary Ellen Avery who was working on respiratory distress syndrome (RDS), and lung problems, and the discoverer that surfactant was necessary for the maintenance of lung expansion, was visiting New Zealand.[15] So we were both going to a meeting in Christchurch where I described my findings in a series of lambs with expanded lungs.

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[14] See Appendix xx, pages xx–xx/

[15] Kotas R V, Avery M E. (1971) Accelerated appearance of pulmonary surfactant in the fetal rabbit. *Journal of Applied Physiology* **30**: 358–61. Motoyama E K, Orzalesi M M, Kikkawa Y, Kaibara M, Wu B, Zigas C J, Cook C D. (1971) Effect of cortisol on the maturation of fetal rabbit lungs. *Pediatrics* **48**: 547–55. See also Avery M E, Fletcher B D, Williams R G. (1981) *The Lung and its Disorders in the Newborn Infant*. 4th edn. Philadelphia, PA: Saunders. First edition, 1964.

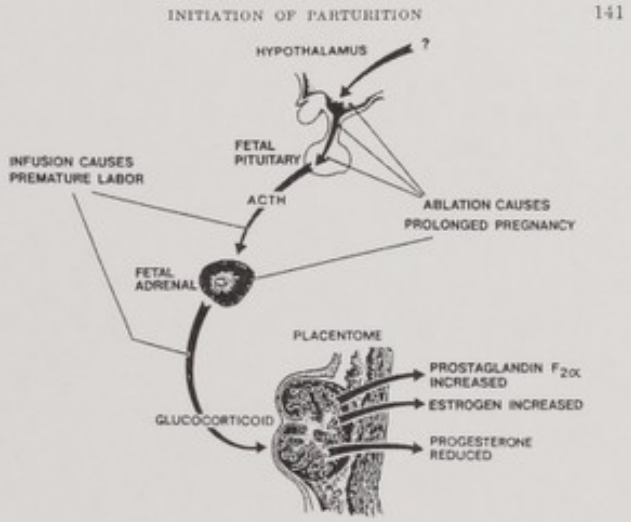

FIG. 19. Schematic diagram of the pathway by which the fetal lamb influences endocrine events in the ewe. Also shown are experimental procedures that have been used to modify the activity of the pathway.

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

Liggins *et al* (1973), 141.

She couldn't get back to Boston fast enough to set up experiments in rabbits – giving fetal rabbits cortisol – and produced the definitive paper on the effects of corticosteroids on lung maturation.[16] 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

[16] Avery M E, Mead J. (1959) Surface properties in relation to atelectasis and hyaline membrane disease. *American Medical Association Journal of Diseases of Children* **97**: 517–23. OR DeLemos R A, Shermeta D W, Knelson J H, Kotas R, Avery M E. (1970) Acceleration of appearance of pulmonary surfactant in the fetal lamb by administration of corticosteroids. *American Review of Respiratory Disease* **102**: 459–61. Avery M E. (2000) Surfactant deficiency in hyaline membrane disease: the story of discovery. *American Journal of Respiratory Critical Care in Medicine* **161**: 1074–5.

> same enzymes as animal lungs. Should we do a clinical trial in premature babies and put it to test? 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, 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.[17]

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 was all Mont's idea. In fact it's my view that it was a quite remarkable partnership. At the time Ross was an MRC research fellow, the only paediatrician at the National Women's Hospital in Auckland and indeed in New Zealand, who was able to ventilate ~~[?very small? small? any?]~~ newborn babies. I would like to quote now from Ross Howie's words describing these events, although I have abbreviated them somewhat:

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

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[17] How should the tape be cited??? Is it held in your library? Liggins and Howie (1972). For the next well-controlled study following Liggins and Howie (1972), see: Papageorgiou *et al.* (1979).

> In total contrast, the lungs of the other remained solid and liver-like, and sank.[18]

There are a couple of things that interest me about these descriptions. One is the unique pairing of an experimental scientist who was also an obstetrician, with the only paediatrician in the country who was capable of looking at [after] the [?premature?] babies. Another is that whatever the later perceptions became, it's clear that both the authors of the study were involved together from the beginning, in the animal laboratory, as well as in the clinical aspects.[19] Finally, I am entranced with Ross's comments that this lamb trial was simply a sideline for both of them. It's an interesting warning against the narrow and predetermined endpoints of some research programmes, and highlights the importance of serendipity in progress.

Ross describes presenting the results of the completed study – not the initial part of the study that was published in 1972, but the completed study – at a symposium hosted by the Royal College of Obstetricians and Gynaecologists of the UK in 1977.[20] He said to me, 'They didn't really want to hear'. He also

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[18] Quoted from 'Prenatal glucocorticoids in preterm birth: a pediatric view of the history of the original studies', a draft memoir by Ross N Howie dated 2 June 2004 and distributed at the Witness Seminar. It will be deposited along with other records of this meeting, GC/253, in Archives and Manuscripts, The Wellcome Library, London.

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

[20] Dr Clive Dash wrote: 'At the time when Ross Howie presented the results to RCOG in 1977, the UK study was in its recruitment phase. Whether knowledge of the status of the UK study played any part in the cool response of the delegates at the meeting, which Ross sensed, would be speculative.' E-mail to Dr Daphne Christie, 10 January 2005.

reported that when he was asked for a recommendation as to what people should be doing, he said that the treatment looked very promising, but that it would be unsafe to initiate a new treatment on the basis of a single trial. He said that he knew what he should do, but that others should wait for ongoing trials. Other people here can talk about the progress of the treatment after that time. My own involvement began perhaps when I entered medical school in 1973. Both of the principal actors were my tutors. The use of antenatal steroids was routine at that time in our hospital and has remained so ever since. By this time Mont had moved onto other studies. Ross was completing the four- and six-year follow up of the original cohort, funded by the World Health Organization.[21] He always believed very strongly that long-term follow up was essential for anything in neonatal care and set about this with his usual thorough approach. The follow-up studies were published in the early 1980s and the ongoing follow-up studies we will talk about later.[22]

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

Harding: I can tell you that story because I specifically asked both of them in recent weeks. To paraphrase a long story: Mont had been doing work in human pregnancy on the effects of steroids on the fetus, and he had a reasonable idea of what dose of steroid was required to suppress progesterone production and he presumed that that would be an adequate dose to do

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[21] WHO studies????? MacArthur B A, Howie R N, Dezoete J A, Elkins J. (1981) Cognitive and psychosocial development of four-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* **68**: 638–43. ? Harding J E, Howie R N. (1987) First-year mortality and hospital morbidity after newborn intensive care. *New Zealand Medical Journal* **100**: 548-52. For erratum, see *New Zealand Medical Journal* (1987): 642.?

[22] Follow-up studies here.

something to the fetus. He knew that he wanted something that would be reasonably long-lasting, so that it didn't have to be given too frequently to pregnant women and decided that something that would last for 24 hours and therefore two doses would give you about a 48-hour effect would be adequate, based on the animal studies. He therefore set about looking for a drug that would be clinically easy to manage, long-lasting, and which had an identically appearing placebo. This is not easy, because all the long-lasting preparations of glucocorticoids are opaque, they are milky substances, and a placebo wasn't easy to find. He wrote to a number of drug companies asking for help, and in the end Glaxo – originally the name of a dried milk power sold by a New Zealand company, and it so happened that the medical director was a mate of Mont's – provided an opaque placebo.[23] Their long-acting preparation was the one he used, because that was the one that was available and they were provided with the placebo. So the placebo was cortisone acetate, which had very low potency but looked the same, and the drug that he selected was the Glaxo drug because that was what was available and because the director was a mate who provided it for free. I might say that the study was unfunded. Mont said to me, 'We didn't need funding to do this trial.' And of course they didn't, because the drug was provided free and both Mont and Ross were fully salaried and were able to put in all of their time.

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

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

Harding: Twelve hundred. The real number was 1218.

Hey: Still the biggest trial.

Harding: Still the biggest trial. The original publication that everybody cites from 1972 was only the first 282. But they continued to recruit long after that trial.

If I could just comment. The other thing that most people aren't aware of is that after the first 717 women were enrolled, when they did the first analysis and thought 'the stuff really does work', they doubled the dose. In the rest of the trial, the other 500 odd actually received twice the dose, to see whether more was better, and they concluded that it was not, and published all of the data as a combined single trial.[24]

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

Harding: That's correct.

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

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

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[24] 1976 results?

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??]

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.

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

Harding: Given a moment I could look it up, but from memory the youngest gestation was about 28 or 29 weeks, and the average gestation at delivery was around 35 weeks.

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

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

Harding: Yes, there have. There have been at least four trials in the 1990s and I am sure Dr Crowley will talk about this. But the new Cochrane Review, which is in the process of being produced, will show clearly that the benefit is still there in the surfactant era, in the ventilator era and in the four randomized placebo control trials done in the 1990s.[32]

Sir Iain Chalmers: Jane, I don't know whether you have tried to do this already, but it would be wonderful if these mothers and children that you are in touch with came to know just how important a contribution they have made to the history of perinatal care. If you haven't planned to do so already, could you think about letting them know that?

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[32] Four trials in the 1990s; new Cochrane Review.

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

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

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

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

Avery: At the meeting in Christchurch, with Liggins in attendance, I had given the most boring paper I have ever given, describing the time of onset of a whole bunch of things that we could measure to map out the terrain of the maturation of different organs in the lamb, knowing that we were particularly interested in lambs. Why did we tumble to that? It was partly that Mont wanted information from sheep, some of which were different from what he

at one stage we did have a figure of £20 000 from the Wellcome Trust for one of these pieces of work, I think it was for the original animal trial.[35] I am not quite sure how that fitted in, how long a period that was, but that is a figure that was quoted. It was obviously a very small grant even in those days.

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

Hey: That included his going to America and learning how to hypophysectomize fetal sheep.[36]

Harding: He did all that before he came back [?to New Zealand from ??California?], and when he came back was when he had the Wellcome funding to start his own lab.[37]

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

Harding: That's correct. He had presumed that that would be the case. When he was on sabbatical at UC-Davies he devised a way of doing the hypophysectomy and did the initial experiments there and then came back to set up a sheep lab in New Zealand with Wellcome Trust funding at that time.

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[35] Hanney and Wellcome funding

[36] Surgical removal of the hypophysis, or pituitary gland, in the pregnant ewe.

[37] See Appendix xx, page xx.

So I think that was probably the one and only grant and a very large one at that time for working expenses.

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

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

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

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

trial, which we will no doubt come to, and the follow up was still going on at the time that the Auckland trial follow up was completed.[38] 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 the trial under other circumstances, and check what specifically was and wasn't helpful about this treatment.

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

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

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[38] Is this the long-term follow up? OR Daliel in note 30? MacArthur B A, Howie R N, Dezoete J A, Elkins J, Liang A Y. (1989) Long-term follow up of children exposed to betamethasone *in utero*. In Tejani N. (ed). *Obstetrical Events and Developmental Sequelae*. Boca Raton: CRC Press, 81–9.

Collaborative Group (1984) (initial phase still going on)

Auckland follow up (MacArthur et al (1981, 1982).

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

I then went to work in the Hammersmith Hospital in London and in 1978 attended a meeting at the Royal College of Obstetricians and Gynaecologists (RCOG) marking the publication of the proceedings of the 1977 RCOG Preterm Labour Study Group. Ross Howie had attended this meeting in 1977, and presented a paper jointly authored with Mont Liggins on the outcome of 1068 women and their babies who had been enrolled in randomized trials of antenatal corticosteroid therapy. This showed a massive reduction in neonatal mortality in those babies who were exposed *in utero* to antenatal steroids.[39] The Proceedings of that Preterm Labour Study Group contained 14 papers on tocolysis and only two papers about fetal lung maturation – a clear indication of where the emphasis of British obstetrics lay at that time when it came to preterm labour. Obstetricians were obsessed with trying to stop preterm labour rather than on trying to improve the outcome for the premature baby by accelerating lung maturation. Despite a dearth of objective evidence of efficacy, a variety of betasympathomimetic drugs were being actively promoted by the pharmaceutical industry at this time, whereas no pharmaceutical company was promoting the use of antenatal steroids.

In 1980 at the Hammersmith Hospital, London, Professor Denis Hawkins founded the *Journal of Obstetrics and Gynaecology*. He received a paper from

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[39] Howie R N, Liggins G C. (1978) Clinical trial of antepartum betamethasone therapy for prevention of respiratory distress in preterm infants. In Anderson A, Beard R W, Brudenell J M, Dunn P M. (eds) *Preterm Labour*: Proceedings of the fifth study group of the Royal College of Obstetricians and Gynaecologists. London: The College, 281–9.

under 10 per cent and never higher than 20 per cent, up to 1990. So the publication of this paper in the *British Journal of Obstetrics and Gynaecology* was a landmark in terms of improving the use of antenatal steroids.

In 1994 the NIH Consensus Conference on antenatal steroids[49] took place. At that meeting I contributed an updated version of the systematic view of antenatal steroids,[50] derived mainly from the electronic review published on what was by then the *Cochrane Pregnancy and Childbirth Database of Perinatal Trials.*[51] The rest of that three-day meeting was taken up with many observational studies, and laboratory based papers on antenatal steroids and following the three-day meeting a strong recommendation was released urging obstetricians in the US to use antenatal steroids.

In 1996 I was invited by the Royal College of Obstetricians and Gynaecologists to update a guideline on the use of antenatal steroids issued in 1992.[52] The revised guideline, based on the systematic review published in the Cochrane Library, strengthened the recommendation from the RCOG on antenatal steroids use. By the late 1990s, 70 per cent of preterm babies delivered in the UK were being treated with antenatal steroids prior to delivery.

Within a year or two of finally adopting the evidence-based practice of prescribing a single course of antenatal steroids to women at risk of delivering a preterm infant, obstetricians started to prescribe repeated courses of antenatal steroids. The practice of repeated courses of antenatal steroids in women who remain undelivered a week or more following the original treatment crept in

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details, see www.cshs.unimelb.edu.au/programs/jnmhu/witness/001.html (visited 2 August 2005).

[49] National Institutes of Health (NIH) (1994). Their recommendation was to give a single course of corticosteroids to all pregnant women between 24 and 34 weeks gestation who are at risk of preterm delivery within 7 days.

[50] Crowley (1995).

[51] The first structured review by Dr Patricia Crowley appeared on the Oxford Database of Perinatal Trials in 1987. The 1996 version appears as an example of a Cochrane Review at www.cochrane.org/reviews/exreview/htm (visited 2 August 2005). See also Figure 5.

[52] See note 141.

rapidly, without any evidence to support its safety or efficacy. All the evidence from randomized trials related to a single course of antenatal corticosteroid therapy.

[Figure 4 here]

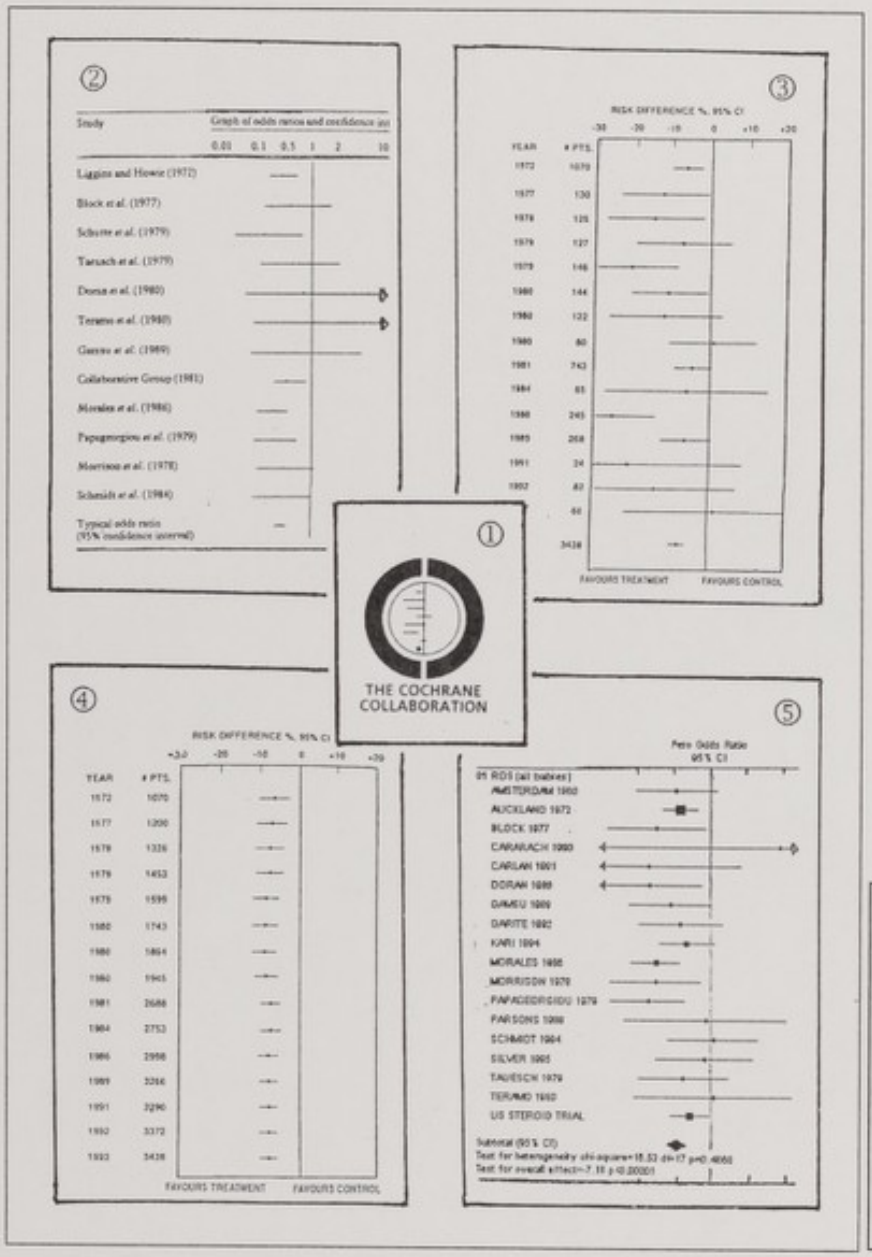

Figure 4: Patricia Crowley' meta-analyses, 1992–2004.

1. 7 trials, original Cochrane logo, 1992;
2. 12 trials, Crowley (1989);
3. 15 trials, Crowley (1994);
4. 15 trials, Sinclair (1995);
5. 18 trials, Cochrane Library (2004, CD000065).

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

Hey: I think it might be sensible to break and explore some of the ……..ation that went on between 1977 and [?when?] Ross's reporting [?reported?] to the [?which?] College in [?and?] 1994 and [?when?] we end up with the NIH conference. It's a long period of time. Mary [?Mel?], you were a witness to much of this.

Avery: It was frustrating.

Hey: Well, you banged the drums quite hard.

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

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 systemati8c 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 include, and concluded that it wasn't worth doing, except perhaps in pregnancies more than 34 weeks.

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

Lewis DF, Brody K, Edwards MS, Brouillette RM, Burlison S, London SN. Preterm premature ruptured membranes: a randomized trial of steroids after treatment with antibiotics. *Obstetrics & Gynecology.* 1996;88(5):801-5.

Silver RK, Vyskocil C, Solomon SL, Ragin A, Neerhof MG, Farrell EE. Randomized trial of antenatal dexamethasone in surfactant-treated infants delivered before 30 weeks' gestation. *Obstetrics & Gynecology.* 1996;87(5 Pt 1):683-91.

Amorim MM, Santos LC, Faundes A. Corticosteroid therapy for prevention of respiratory distress syndrome in severe preeclampsia. *American Journal of Obstetrics & Gynecology.* 1999;180(5):1283-8.

Pattinson RC, Makin JD, Funk M, Delport SD, Macdonald AP, Norman K, et al. The use of dexamethasone in women with preterm premature rupture of membranes--a multicentre, double-blind, placebo-controlled, randomised trial. Dexiprom Study Group.[see comment]. *South African Medical Journal. Suid Afrikaanse Tydskrif Vir Geneeskunde* 1999;89(8):865-70.

Qublan HS, Malkawi HY, Hiasat MS, Hindawi IM, Al-Taani MI, Abu-Khait SA, et al. The effect of antenatal corticosteroid therapy on pregnancies complicated by premature rupture of membranes. *Clinical & Experimental Obstetrics & Gynecology* 2001;28(3):183-6.

Fekih M, Chaieb A, Sboui H, Denguezli W, Hidar S, Khairi H. [Value of prenatal corticotherapy in the prevention of hyaline membrane disease in premature infants. Randomized prospective study]. *Tunisie Medicale* 2002;80(5):260-5.

P22 line 1. "We tried very hard to how important they are; this is part of…."

P25 para 4. "He did all that before he came back to New Zealand from California, and when he came back…"

P25 para 5. "discovering that the ewe never goes into labour…"

P27 line 1-2 and footnote 38. Perhaps this sentence needs 2 footnotes. The initial phrase "the follow-up was still going on" refers to the follow-up of the NIH trial, which was published as:

Collaborative Group on Antenatal Steroid Therapy. Effects of antenatal dexamethasone administration in the infant: long-term follow-up. J Pediatr 1984;104:259-267.

The next line "at the time the Auckland trial follow-up was completed" refers to follow-up of the Auckland trial, which was published in the two papers by MacArthur listed above for footnote 21.

P33 Footnote 49. The NIH consensus statement was published as:

Anonymous. Effect of corticosteroids for fetal maturation on perinatal outcomes. *NIH Consensus Statement* 1994;12(2):1-24.

P36 para 2. This should perhaps read :"..to break and explore some of the events that went on between 1977, when Ross was reporting to the College (RCOG), and 1994 when we end up the NIH conference…"

P39 para 2. Typo in first line "systematic".

P40 para 3. Typo in line 2 "include"

P40 Footnote 58. Correct title is "Prenatal glucocorticoid treatment: prevention of respiratory distress syndrome".

cent of women who get antenatal steroids do not deliver preterm and therefore if there is long-term harm, it will be in these babies that it will manifest itself, and if we could target our use of steroids better, we would all probably feel a bit more comfortable. So I think we are beginning to go the other way, where people are actually being more cautious now with steroids than they were maybe even five years ago.

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

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

To come back to the issue of ruptured membranes, and I think it is fair to say in the mid-1990s there was still confusion about the issue, but the solution was not to do a new trial. The solution was to go back to the old trials. At that time there had been over 4000 women randomized, and the data was present from the original trials, they had just never been analysed. In about 1994/5 – I cannot remember the exact date – we had a debate around a clinical case at a clinical conference at my hospital, after which David Knight, who was the Director of the nursery at the time, said to me, 'Isn't that question answered?

Surely the data must be there?' Now just parenthetically, David Knight was at the Barcroft Symposium in 1973 at which Mont presented the data.[81] That was one of the reasons that David came to New Zealand and ended up as Director of the nursery. He got all excited about antenatal steroids and thought that he would come to Auckland. That's a slight aside. But it was David's question to me that prompted me for the first time to go back to Mont and Ross to ask, 'You know all those files in the locked cupboard in the corridor where my office was, how would you feel about our getting them out and doing a new analysis, because I think the data might be there and we need to know the answer to a question that you hadn't asked at the time'.

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

Hey: The answer for Gill Gyte was that the data was there but, 20 years later, it had still not even been analysed. Who can put their hands up and say that, of a

[81] Liggins and Howie (1973).

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 costs 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).

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.

Part of the Centre's logo shows the results of the first seven trials of prenatal corticosteroids (I overlooked, inadvertently, an eighth trial that had been published during this time period. It happened to have exactly the same confidence interval as one of the others, and I had thought that we might have been double counting). The reason that we used the steroid trials was that we wanted to show that within ten years of the Liggins and Howie trial,[112] there had been crystal clear evidence that this was a very important way of reducing neonatal deaths. In launching the Cochrane Centre, we wanted to make the point that this very important information had been available more than a decade earlier, yet it was still not being acted upon sufficiently, in practice. In the brochures we produced and the talks we gave to introduce the objectives of the Centre to others, we made the point that tens of thousands of babies had suffered and died unnecessarily (and cost health services more than they need have done) because information had not been assembled in a systematic review, and meta-analysis used to show the strength of the evidence. In 1993, a year after the Cochrane Centre had opened for business, we convened the meeting at which the International Cochrane Collaboration was founded, and the Centre's logo was adopted by the new organization.[113] [See Figure 5]

I want to end with a statement that may sound rather carping, but I am keen that it should be on the record, given that this seminar is [also] upported by the Wellcome Trust. Although the Trust supports clinical trials in some other parts of the world, it has always discouraged applications for support of clinical trials in the UK. In addition, I have it on good authority that some of the governors of the Trust have not only been unsupportive, but actually dismissive of the kind of research I have described here – RCT registration, systematic reviews and meta-analysis. Indeed, the Trust's website declares unambiguously that it will not support systematic reviews of clinical trials.[114] Given that those

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[112] Liggins and Howie (1972).

[113] Chalmers (1993); Chalmers *et al.* (1997).

[114] See the Wellcome Trust Funding for Clinical Trials at www.wellcome.ac.uk/doc%5Fwtx022708.html (accessed 5 August 2005).

assessing payback from research and others recogniz the crucial importance of systematic reviews of clinical trials for patient benefit, I and others continue to resent the Trust's unwillingness to engage in discussion with outsiders about the scientific rationale for its attitudes to clinical trials and systematic reviews.[115] It is time that the Trust and other funders of biomedical research assessed more rigorously and transparently the cost-effectiveness of their research funding decisions.[116]

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: It's a great honour to be here today to say a few words about moving knowledge into clinical practice. I was plucked from obscurity in 1991, I think it was, by the then President of the Royal College of Obstetricians and Gynaecologists, Stan Simmons. He called me into his office and said that he wanted me to take over the Audit Committee. I had not been on the committee before I went down to the first meeting as their Chair. It was a very boring meeting; it didn't seem to go anywhere. The idea of guidelines was coming into people's consciousness at around this time and on the train back home the idea came into my head that what I should do with the committee

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[115] Hanney *et al.* (2005).

[116] Chalmers (2000).

P40 Footnote 59. I regret I have been unable to find the page numbers. Perhaps you will be able to check this reference directly.

P51 para 3 line 3. Perhaps this systematic review should be referenced here.
McLaughlin KJ, Crowther CA, Walker N, Harding JE. Effects of a single course of corticosteroids given more than 7 days before birth: A systematic review. Australian & New Zealand Journal of Obstetrics and Gynecology 43: 101-106, 2003.

P52 para 2 last line. Perhaps this systematic review should be referenced here.
Harding JE, Pang J-M, Knight DB, Liggins GC. Do antenatal corticosteroids help in the setting of preterm rupture of membranes? American Journal of Obstetrics and Gynecology 184: 131-139, 2001.

P53 para 3. First line should read "If I could just go on to the other issue…" "Onto" implies on top of.

P54 line 1. " ..risks and benefits for the group who receive steroids but then don't deliver within the next week; the group who don't stand to achieve…."

P54 line 9. Delete full stop. Sentence should read "It took so long to publish that I think it's had very little effect on recruitment…"

P55 Footnote 87. A large amount of Prof Newnham's animal work has been published, but obviously the speakers here were not familiar with this. Some of the relevant articles include:

Moss TJ. Nitsos I. Harding R. Newnham JP. Differential effects of maternal and fetal betamethasone injections in late-gestation fetal sheep. Journal of the Society for Gynecologic Investigation. 10(8):474-9, 2003 Dec.

Sloboda DM. Newnham JP. Challis JR. Repeated maternal glucocorticoid administration and the developing liver in fetal sheep. Journal of Endocrinology. 175(2):535-43, 2002 Nov.

Moss TJ. Harding R. Newnham JP. Lung function, arterial pressure and growth in sheep during early postnatal life following single and repeated prenatal corticosteroid treatments. Early Human Development. 66(1):11-24, 2002

Sloboda DM. Moss TJ. Gurrin LC. Newnham JP. Challis JR. The effect of prenatal betamethasone administration on postnatal ovine hypothalamic-pituitary-adrenal function. Journal of Endocrinology. 172(1):71-81, 2002 Jan.

Huang WL. Harper CG. Evans SF. Newnham JP. Dunlop SA. Repeated prenatal corticosteroid administration delays myelination of the corpus callosum in fetal sheep. International Journal of Developmental Neuroscience. 19(4):415-25, 2001 Jul.

Sloboda DM. Newnham JP. Challis JR. Effects of repeated maternal betamethasone administration on growth and hypothalamic-pituitary-adrenal function of the ovine fetus at term. Journal of Endocrinology. 165(1):79-91, 2000 Apr.

Quinlivan JA. Archer MA. Dunlop SA. Evans SF. Beazley LD. Newnham JP. Fetal growth retardation, particularly within lymphoid organs, following repeated maternal injections of betamethasone in sheep. Journal of Obstetrics & Gynaecology Research. 24(3):173-82, 1998 Jun.

P56 para 2 line 10. Hyphen in the wrong place. Should be "systematic paid-for archive".

P61 para 2 line 12. Typo, should be cots not costs.

P70 line 1. Typo. "Recognize"

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 Bromholtz 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 why embark on all these activities? That was what our study was designed to find out. We took four guidelines: the Ventouse, stitching up of the perineum using the correct materials, antenatal steroids, and antibiotics in preterm labour. Then we added one on the hoof, because during the course of the study, Lelia Duley and her colleagues published a spectacular trial – it must be *the* trial of the 1990s – which showed that magnesium was the optimum treatment for eclampsia.[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

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[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 [??was the proportion??] of women receiving steroids (a) who were recognized to be in preterm labour; (b) in whom birth was not so imminent as to negate any possible benefit; and (c) 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

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[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.

multiple courses of steroids. So it looks likely that we may end up with about 3000 women recruited around the world in trials on multiple courses of steroids versus the a single course, instead of the 10 000 women. I am very sceptical whether in five years time we will actually have enough information to answer the question of the long-term outcomes. The short-term respiratory outcomes look as if they may be favourable for multiple courses of steroids, but clearly that is only part of the question. So the fact that we didn't get the original trials into practice very quickly has not necessarily taught us to improve on past performance when it comes to antenatal corticosteroids.

The other thing to mention, I suppose, is that in the absence of trial evidence about long-term outcome, people will rely on observational studies of long-term outcome. The one observational study with repeated courses of steroids which has been published is from the Western Australian group, which suggested a statistically significantly decreased incidence of cerebral palsy with multiple courses of steroids versus a single course, but a statistically significant increase in significant behavioural problems among the children who survived to the age of six years.[171] I was discussing this with Jane [Harding] during the break this afternoon that in Australia and New Zealand the amount of steroid used is going down. I think it is going down in the UK when I talk to clinicians, because of these uncertainties and concerns about the harm associated with multiple courses of steroids. How we ever get people to interpret what we say correctly, I am not sure. Clearly the messages that are coming out at the moment are not that steroids are bad, but that we need to be more sophisticated in how we use them and how that information is interpreted appears to be to stop using them.

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

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[171] Is this the correct Western Australia group reference?? Ee L, Hagan R, Evans S, French N. (1998) Antenatal steroids, condition at birth and respiratory morbidity and mortality in very preterm infants. *Journal of Paediatrics and Child Health* 34: 377–83.

French Hagan Evans Newham (2004).

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

As to the gestational age at which to use steroids, what formulation, what dose, and what route of administration, I think these are questions that we will have to tackle in the future. What gestational age to give steroids? Nobody has mentioned yet the trial that has only been published in abstract that Peter Stutchfield did in Wales where they recruited women who were going for elective caesarean section at greater than 37 weeks.[172] They randomized nearly 1000 women to receive steroids or not and showed a significantly decrease in admissions to the neonatal unit with respiratory symptoms in the group given [receiving?] steroids. So even beyond 37 weeks, if you deliver electively by caesarean section, steroids seem to offer some advantages. The issue about whether there is a cut-off when you don't give them is going to be re-opened. The multiple course of steroids debate is, as I said, still wide open, although we will see more evidence about this over the coming years, and it may hopefully answer some of our questions.

A big lesson that has come out of the steroids trials – not only antenatal steroids, but postnatal steroids – is that with perinatal interventions we really, really have to look at the children, if not the mothers as well, in the longer term, because these babies don't stop developing the minute they are born, they go on and on and on.[173] I was reading in *Time Magazine* recently about a study where they had done serial MRI scans in teenagers and they are suggesting that the brain does not stop developing until age 25, which seems a

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[172] Where was the abstract printed?

[173] Dr Clive Dash wrote: 'The response by the delegates at the RCOG meeting in 1977 may also have been tempered by the anxiety, certainly among many clinicians with whom I spoke at that time, that the long-term effects might prove to be significant.' E-mail to Dr Daphne Christie, 10 January 2005. See also note 20.

P73 para 3 line 7. Typo. "Why embark on …"

P74 line 6 Typo. "Imminent"

P84 para 2 lines 6&7. Typos. "..we know that less than 6% were really using steroids nationally. Did being involved…."

P97 Footnote 171. Correct reference is:
French NP. Hagan R. Evans SF. Mullan A. Newnham JP. Repeated antenatal corticosteroids: effects on cerebral palsy and childhood behavior. American Journal of Obstetrics & Gynecology. 190(3):588-95, 2004 Mar.

P114 Harding. Faculty of Medicine, University of Auckland

P115 Liley. I would suggest just leaving it as "until his death in 1983."

Jane Harding
ONZM MBChB DPhil FRACP FRSNZ (b. 1955) obtained her medical degree at the University of Auckland in 1978, then completed a D Phil 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 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 in and is Deputy Director of the University's Liggins Institute.

References for footnotes:

P54.
Harding JE, Pang J-M, Knight DB, Liggins GC. Do antenatal corticosteroids help in the setting of preterm rupture of membranes? American Journal of Obstetrics and Gynecology 184: 131-139, 2001.

P55
McLaughlin KJ, Crowther CA, Walker N, Harding JE. Effects of a single course of corticosteroids given more than 7 days before birth: A systematic review. Australian & New Zealand Journal of Obstetrics and Gynecology 43: 101-106, 2003.

P59
Dalziel SR, Liang A, Parag V, Rodgers A, Harding JE. Blood pressure at 6 years of age after prenatal exposure to betamethasone: Follow-up results of a randomized, controlled trial. Pediatrics, 114:e373-377, 2004.

Lois Reynolds

From: Jane Harding [j.harding@auckland.ac.nz]
Sent: 11 September 2005 21:00
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal Corticosteroids : thanks for photo

Dear Lois,

It is most correct, and I think probably most appropriate, to refer to them as Professor Sir Graham (Mont) Liggins and Associate Professor Ross Howie.

Regarding the photo caption, I would suggest something like:
Investigators in the original Auckland trial (Liggins and Howie, 1972) and its 30 year follow-up (Dalziel et al 2005). L to R: Stuart Dalziel (Research Fellow), Mont Liggins, Ross Howie and Jane Harding, July 2005.

Regarding the results of the follow-up, I'm not sure whether they are really appropriate in a review of the history. The transcript tells that the infants exposed to steroids had normal blood pressure and psychological outcomes, and refers to the relevant publications which provide more detail. The other outcomes that we measured (bone density and lung function) are not yet published, though are also normal. If you felt, on final review of the transcript, your would like a short footnote on the overall outcomes I'm happy to provide one, but am just unsure about the appropriateness of this.

Best wishes

Jane

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Lois Reynolds

From: Lois Reynolds [ucgarey@ucl.ac.uk]
Sent: 12 September 2005 10:38
To: Jane Harding
Subject: RE: Witness Seminar: Prenatal Corticosteroids : thanks for photo

Thanks, Jane, for the caption. We shall have a think about the Mullinger query. There is a case for describing what tests were done. May I get back to you?
Best wishes from Lois

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 11 September 2005 21:00
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal Corticosteroids : thanks for photo

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Best wishes

Jane

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17 AUG 2005

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11 August, 2005

Dear Professor Harding,

Witness Seminar: Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth, 15 June 2004

Enclosed is the final proof of the transcript, *Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth* to which you contributed, for your final approval.

Please return your corrected proofs NO LATER THAN **Wednesday, 7 September 2005** Alternatively, if you have access to e-mail, please send any corrections to me at *l.reynolds@ucl.ac.uk* If you think I could answer any queries over the telephone, I am also available between Monday and Thursday on 020 7679 8123, after 31 August 2005.

Please look very carefully at your own contribution on pages 7, 8-22, 24-26, 39-41, 51-54, 58, 89, 100-01 and your biographical note on page 114 to check that the added footnotes and highlighted phrases are correct.

The transcript will be published by the Wellcome Trust Centre for the History of Medicine at UCL in November 2005 as volume 25 of *Wellcome Witnesses to Twentieth Century Medicine*. It will be freely available immediately as a downloadable Adobe Acrobat file from *www.ucl.ac.uk/histmed* following the link to Publications and as a hard copy ordered from *www.amazon.co.uk* for £6 and *www.amazon.com* for $10, plus postage. A complimentary copy will be sent to you on publication. A complimentary copy will be sent to you on publication.

We would also be grateful if you would suggest a journal, website or information group that might be willing to review this volume, or who might be willing to include a paragraph about it as a new publication.

Yours sincerely,

Lois Reynolds.

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey

enc. Wit25 final

√ corrected 24/10/05.

Lois Reynolds

To: Jane Harding

Subject: RE: Witness Seminar: prenatal corticosteroids: further queries 18/10/05

Thanks, Jane, for your reply. These last few queries

-----Original Message-----
From: Jane Harding [mailto:j.harding@auckland.ac.nz]
Sent: 21 October 2005 23:31
To: ucgarey@ucl.ac.uk
Subject: FW: Witness Seminar: prenatal corticosteroids: further queries 18/10/05

Dear Lois,

Unfortunately my e-mail does not give me yellow highlights, but I've commented in italics where there seem to be queries. Hope this helps, but get back to me if there are further queries.

Regards

Jane Harding
------ Forwarded Message
From: Lois Reynolds <ucgarey@ucl.ac.uk>
Reply-To: <ucgarey@ucl.ac.uk>
Date: Wed, 19 Oct 2005 06:08:26 +1300
To: Jane Harding <j.harding@auckland.ac.nz>
Subject: Witness Seminar: prenatal corticosteroids: further queries 18/10/05

Dear Jane,
Two further queries today, and a reply on your return on 21 October would be fine. Yellow highlights require clarification. Best wishes from Lois

(2) 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 [?neonatal?] *these words are used interchangeably here. I don't feel strongly about either* intensive care in New Zealand. It's fair to say that the state [?level?] *I really meant state. This was in the very early days of intensive care, and the formal differentiation of levels was not what I was referring to.* of intensive care varied around the country. The National Women's Hospital was opened in 1964, I think, but I would need to check that, specifically to 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. 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. 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. I think he also describes in that paper, but certainly *has described* to me *in person* [?sense? personally to me, later??? certainly to me, personally, later??] 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.

(3) 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. (fn1) 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. (fn2)

(fn1) A further mention of the importance of a further follow up was made, but no reason given. At the end of the meeting you mentioned the 50-year follow-up. WOuld you like to comment here?
Some of the findings of the 30 year follow-up suggest that there may be subtle changes in insulin responses in those exposed to antenatal glucocorticoids. These are of no clinical significance in 30 year olds, but we think that it would be of great interest to see whether those changes persist, and whether they develop into changes of any clinical significance, as these people age.

(fn2) Tilli asks: Did any mother receiving corticosteroids have their baby die? Was any attempt made during the subsequent follow-ups to trace these mothers?
Yes many babies died in both groups, most in the neonatal period but also a few after this period. We did not make any attempt to trace these mothers; indeed we tried to avoid contacting any whose babies had died, to avoid any distress that might be caused by reminding the parents of their loss.

(4) Shortly after your contribution above (3), Prof Dafydd Walters said: 'Time moves on, and obviously steroids are now used for much shorter gestation babies.' Could you suggest a reference discussing steroids and gestation shorter than 20 weeks?
I do not think anybody is using steroids before 20 weeks (which would be pre-viable). The point here is that although there was a wide range of gestations at which steroids were given in the original trial, the majority of babies were born at what is now regarded as only very slightly preterm gestations. Many more babies are surviving at much younger gestations now. There have been subsequent trials specifically looking at the effects of steroids at younger gestations, but I don't think the statement as it stands needs referencing at all.

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------ End of Forwarded Message

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1·8·05

Dear Mrs Reynolds,

Thank you for your letter.

The author of the paper to which you refer was Ben Sachs. When I last heard of him he was professor at the Beth Israel Hospital in Boston. Should you wish to contact him his current address should be in the American Indices at the R.S.M. library.

Sachs did not condemn antenatal steroids, He merely pointed out potential side effects and advocated caution in the use of the manoeuvre and further research into efficacy. Miss Crowley's own review was published alongside Sach's and she more or less agreed with his appraisal.

Copies of both papers are enclosed.

Yours sincerely

D.F Hawkins

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rec'd back 2/8/05.

Reader 10/8/05

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10 August 2005

Dear Professor Hawkins,

Thank you very much for your letter of 1 August in reply to my query about the Ben Sachs paper, and the photocopies of both Sachs and Crowley.

I hope you will be able to help us with our current Witness Seminar transcript, *Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth*. The text needs to be read by an expert with an eye for the needs of the non-expert, particularly general sense and understandability. The intended audience are historians of science and medicine as well as those in the field. A glossary will be added with that in mind, but it would be helpful to know which terms should be more fully explained.

If you would like to see earlier volumes in the series, Wellcome Witnesses to Twentieth Century Medicine, which are freely available online on publication following the links to Publications at *www.ucl.ac.uk/histmed* or we would be happy to send you a copy of one of our meetings.

I enclose a copy of the transcrript of *Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth*, which has been sent to the contributors today for their final corrections. If you thought you would be able to help us, we should be grateful for your comments by the beginning of **September 2005**. We will acknowledge your help and send you a complimentary copy of the volume, due to be published by the Wellcome Trust Centre for the History of Medicine at UCL in November 2005.

Yours sincerely

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey

enc. Volume 25,

Professor D.F.Hawkins
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31st August 2005

Mrs Lois Reynolds
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Dear Mrs Reynolds

Thank you for your letter of 10th August 2005 and the enclosure.

Major points are:-

(a) I have read Dr Edmund Hey's contribution on pages 3 and 4 three times now, and I still don't understand what Medawar meant when he said most successful papers are a fraud. I suspect it was just a piece of provocative nonsense which is certainly untrue. The great majority of the many thousands of scientific papers I have read start with the statement of a problem, proceed to formulate a hypothesis to solve it, continue to test that hypothesis, and then draw a conclusion. What is fraudulent about that?

(b) Professor Jane Harding's remarks on page 40 on Ross and Mont's comments in the last paragraph on page 40 about "Nothing good could come from the Colonies" should be withdrawn. Old men's paranoia should have no place in a document like this. The comments are absolute nonsense. Liggins' work was given the highest respect in this country. The reasons for the delay were firstly a defect in Liggins' original trial - I think it was something to do with imbalance between male and female babies - and secondly a reluctance to give large doses of a highly potent synthetic steroid to pregnant women without corroborative studies. Remember that Lenz's report on thalidomide had come out in 1961.

(c) I'm not at all sure that people's 30 year old recollections of conversations over coffee qualify as "history"!

You will find many comments on points that puzzled me and typographical errors marked in red on the enclosed draft.

Your document reminded me of the very sad story, as it was told to me, of the man who discovered surfactant - though he did not call it that. I'm ashamed to say I have forgotten his name. I think he was a lecturer in a technical college in or near Southampton, and I think he worked with rabbits. He presented his work at a meeting of the Physiological Society in the 1920's or early 1930's. Many years ago I came across the abstract in the Proceedings of the Physiological Society meetings but again I am ashamed I did not make a note of it. In these days Henry Dale and his cronies dominated Physiological Society meetings and they turned on this man and rubbished his work. His great sin was that he did not work in one of their laboratories, he was not a "member of the club". He left the meeting a broken man. He gave up physiological research and I think he ended up as a school teacher. I read his obituary somewhere a few years ago.

I regret I am rather frail these days and lack the ability or facilities to go through the Proceedings of the Physiological Society, but can only hope you will have someone with the energy to do this.

Yours sincerely

D. F. Hawkins

D.F.HAWKINS

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5 September 2005

Dear Professor Hawkins,

Thank you very much for reading the Witness Seminar transcript, *Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth*, and for your very interesting comments and for taking the time to do so.

I shall endeavour to find the piece in the *Journal of Physiology*, and will get back to you with my findings.

A complimentary copy of the volume will be sent to you on publication.

Yours sincerely,

not sure this is important - for this transcript

Lois - are his remarks the ones in red? If so, they need to be taken with care.

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey

CORRECTIONS added 27/10/05

Hawkins

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

-3 10.3.05; -4 7.07.05; -5 28.7.05;-6 4.8.05 (2nd); printed: 5 August 2005

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checked 27/10/05.

Please return by 12 September 2005.

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

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

I was provoked into checking up what Wellcome History of Medicine people had to say about Sir Peter Medawar and his statement that most scientific papers are a fraud.[1] I would encourage you to read what he actually wrote, because it isn't quite how it gets quoted nowadays. It was an unscripted talk, which I find quite amazing, on the third programme – yes, it was called the third programme, back in 1963. Since we are in reminiscing mood, I had just started my first job as a Medical Research Council (MRC) physiologist/clinician/animal worker, working with Kenneth Cross. I heard Medawar talk on the day [it was given] and it had an absolutely profound effect on me. I thought I might read a bit of it, but then I found another talk in which he was actually interviewed defending this [statement], just three years later. I think we will come back to this at the end of the day. The issue is what he meant about research being fraudulent. I will just read a couple of sentences. The interviewer says, 'Arising out of your paper, "Is the scientific paper a fraud?", which was written under the influence of Karl Popper's ideas on scientific methods your answer was "Yes, it *is* a fraud" in the sense that it systematically conceals or distorts the way in which the ideas were thought out or developed. Have any of your scientific papers been, in this sense, fraudulent?' And Peter Medawar replied,

> A good many of my scientific papers have been moderately fraudulent. Let me put it this way:…I have never pretended that the research I reported in the scientific paper was done in the inductive style – that is to say by the vacuous collection of facts which then tumbled somehow or other into

[1] Medawar (1963): xx-xx. Freely available at www.dpi.inpe.br/cursos/ser212/artigos/medawar_paper_fraud.pdf (visited 2 August 2005). See also 'What is a Witness Seminar?', introduction by Tilli Tansey to Tansey *et al.* (eds) (1997): i–v.

> place. I think I have adopted a compromise. I have not practised what I have preached, but then I am not the first person to fail to do so.

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

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

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

I think that we should start by asking Mel Avery, who has come all the way from Boston – although I think she's been on the Rhine until a few days ago – to set the scene, because 30, 40 years ago clinicians and physiologists and animal research workers were much closer together than they are often are nowadays. Certainly in the UK it's very uncommon for you to meet a person who spends some days in the lab and some days on the farm or in the animal laboratory. But you can tell us your story, because years ago much of what we

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[2] 'My Life in Science', a transcript of an interview of Peter Medawar conducted by xxx Wilson, broadcast on the BBC Third Programme on 25 April 1966. Published in *The Threat and the Glory: Reflections on science and scientists.* Oxford University Press 1990, p.??? Quotes from pages 5–6.

understand now about the lung came from the combination of those interests, didn't it?

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

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

My research fellows at Johns Hopkins set out to map the course of events in the developing fetal lung of the lamb, the animal of choice. I have often wondered why, and I think it's because babies and lambs are about the same

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[3] See, for example, Barclay A E, Barcroft J, Barron D H *et al.* (1939) A radiographic demonstration of the circulation through the heart in the adult and in the fetus, and the identification of the ductus arteriosus. Br. J. Radiol. 12: 505–???. Barclay A R, Franklin K J, Pritchard M M. (1944) *The Foetal Circulation and Cardiovascular System, And the Changes that they Undergo at Birth*. Oxford: Blackwell. Born G V R, Dawes G S, Mott J. C., *et al.* (1954) Changes in the heart and lungs at birth. In *Cold Spring Harbor Symposia on Quantitative Biology*, Vol. XIX. New York. Young M. (19xx) ???? [could you suggest an appropriate article?]

[4] Smith C A. (1945) *The Physiology of the Newborn Infant*. Springfield, IL: C C Thomas. Strang L B. (1977) *Neonatal Respiration: Physiological and clinical studies*. Oxford: Blackwell Scientific. For Professor Sir Robert Boyd's appreciation of Strang's work on the adaptation of the fetal lung to air breathing, see Christie and Tansey (eds) (2001): 16.

size at birth and the equipment you had for one worked for the other. I don't know if that is quite true or not, but those are my thoughts on the matter.

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

That was 1962. Then we said we have to know about the normal appearance of various enzymes and so on in the developing lamb. That's when all the people in the laboratory – which then numbered 15 or 20 – produced a paper about the timing of various enzymes and other events in the normal lamb lungs.[6] I went to New Zealand [in 19xx] as a guest of the Society of Obstetricians and the Paediatric Society. Mont Liggins was there and after I said that lambs were perfectly normal by 147 days gestation, Mont said, 'What if I told you we can identify accelerated maturation in the lambs' lungs at 115 days?' That's too big [a difference] to be an error. Were New Zealand lambs that different from the lambs in the USA? I didn't believe that, neither did he. It appeared that, in fact, glucocorticoids could accelerate lung maturation of lambs.[7]

STET

The story of the glucocorticoids moved ahead when Liggins and Howie proposed a randomized control trial, I think 100 days before the birth of the lamb, and it was obvious that the effect was reproducible.[8] I would also like to pay tribute to Sue Buckingham, a Fellow at the Columbia Presbyterian

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[5] Moog F. (1953) The influence of the pituitary–adrenal system on the differentiation of phosphatase in the duodenum of the suckling mouse. *Journal of Experimental Zoology* 124: 329–46.

[6] ??1962 paper from your laboratory??

[7] Liggins (1969).

[8] Liggins and Howie (1972).

Medical School, probably well known to you. At the Federation of American Societies for Experimental Biology meeting she presented a paper on the effects on mice.[9] She made the point [??that .....??] in 1968 and I thought it was frivolous. Then we had a series of observations, not well put together at that time, but confirmed over and over, that glucocorticoids accelerated maturation, not only of Moog's mice intestine, but also of the fetal lung. By then I had finished my fellowship – Sue, alas, died shortly after that meeting, which was a great tragedy, for her contribution was valuable.

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

Hey: I don't think we will take questions at this stage, because Mel has just set the scene. She's been very modest, our main American witness, and she will be able to tell us a lot more later about the way in which things rolled out. We shall want to hear from her about when the collaborative [??US NIH Collaborative Group??] trial was done and how it was done, and why it was done the way it was. But that's a long way down the line this afternoon. What we should do now, before we have our first break for discussion and questions is to hear from Jane Harding, who works in the room Ross [Howie] once

[9] Buckingham *et al.* (1968).

worked in. I get the impression she almost had to sit on the papers that he had left behind, because he had left rather a lot, and it's surprising how much more is still coming out of those papers. So we haven't got Ross here in person, but you might just hear his voice.

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

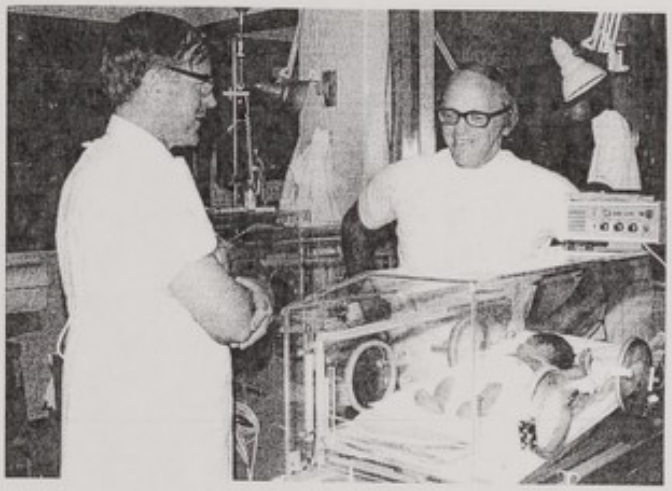

Figure 1: Ross Howie and Mont Liggins, *c.* 1972

I will start by reading from a letter written by Mont Liggins to Iain Chalmers earlier this year and I quote:[10]

> When I returned to a position as a Senior Lecturer in O[bs] and G[ynae], at National Women's Hospital in 1959, I asked my friend Bill Liley, of fetal

[10] Letter from Mont Liggins to Iain Chalmers, 6 April 2004. See appendix??, xxx

> transfusion fame,[11] how to choose a topic. He said to look for a major problem that was potentially solvable. The major problem was easy. Prematurity stood out above everything else. I naively thought that all I had to do was solve the ancient question of what controlled the onset of labour at term and the reason for premature onset would become apparent.

Mont then described how he worked on his idea that the onset of labour was controlled by the fetus not the mother, and how he spent a sabbatical period at the veterinary school at the University of California at Davis, to assess the role of cortisol[12] 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.[13] 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 [2003], as part of a recording of an oral history project undertaken by the place at which I now work, the Liggins Institute. It is named after him, and we asked Mont to record essentially his life story. He agreed that I could play a part of it to you, as it relates to this story.

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[11] Liley A W.(1964) The technique of fetal transfusion in the treatment of severe haemolytic disease. *Australian and New Zealand Journal of Obstetrics and Gynaecology* **30**: 145–8.

[12] Cortisol (hydrocortisone) is a glucocorticoid, whose synthetic derivative is prednisolone for patients who cannot take cortisol orally, used clinically to suppress immune responses. ACTH (adrenocorticotropic hormone) is a polypeptide whose release from the pituitary gland is regulated by corticotrophin-releasing hormone (CRH). At this time cortisol was dervied from xxxx. See Pearson O H, Eliel L P. (1950) Use of primary adrenocorticotropic hormone (ACTH) and cortisone in lymphomas and leukemias. *Journal of the American Medical Association* **144**: 1349–53. See also Vale W, Spiess J, Rivier C, Rivier J. (1981) Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science* **213**: 1394–7.

[13] The Wellcome Trust gave £40 000 in grants for research assistance over eight years from 1969 to 1976. See Appendix xx, pages xx–xx.

Mont Liggins [from a tape recording]: I had always been meticulous in doing a complete autopsy of all the lambs that I delivered, weighed organs, helped I must say by my secretary. 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 I speculated that the cortisol had accelerated the maturation of enzymes in the lung that caused accelerated maturation. Now at that time my facilities were fully occupied in studying the question of parturition and I didn't have time to pursue this problem.[14] But it so happened that Mary Ellen Avery who was working on respiratory distress syndrome (RDS), and lung problems, and the discoverer that surfactant was necessary for the maintenance of lung expansion, was visiting New Zealand.[15] So we were both going to a meeting in Christchurch where I described my findings in a series of lambs with expanded lungs.

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[14] See Appendix xx, pages xx–xx/

[15] Kotas R V, Avery M E. (1971) Accelerated appearance of pulmonary surfactant in the fetal rabbit. *Journal of Applied Physiology* **30**: 358–61. Motoyama E K, Orzalesi M M, Kikkawa Y, Kaibara M, Wu B, Zigas C J, Cook C D. (1971) Effect of cortisol on the maturation of fetal rabbit lungs. *Pediatrics* **48**: 547–55. See also Avery M E, Fletcher B D, Williams R G. (1981) *The Lung and its Disorders in the Newborn Infant.* 4th edn. Philadelphia, PA: Saunders. First edition, 1964.

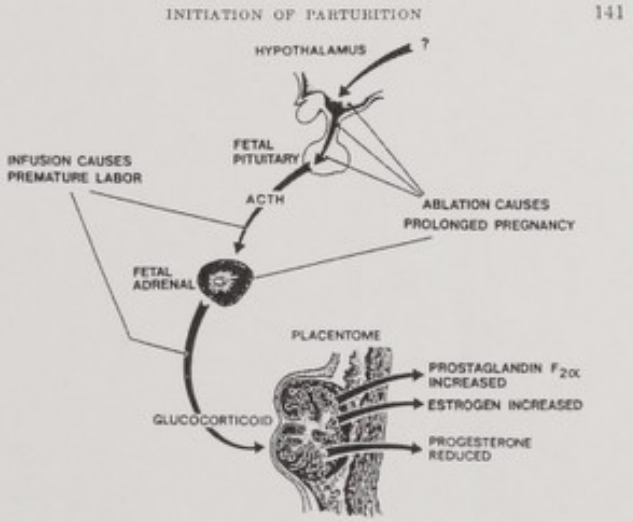

FIG. 19. Schematic diagram of the pathway by which the fetal lamb influences endocrine events in the ewe. Also shown are experimental procedures that have been used to modify the activity of the pathway.

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

Liggins *et al* (1973), 141.

She couldn't get back to Boston fast enough to set up experiments in rabbits – giving fetal rabbits cortisol – and produced the definitive paper on the effects of corticosteroids on lung maturation.[16] 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

[16] Avery M E, Mead J. (1959) Surface properties in relation to atelectasis and hyaline membrane disease. *American Medical Association Journal of Diseases of Children* **97**: 517–23. OR DeLemos R A, Shermeta D W, Knelson J H, Kotas R, Avery M E. (1970) Acceleration of appearance of pulmonary surfactant in the fetal lamb by administration of corticosteroids. *American Review of Respiratory Disease* **102**: 459–61. Avery M E. (2000) Surfactant deficiency in hyaline membrane disease: the story of discovery. *American Journal of Respiratory Critical Care in Medicine* **161**: 1074–5.

> same enzymes as animal lungs. Should we do a clinical trial in premature babies and put it to test? 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, 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.[17]

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 was all Mont's idea. In fact it's my view that it was a quite remarkable partnership. At the time Ross was an MRC research fellow, the only paediatrician at the National Women's Hospital in Auckland and indeed in New Zealand, who was able to ventilate [?very small? small? any?] babies. I would like to quote now from Ross' Howie's words describing these events, although I have abbreviated them somewhat:

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

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[17] How should the tape be cited??? Is it held in your library? Liggins and Howie (1972). For the next well-controlled study following Liggins and Howie (1972), see: Papageorgiou *et al.* (1979).

> In total contrast, the lungs of the other remained solid and liver-like, and sank.[18]

There are a couple of things that interest me about these descriptions. One is the unique pairing of an experimental scientist who was also an obstetrician, with the only paediatrician in the country who was capable of looking at [after] the [?premature?] babies. Another is that whatever the later perceptions became, it's clear that both the authors of the study were involved together from the beginning, in the animal laboratory, as well as in the clinical aspects.[19] Finally, I am entranced with Ross's comments that this lamb trial was simply a sideline for both of them. It's an interesting warning against the narrow and predetermined endpoints of some research programmes, and highlights the importance of serendipity in progress.

Ross describes presenting the results of the completed study – not the initial part of the study that was published in 1972, but the completed study – at a symposium hosted by the Royal College of Obstetricians and Gynaecologists of the UK in 1977.[20] He said to me, 'They didn't really want to hear'. He also

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[18] Quoted from 'Prenatal glucocorticoids in preterm birth: a pediatric view of the history of the original studies', a draft memoir by Ross N Howie dated 2 June 2004 and distributed at the Witness Seminar. It will be deposited along with other records of this meeting, GC/253, in Archives and Manuscripts, The Wellcome Library, London.

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

[20] Dr Clive Dash wrote: 'At the time when Ross Howie presented the results to RCOG in 1977, the UK study was in its recruitment phase. Whether knowledge of the status of the UK study played any part in the cool response of the delegates at the meeting, which Ross sensed, would be speculative.' E-mail to Dr Daphne Christie, 10 January 2005.

reported that when he was asked for a recommendation as to what people should be doing, he said that the treatment looked very promising, but that it would be unsafe to initiate a new treatment on the basis of a single trial. He said that he knew what he should do, but that others should wait for ongoing trials. Other people here can talk about the progress of the treatment after that time. My own involvement began perhaps when I entered medical school in 1973. Both of the principal actors were my tutors. The use of antenatal steroids was routine at that time in our hospital and has remained so ever since. By this time Mont had moved onto other studies. Ross was completing the four- and six-year follow up of the original cohort, funded by the World Health Organization.[21] He always believed very strongly that long-term follow up was essential for anything in neonatal care and set about this with his usual thorough approach. The follow-up studies were published in the early 1980s and the ongoing follow-up studies we will talk about later.[22]

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

Harding: I can tell you that story because I specifically asked both of them in recent weeks. To paraphrase a long story: Mont had been doing work in human pregnancy on the effects of steroids on the fetus, and he had a reasonable idea of what dose of steroid was required to suppress progesterone production and he presumed that that would be an adequate dose to do

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[21] WHO studies????? MacArthur B A, Howie R N, Dezoete J A, Elkins J. (1981) Cognitive and psychosocial development of four-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* **68**: 638–43. ? Harding J E, Howie R N. (1987) First-year mortality and hospital morbidity after newborn intensive care. *New Zealand Medical Journal* **100**: 548-52. For erratum, see *New Zealand Medical Journal* (1987): 642.?

[22] Follow-up studies here.

something to the fetus. He knew that he wanted something that would be reasonably long-lasting, so that it didn't have to be given too frequently to pregnant women and decided that something that would last for 24 hours and therefore two doses would give you about a 48-hour effect would be adequate, based on the animal studies. He therefore set about looking for a drug that would be clinically easy to manage, long-lasting, and which had an identically appearing placebo. This is not easy, because all the long-lasting preparations of glucocorticoids are opaque, they are milky substances, and a placebo wasn't easy to find. He wrote to a number of drug companies asking for help, and in the end Glaxo – originally the name of a dried milk power sold by a New Zealand company, and it so happened that the medical director was a mate of Mont's – provided an opaque placebo.[23] Their long-acting preparation was the one he used, because that was the one that was available and they were provided with the placebo. So the placebo was cortisone acetate, which had very low potency but looked the same, and the drug that he selected was the Glaxo drug because that was what was available and because the director was a mate who provided it for free. I might say that the study was unfunded. Mont said to me, 'We didn't need funding to do this trial.' And of course they didn't, because the drug was provided free and both Mont and Ross were fully salaried and were able to put in all of their time.

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

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

Harding: Twelve hundred. The real number was 1218.

Hey: Still the biggest trial.

Harding: Still the biggest trial. The original publication that everybody cites from 1972 was only the first 282. But they continued to recruit long after that trial.

If I could just comment. The other thing that most people aren't aware of is that after the first 717 women were enrolled, when they did the first analysis and thought 'the stuff really does work', they doubled the dose. In the rest of the trial, the other 500 odd actually received twice the dose, to see whether more was better, and they concluded that it was not, and published all of the data as a combined single trial.[24]

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

Harding: That's correct.

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

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

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[24] 1976 results?

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??]

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.

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

Harding: Given a moment I could look it up, but from memory the youngest gestation was about 28 or 29 weeks, and the average gestation at delivery was around 35 weeks.

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

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

Harding: Yes, there have. There have been at least four trials in the 1990s and I am sure Dr Crowley will talk about this. But the new Cochrane Review, which is in the process of being produced, will show clearly that the benefit is still there in the surfactant era, in the ventilator era and in the four randomized placebo control trials done in the 1990s.[32]

Sir Iain Chalmers: Jane, I don't know whether you have tried to do this already, but it would be wonderful if these mothers and children that you are in touch with came to know just how important a contribution they have made to the history of perinatal care. If you haven't planned to do so already, could you think about letting them know that?

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[32] Four trials in the 1990s; new Cochrane Review.

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

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

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

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

Avery: At the meeting in Christchurch, with Liggins in attendance, I had given the most boring paper I have ever given, describing the time of onset of a whole bunch of things that we could measure to map out the terrain of the maturation of different organs in the lamb, knowing that we were particularly interested in lambs. Why did we tumble to that? It was partly that Mont wanted information from sheep, some of which were different from what he

expected. And the difference turned out to have been that some of the animals got steroids and some didn't, and the ones that were advanced had received the steroids. There was a concern that that would be a permanent effect if they were treated *in utero*, but injured in some way by the steroid; that they would grow up with small lungs or the lung would fail to perform in some way, and so he needed all the information he could get about safety. I think we published our first paper on six sets of twins. That wasn't a very big series, but six out of six showed the same result. It meant that the data were pretty secure, but the next question was, 'What happens when they are ten years old?'

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

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

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

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

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

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, but I could go back and ask him. He commented about who gave him the money and I think probably he simply asked for research funding to look at preterm labour.[33] 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.

Dr Daphne Christie: Dr Tilli Tansey has tried to find out some information about this, so we might be able to get back to you later on this.[34]

Dr Stephen Hanney: We have been looking at the 'payback' or benefits from this whole stream of work, and I will be talking later. On this specific question,

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[33] See Appendix xx, pages xx –xx, for details of the eight years of funding for research assistance from the Wellcome Trust, 1969–76.

[34] See Tansey???Appendix???

at one stage we did have a figure of £20 000 from the Wellcome Trust for one of these pieces of work, I think it was for the original animal trial.[35] I am not quite sure how that fitted in, how long a period that was, but that is a figure that was quoted. It was obviously a very small grant even in those days.

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

Hey: That included his going to America and learning how to hypophysectomize fetal sheep.[36]

Harding: He did all that before he came back [?to New Zealand from ??California?], and when he came back was when he had the Wellcome funding to start his own lab.[37]

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

Harding: That's correct. He had presumed that that would be the case. When he was on sabbatical at UC-Davies he devised a way of doing the hypophysectomy and did the initial experiments there and then came back to set up a sheep lab in New Zealand with Wellcome Trust funding at that time.

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[35] Hanney and Wellcome funding

[36] Surgical removal of the hypophysis, or pituitary gland, in the pregnant ewe.

[37] See Appendix xx, page xx.

So I think that was probably the one and only grant and a very large one at that time for working expenses.

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

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

How?

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

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

trial, which we will no doubt come to, and the follow up was still going on at the time that the Auckland trial follow up was completed.[38] 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 the trial under other circumstances, and check what specifically was and wasn't helpful about this treatment.

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

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

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[38] Is this the long-term follow up? OR Daliel in note 30? MacArthur B A, Howie R N, Dezoete J A, Elkins J, Liang A Y. (1989) Long-term follow up of children exposed to betamethasone *in utero*. In Tejani N. (ed). *Obstetrical Events and Developmental Sequelae*. Boca Raton: CRC Press, 81–9.

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

I then went to work in the Hammersmith Hospital in London and in 1978 attended a meeting at the Royal College of Obstetricians and Gynaecologists (RCOG) marking the publication of the proceedings of the 1977 RCOG Preterm Labour Study Group. Ross Howie had attended this meeting in 1977, and presented a paper jointly authored with Mont Liggins on the outcome of 1068 women and their babies who had been enrolled in randomized trials of antenatal corticosteroid therapy. This showed a massive reduction in neonatal mortality in those babies who were exposed *in utero* to antenatal steroids.[39] The Proceedings of that Preterm Labour Study Group contained 14 papers on tocolysis and only two papers about fetal lung maturation – a clear indication of where the emphasis of British obstetrics lay at that time when it came to preterm labour. Obstetricians were obsessed with trying to stop preterm labour rather than on trying to improve the outcome for the premature baby by accelerating lung maturation. Despite a dearth of objective evidence of efficacy, a variety of betasympathomimetic drugs were being actively promoted by the pharmaceutical industry at this time, whereas no pharmaceutical company was promoting the use of antenatal steroids.

In 1980 at the Hammersmith Hospital, London, Professor Denis Hawkins founded the *Journal of Obstetrics and Gynaecology*. He received a paper from

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[39] Howie R N, Liggins G C. (1978) Clinical trial of antepartum betamethasone therapy for prevention of respiratory distress in preterm infants. In Anderson A, Beard R W, Brudenell J M, Dunn P M. (eds) *Preterm Labour*: Proceedings of the fifth study group of the Royal College of Obstetricians and Gynaecologists. London: The College, 281–9.

Ben Sachs, a British obstetrician working in the US, which reviewed the adverse effects of antenatal steroids and the lack of evidence to support their efficacy.[40] He challenged me to write an opposing view to this manuscript. This led to a paper written in 1980 and published in 1981, entitled 'Corticosteroids in pregnancy: the benefits outweigh the costs'[41]. I was either lucky or lazy, because I decided to ignore observational evidence. Although I had never been taught that the randomized controlled trial was the best form of evidence, instinct led me in that direction. My literature search yielded four randomized controlled trials of antenatal steroids. And I based the paper on two tables derived from amalgamating the results of the four trials, showing substantial reductions in neonatal mortality and morbidity in babies whose mothers were randomized to receive antenatal steroids. [See Figure 3.]

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

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

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

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

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

Figure 3. Patricia Crowley's 1981 results.
Crowley (1981): 148.

[40] Sachs B P. (1981) Corticosteroids in pregnancy: their potential hazards and track record. *Journal of Obstetrics and Gynaecology* 1: 143–46.

[41] Crowley P. (1981) Corticosteroids in pregnancy – the benefits outweigh the costs. *Journal of Obstetrics and Gynaecology* 1: 147–50.

By the time this paper was published in 1981 I had started a 9-month attachment at the National Perinatal Epidemiology Unit (NPEU), which was one of the most rewarding periods of my professional life. Anne Anderson and Iain Chalmers read the paper and invited me to contribute a chapter on antenatal steroids to a book that they were planning on *Effective Care in Labour and Delivery*. This was intended to follow *Effectiveness and Satisfaction in Antenatal Care*.[42] I started work on a chapter on fetal lung maturation, examining the evidence in relation to antenatal corticosteroids and any other agents that aimed to accelerate pulmonary maturation.

Progress on this proposed book was delayed by the illness and eventual death of Anne Anderson. It was eventually subsumed into a much more ambitious venture, *Effective Care in Pregnancy and Childbirth*[43]. Meanwhile, led by Iain Chalmers, a group of individuals based at or associated with the National Perinatal Epidemiology Unit, became involved with the development of the Oxford Database of Perinatal Trials, which aimed to identify, assemble and analyse all published and unpublished randomized controlled trials available in the world literature in perinatal medicine.

I left Oxford in 1981 and returned to Dublin to continue to train as an obstetrician but maintained my contact with the NPEU. My associates working with the Oxford Database regularly alerted me to a new trial that had been uncovered by enthusiasts who were hand-searching the literature to find randomized trials. The next three years saw the publication of follow-up data from the Auckland trials and of the results of the US NIH Collaborative Group on Antenatal Steroid Therapy study.[44] With hindsight we could ask

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[42] Enkin M, Chalmers I. (eds) (1982) *Effectiveness and Satisfaction in Antenatal Care*. London: Spastics International Medical Publications, distributed by Heinemann Medical.

[43] Chalmers I, Enkin M, Keirse M J N C. (Eds) (1989) *Effective Care in Pregnancy and Childbirth*, vol. 1: Pregnancy; vol. 2: Childbirth. Oxford: Oxford University Press.

[44] Collaborative Group on Antenatal Steroid Therapy (1981) Effect of antenatal dexamethasone therapy on prevention of respiratory distress syndrome. *American Journal of Obstetrics and Gynaecology* 127: 529–32.

whether the Collaborative Group trial should ever have taken place, because at the time when recruitment was taking place for that trial there was already substantial evidence in the literature that antenatal steroids were effective and safe. If we look at the 1000 or so babies who received antenatal steroids in the randomized trials prior to 1980, and the 1000 babies who received placebo in these trials, 130 of the babies who received placebo died, compared with 70 of the babies who received antenatal steroids. Were those individuals recruiting participants for the NIH Collaborative Group trials unaware of these results? Had clinicians or parents been aware of these results it would have been difficult to persuade anyone to be randomized to placebo in the late 1970s or early 1980s.

As the 1980s progressed, I regularly updated my collection of randomized trials. Because of a series of subgroup analyses emerging from the US NIH Collaborative Group trials, I became interested in sub-group analysis of the outcomes of the accumulated trials. Commentators on the NIH trial reported that antenatal steroids were effective mainly in babies of between 32 and 34 weeks, and 'worked' in black females but not in white males.[45] I went back to the collection of trials that I had accumulated and looked at what happened to white males in Auckland and found they benefited from antenatal steroids. This was how many of the sub-group analyses produced in the original systematic review of randomized trials came into being. It was driven by a need to refute a number of reviews questioning the efficacy of antenatal steroids based on these sub-group analyses, principally from the NIH Collaborative Group study.

Some form of systematic review of antenatal steroids was part of my life in various ways throughout the early 1980s. The proceedings from a conference I attended in Italy in 1984 show that by then I was looking at the outcome of

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[45] Roberton N R C. (1982) Editorial: Advances in respiratory distress syndrome. *British Medical Journal* 284: 917–18.

seven trials, loosely synthesising the outcomes.[46] In 1987 to 1988 the technology became available at the NPEU to produce a meta-analysis with electronically entered data, and to generate results in the form of Odds Ratios with confidence intervals. The review of antenatal steroids became the first to be entered to the Oxford Database of Perinatal Trials. This was a very exciting time, when, after years of collecting data, I saw graphic evidence of the efficacy of antenatal steroids in preterm babies in general and in all relevant sub-groups.

By 1989, when the results of the antenatal corticosteroid review were available in an attractive, accessible electronic format on the Oxford Database of Perinatal Trials and on paper in the book *Effective Care in Pregnancy and Childbirth*, I thought that this information was accessible to obstetricians around the world, and believed that no further publications were necessary to promote the use of antenatal corticosteroids. However, I was eventually persuaded by Iain Chalmers to publish a paper version of this systematic review in the *British Journal of Obstetrics and Gynaecology*[47].

Looking at practice throughout the world with respect to antenatal steroid use, it is only after 1990 that we can see any more than 20 per cent of preterm babies being exposed to antenatal steroids in any country, with the exception of Australia and New Zealand. Work from Bill Kitchen in Melbourne in the 1970s, showed 45 per cent of Melbourne babies in the 1970s were treated with antenatal steroids prior to delivery.[48] Elsewhere around the world, it fell often

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[46] Crowley P. (1986) Enhancement of fetal lung maturity with corticosteroids. In Cosmi E V, Di Renzo G C. (eds). *Selected Topics in Perinatal Medicine*. Rome: CIC Edizioni Internationali, 143–9.

[47] Crowley *et al.* (1990).

[48] [Which reference??] Doyle L W, Kitchen W H, Ford G W, Rickards A L, Lissenden J V, Ryan M M. (1986) Effects of antenatal steroid therapy on mortality and morbidity in very low birth weight infants. *Journal of Paediatrics* **108**: 287–92. OR these two from the Australian Wit Sem: Kitchen W H, Ryan M M, Rickards A *et al.* (1978) A longitudinal study of very low-birthweight infants I: Study design and mortality rates. *Developmental Medicine and Child Neurology* 20, 605–18. Kitchen W H, Rickards A, Ryan M M *et al.* (1979) A longitudinal study of very low-birthweight infants II: Results of controlled trial of intensive care and incidence of handicaps. *Developmental Medicine and Child Neurology* **21**: 582-589. For further

under 10 per cent and never higher than 20 per cent, up to 1990. So the publication of this paper in the *British Journal of Obstetrics and Gynaecology* was a landmark in terms of improving the use of antenatal steroids.

In 1994 the NIH Consensus Conference on antenatal steroids[49] took place. At that meeting I contributed an updated version of the systematic view of antenatal steroids,[50] derived mainly from the electronic review published on what was by then the *Cochrane Pregnancy and Childbirth Database of Perinatal Trials.*[51] The rest of that three-day meeting was taken up with many observational studies, and laboratory based papers on antenatal steroids and following the three-day meeting a strong recommendation was released urging obstetricians in the US to use antenatal steroids.

In 1996 I was invited by the Royal College of Obstetricians and Gynaecologists to update a guideline on the use of antenatal steroids issued in 1992.[52] The revised guideline, based on the systematic review published in the Cochrane Library, strengthened the recommendation from the RCOG on antenatal steroids use. By the late 1990s, 70 per cent of preterm babies delivered in the UK were being treated with antenatal steroids prior to delivery.

Within a year or two of finally adopting the evidence-based practice of prescribing a single course of antenatal steroids to women at risk of delivering a preterm infant, obstetricians started to prescribe repeated courses of antenatal steroids. The practice of repeated courses of antenatal steroids in women who remain undelivered a week or more following the original treatment crept in

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details, see www.cshs.unimelb.edu.au/programs/jnmhu/witness/001.html (visited 2 August 2005).

[49] National Institutes of Health (NIH) (1994). Their recommendation was to give a single course of corticosteroids to all pregnant women between 24 and 34 weeks gestation who are at risk of preterm delivery within 7 days.

[50] Crowley (1995).

[51] The first structured review by Dr Patricia Crowley appeared on the Oxford Database of Perinatal Trials in 1987. The 1996 version appears as an example of a Cochrane Review at www.cochrane.org/reviews/exreview/htm (visited 2 August 2005). See also Figure 5.

[52] See note 141.

rapidly, without any evidence to support its safety or efficacy. All the evidence from randomized trials related to a single course of antenatal corticosteroid therapy.

[Figure 4 here]

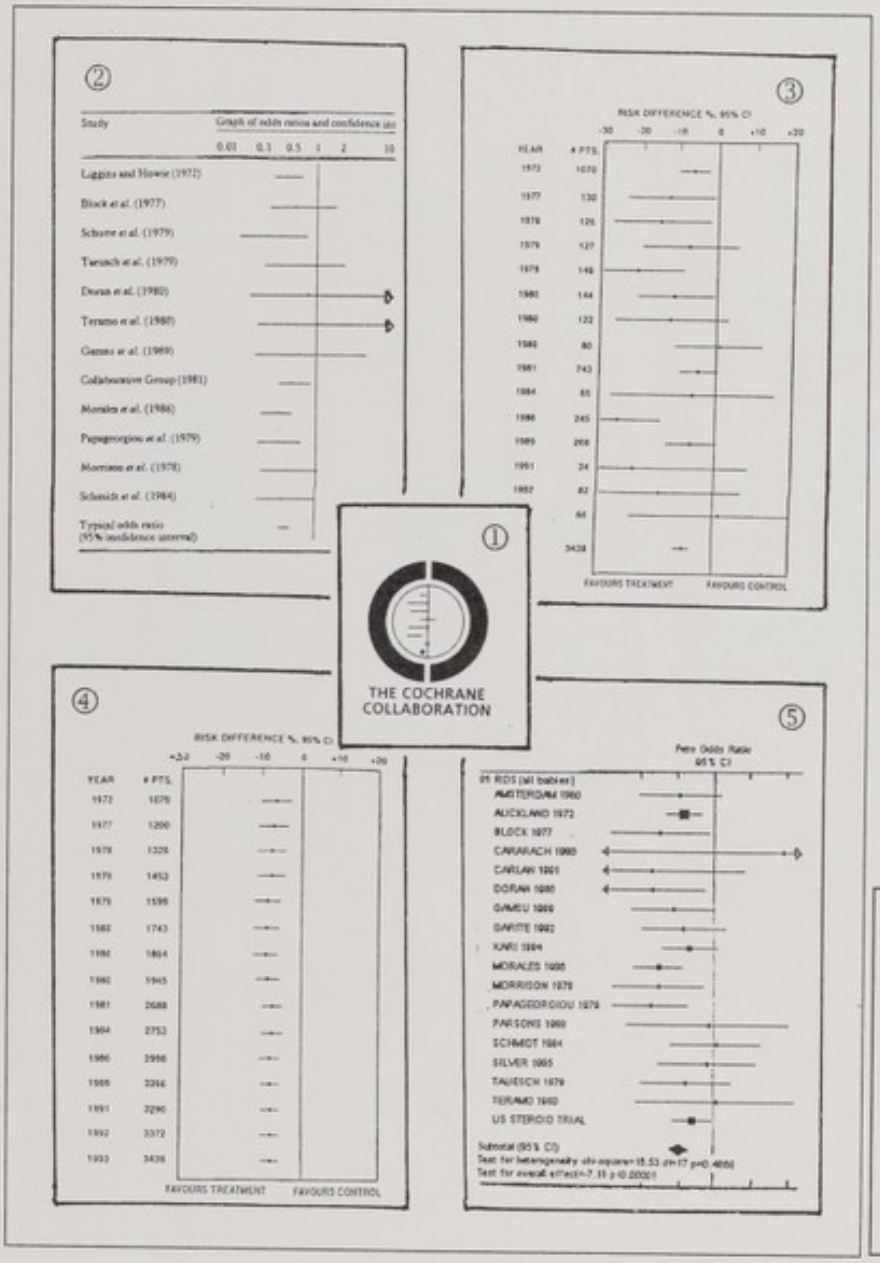

Figure 4: Patricia Crowley' meta-analyses, 1992–2004.

1. 7 trials, original Cochrane logo, 1992;
2. 12 trials, Crowley (1989);
3. 15 trials, Crowley (1994);
4. 15 trials, Sinclair (1995);
5. 18 trials, Cochrane Library (2004, CD000065).

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

Hey: I think it might be sensible to break and explore some of the ……..ation that went on between 1977 and [?when?] Ross's reporting [?reported?] to the [?which?] College in [?and?] 1994 and [?when?] we end up with the NIH conference. It's a long period of time. Mary [?Mel?], you were a witness to much of this.

Avery: It was frustrating.

Hey: Well, you banged the drums quite hard.

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

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]

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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 include, and concluded that it wasn't worth doing, except perhaps in pregnancies more than 34 weeks.

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

their toes. It was actually paediatric versus obstetric issues in many centres that discouraged its use.

Mr John Williams: I am a humble obstetrician, who is a recipient of the literature rather than a contributor, but I was developing [working??] during the era of these publications, and here are some of the things that struck me. The first was an oration by Sir Stanley Clayton [President of the Royal College of Obstetricians and Gynaecologists, 1972–75] in 1975 at the American Congress [??College??] of Obstetrics and Oncologists[??Obstetricians and Gynecologists??], where he said that in his experience as the editor of the grey journal, the *Commonwealth Journal* as it was then, how much rubbish was submitted for publication.[60] He wished that registrars didn't have to do research to get jobs, and it was time it was all stopped. That was the first thing that hit me. And I was then at a meeting in Cardiff where Cliff Roberton spoke, and he seemed to be of the opinion that obstetricians shouldn't be treading on the toes of paediatricians, and that they were very good at looking after babies and we didn't need to interfere. He went on to pour scorn on quite a lot of the uncontrolled and poor publications, and again this struck me. I said, 'Why were these published if they were such bad studies?', and he said, 'You know, people having a glass of whisky and refereeing a paper, if it's somebody they know they will put it in, if it's not they won't'. He was fairly scornful of the poor quality publications, and it gave the impression certainly in Cardiff that we shouldn't be using steroids. And that set me back a little way.

The poor publications continued to come out and were very confusing. In fact I wrote to Iain [Chalmers] asking what was going on: 'I want to carry out best practice.' Paediatricians where I was then working in Chester were very keen that we should be using steroids based on the original work, and I said that everyone else says it's rubbish. And it wasn't until the systematic reviews and

[60] Was this published?

the guidelines came out that we actually introduced it as an overall practice, we gave it to certain selected patients, but not overall. I think that was a common view among obstetricians in this country in the non-academic world.

Dr Roger Verrier Jones: There are two hospitals in Cardiff, two maternity hospitals, and John worked in the other one. The reason I am here is that Iain kindly asked me because he reminded me of a letter that I wrote to him in 1980, saying that we had done a retrospective study using steroids in St David's Hospital in Cardiff, and that the results seemed to be quite startling. Now we had started using steroids in the late 1970s, I think, I am not 100 per cent certain, based on the work that Liggins and Avery and others had done. We were using steroids, although our obstetricians, in particular Joan Andrews, were relatively conservative, but we were using them. I did a retrospective study, which I sent up to Iain, who by then had moved from Cardiff to the National Perinatal Epidemiology Unit (NPEU) in Oxford, and the third figure seemed to be quite striking, in that we looked at 47 babies of which 11 had steroids and 36 didn't. The mortality rate was zero in the steroid group and 28 per cent in the control group. When you looked at the incidence of RDS, the incidence in the steroid group was 18 per cent and in the control group 59 per cent. So on the basis of that certainly in St Davids Hospital, John [?Williams?] you worked in the [?University Hospital of Wales??] UHW, the University Hospital, we were using steroids, and continued to use them, but my memory is that as time went on and ventilation techniques got better, that the controversy about steroids seemed to be reduced and then surfactants came along, so that there wasn't a controversy about whether one should use steroids or not.

Hanney: The point was raised by Jane that Ross Howie felt about the attitude that there was in the UK. I don't know whether people here were at the earlier Witness Seminar on 'Neonatal Intensive Care' that was undertaken a few years ago, but exactly that point was made by somebody who felt that in the UK

there was this attitude and that was one of the reasons why there had been a lower [?slower?] [prenatal/antenatal steroid] uptake.[61] I am very interested, Patricia, when you raised the issue of the role of the NIH Collaborative Group trial because we were trying to trace through uptake levels and it did seem to us that in the 1970s there had been some increase in uptake: there was a supportive review in the *Lancet* for example in 1979,[62] and there had been the survey of use by Members and Fellows of the Royal College [??RCOG??] which showed that quite a lot of them were using it in 1980.[63] It then seemed that things happened in the 1980s, as I think you were saying, that did seem if anything to increase the opposition, and there was, for example, the editorial in the *British Medical Journal (BMJ)* written by Cliff Roberton, based on the NIH Collaborative Group sub-group analysis that's got criticized.[64] So I would just like to ask you how far you think that sub-group analysis perhaps did reduce usage?

Crowley: I think first the results of the US Collaborative Group trial set things back, because this was the first of the randomized trials published which didn't show any difference in neonatal mortality even though it showed a difference in respiratory distress and in particular the duration and the cost of neonatal care. This was the first trial that looked at economic outcomes. But nonetheless, the lack of difference in neonatal mortality seemed to get a lot of press and then the excessive performance of sub-group analyses was given undue emphasis even though these sub-groups had not been specified at the start of the trial. They were produced following data dredging after the trial had concluded, and these were emphasized, for instance, in that editorial by

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[61] Christie and Tansey (eds) (2001): 55–60.

[62] Ritchie and McClure (1979).

[63] Lewis *et al.* (1980).

[64] Roberton (1982). Dr Crowley, could you elaborate on the sub-group analysis? Is there a table that could illustrate this point?

Cliff Roberton.[65] You referred to the survey of Members and Fellows of the Royal College of Obstetricians and Gynaecologists, which asked obstetricians about their practice and what they said they did, which is not the same as what we actually do.[66] While 44 per cent of obstetricians surveyed in 1979 said that they used antenatal corticosteroids 'often',[67] only 12 per cent of preterm babies recruited to the UK Ten Centre Study of artificial surfactant had been exposed to steroids antenatally.[68]

Hey: That was a huge trial in 40 or 50 hospitals, wasn't it?[69] It was the first time any paediatrician in the UK had been able to get their hands on surfactants. And it was free, so everybody joined the trial. The analysis of that study when it came out showed that nationally in 1990/1 – which was when that trial ran – less than 12 per cent of British babies who were potentially eligible for treatment were being treated.

Dr Sam Richmond: That's absolutely true. We did a sub-analysis of the regional data. The whole of the northern region entered this study and we published results looking back at steroid usage and found very similar results.[70]

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[65] See note 64.

[66] Lewis *et al.* (1980).

[67] Lewis *et al.* (1980).

[68] Ten Centre Study Group (1987).

[69] Open Study of Infants at High Risk of or with Respiratory Insufficiency – the Role of Surfactant (OSIRIS) Collaborative Group (1992). In 1990–91, 6774 babies were recruited to an international multicentre trial to assess when administration of Exosurf, a synthetic surfactant, should be started and how often it should be given.

[70] Khanna and Richmond (1993). Dr Sam Richmond wrote: 'I would point out that the price difference between steroids and surfactant mentioned in the last paragraph of this letter [Khanna and Richmond (1993)] contains a basic arithmetical error – the price of surfactant being nearly 100 times that of steroids rather than 10 times.' Letter to Mrs Lois Reynolds, 26 June 2005.

there was this attitude and that was one of the reasons why there had been a lower [?slower?] [prenatal/antenatal steroid] uptake.[61] I am very interested, Patricia, when you raised the issue of the role of the NIH Collaborative Group trial because we were trying to trace through uptake levels and it did seem to us that in the 1970s there had been some increase in uptake: there was a supportive review in the *Lancet* for example in 1979,[62] and there had been the survey of use by Members and Fellows of the Royal College [??RCOG??] which showed that quite a lot of them were using it in 1980.[63] It then seemed that things happened in the 1980s, as I think you were saying, that did seem if anything to increase the opposition, and there was, for example, the editorial in the *British Medical Journal (BMJ)* written by Cliff Roberton, based on the NIH Collaborative Group sub-group analysis that's got criticized.[64] So I would just like to ask you how far you think that sub-group analysis perhaps did reduce usage?

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[61] Christie and Tansey (eds) (2001): 55–60.

[62] Ritchie and McClure (1979).

[63] Lewis *et al.* (1980).

[64] Roberton (1982). Dr Crowley, could you elaborate on the sub-group analysis? Is there a table that could illustrate this point?

Some hospitals approaching 25 to 30 per cent usage, and others, by far the majority, scarcely reaching 10 per cent.

I wanted to ask two other things. A number of the sub-analysis [?which sub-analyses?] that I think were useful from my perspective at that stage as a paediatric registrar interested in neonates and the business of steroids, was with the sub-analyses and the long-term outcome worries which were one of the major concerns, sub-analysis in the US Collaborative Group study.[71] What I found interesting was two aspects of that study. One was the vast number of mothers who were eligible but excluded, 88 per cent of those thought to be eligible to be considered but not actually entered, they were excused for various reasons, the vast majority being excluded because they weren't thought to be delivering within the time frame. I wondered what actually happened, whether they did or they didn't deliver within the time frame, I cannot find evidence to show what happened. But the other issue is was there ever any biological plausibility to the reasons for the subject analysis. Why would we expect betamethasone to work differently according to sex of the fetus? I wondered if anyone had any clues as to that. I am not a laboratory person, but I cannot see any particular reason why one should divide on the basis of the sex of the fetus in relation to likely outcome. I could be completely wrong. But that seemed to be one of the major issues that unless you were expecting a black female baby, it was a waste

[71] Dr Sam Richmond wrote: 'I was particularly interested in the sub-analyses of the collaborative study [Collaborative Group on Antenatal Steroid Therapy (1981)] because of the general felt concern over possible long-term adverse effects in babies exposed to antenatal steroids and the possibility of being able to be more discriminating in which mothers were offered steroids based on these sub-analyses. What concerned me and significantly undermined the trust one might place in these sub-analyses were two things: firstly the vast proportion of eligible mothers (7197/7893=91 per cent) who were excluded from the study, which must raise some questions, and secondly the illogical interpretation of some of the sub-analyses. While I can understand that one might expect that a medication will have a greater effect among a subgroup at greater risk – such as among Caucasians rather than American blacks of equivalent gestation, or among male babies rather than females of equivalent gestation – however, that does not translate to the conclusion that steroids don't work in the low risk group – it merely means that one requires a larger sample of the low-risk group to show an effect.' Note on draft transcript, 26 June 2005.

of time, and that's clearly incorrect.[72] But why did anyone think to look in the first place?

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

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

Avery: I cannot give you chapter and verse, but I think there is a difference.[73] Maybe somebody else has a reference.

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[72] Dr Sam Richmond wrote: 'I know of no reason why one might expect any such difference (other than the well-known fact that girls of an equivalent gestation are at less risk of death than boys) and thus I could not understand why the sub-analyses by sex were made in the first place – nor why this aspect was so vigorously pursued. If one undertakes a large number of sub-analyses of any dataset one will find some statistically significant differences purely by chance – it therefore behoves one to limit sub-analyses to those with some biological plausibility. However, what was suggested by the Roberton editorial [Roberton (1982)] was that steroids were only effective in white male babies (~~even though~~ the Collaborative Group study [Collaborative Group on Antenatal Steroid Therapy (1981)] showed an effect only in females).' Note on draft transcript, 25 June 2005.

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

Chalmers: I want to comment on extrapolation from data in animals, pathophysiological data in humans, and observational data in humans. One of the most remarkable things about the Auckland story is that Mont and Ross went directly from hypotheses they had tested in animals to assess the relevance of the hypotheses to women and their babies. People working with animals who generate hypotheses – whether it's about brain damage in the long term or some other matter – too often fail to exercise the scientific self-discipline shown by Mont Liggins and Ross Howie. I'll give you an example. Geoffrey Dawes was one of the hubs of perinatal physiological research in this country.[74] He and I often had arguments about the behaviour that I have just been complaining about. I had the impression that he was very annoyed that he hadn't made the discovery that Mont and Ross had made. I remember how in the 1990s he telephoned me in some glee to say that he had discovered – in an observational study – that prenatal steroid administration was associated with a pattern of fetal breathing movements that he regarded as worrying. I said to him, 'So what? You have now a mass of data from women and babies. If you have a hypothesis that is worth testing in terms of the relevance of your observations to human health, then test it, using the mass of data that's now available from human experiments'. There is this bizarre lack of scientific self-discipline among people who know how to design experiments in animals, but actually don't know how to design, or even exploit, experiments in human beings.

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[74] See biographical note on page xx. Sir Iain Chalmers provided an audiotape of the James Young Simpson Lecture given by Mont Liggins at the Silver Jubilee Congress of Obstetrics and Gynaecology in London, 4–7 July 1989, which will be deposited along with the records and tapes from this meeting in GC/253, Archives and Manuscripts, Wellcome Library, London. Sir Ian wrote: 'Liggins notes that Joseph Barcroft's work on fetal physiology was largely ignored by obstetricians until the mid-1960s, when Geoffrey Dawes' Nuffield Institute became the "hub of the universe" in terms of fetal physiology.' E-mail to Edmund Hey, copy to Tilli Tansey and Daphne Christie, 17 April 2004.

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

Avery: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically told Dawes that he would not allow anyone to do any work, even discuss, surfactants for the whole time that Mont was there. [75]

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

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

Hey: I will just interject that in the Ross conference report that you mentioned in 1976, there are five papers from the US saying that they tried to do a trial

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[75] Professor Mont Liggins wrote: '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 144]. I think the evidence deserves your critical comment. 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. Prof Liggins wrote: '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 Nathanielsz P W. (1996) *Life Before Birth: The challenges of fetal development*. New York, NY: W H Freeman. First published by Promethean Press, NY, 1992.

and it was too difficult.[76] We moan now about trials being difficult. You go back and find that they have always been saying that they are difficult. I think they are getting more difficult, but it's always been difficult. Yet sometimes it goes very well.

Gyte: I am moving away and back to a theme that was mentioned before. As a consumer representative, I have always been very interested in the implementation of research findings, and my experience in this area came when I was a consumer representative on the ORACLE trial, which was a trial looking at antibiotics in preterm labour.[77] In the development of that protocol, the researchers wanted to do a second randomization of steroids within the main trial, and as it was actually not our organization, the National Childbirth Trust (NCT), but another consumer organization, the Association for the Improvement in Maternity Services (AIMS), who put their foot down and said it was unethical to randomize women to steroids, and that actually all women should be given them within this multicentre trial and that second randomization was removed.

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

Gyte: I cannot quite remember. We are doing a seven-year follow up now, so it was 1995.

Hey: It was 1995, the results came out three years ago in the *Lancet*.[78] The relevance is that one of the uncertainties that remains about steroid use is whether it is a wise thing to do for the mother's sake, when there is premature

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[76] See note 58. Dr Hey, could you list the five papers?

[77] Kenyon *et al.* (ORACLE Collaborative Group) (2001a and b).

[78] See Kenyon *et al.* (2001a, b).

rupture of membranes, because you may, in doing something good for the baby, increase the risk of the mother developing a generalized septicaemia. So presumably the people [?authors?] couldn't see the unanswered question there.

Gyte: I went to *Effective Care in Pregnancy and Childbirth*[79] to read Patricia's chapter to find an NCT perspective, and I remember thinking that there were some areas of uncertainty, but certainly that randomization was removed from the study.

Dr Peter Brocklehurst: I suppose I was just thinking about how we now approach the use of antenatal steroids, how we have heard today that it was very difficult to get antenatal steroids used in clinical practice, particularly in the UK, and then, within a very short space of time, we were throwing them around like Smarties. I suppose what nobody has mentioned yet is that in order to get 90 per cent coverage of babies admitted to the neonatal unit exposed to antenatal steroids, you have to give them to an awful lot of pregnant women. I have heard it said that in some hospitals a pregnant woman under 34 weeks only has to burp to be given antenatal steroids. And then there was the use of multiple courses of steroids that is becoming very frequent. Now, of course, what is being considered more and more in the literature are the potential adverse effects, not just of multiple courses of steroids, but the potential long-term hazardous effect of a single course of antenatal steroids on brain development, as John Newnham's group at Perth are coming up with evidence about.[80]

I think a lot of what is difficult about this issue is that we are not very good at predicting preterm birth, and if we were better at predicting who was going to deliver preterm we would probably feel much more comfortable about using steroids in a more targeted way. The concern is that currently at least 50 per

[79] See note 43.

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

cent of women who get antenatal steroids do not deliver preterm and therefore if there is long-term harm, it will be in these babies that it will manifest itself, and if we could target our use of steroids better, we would all probably feel a bit more comfortable. So I think we are beginning to go the other way, where people are actually being more cautious now with steroids than they were maybe even five years ago.

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

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

To come back to the issue of ruptured membranes, and I think it is fair to say in the mid-1990s there was still confusion about the issue, but the solution was not to do a new trial. The solution was to go back to the old trials. At that time there had been over 4000 women randomized, and the data was present from the original trials, they had just never been analysed. In about 1994/5 – I cannot remember the exact date – we had a debate around a clinical case at a clinical conference at my hospital, after which David Knight, who was the Director of the nursery at the time, said to me, 'Isn't that question answered?

Surely the data must be there?' Now just parenthetically, David Knight was at the Barcroft Symposium in 1973 at which Mont presented the data.[81] That was one of the reasons that David came to New Zealand and ended up as Director of the nursery. He got all excited about antenatal steroids and thought that he would come to Auckland. That's a slight aside. But it was David's question to me that prompted me for the first time to go back to Mont and Ross to ask, 'You know all those files in the locked cupboard in the corridor where my office was, how would you feel about our getting them out and doing a new analysis, because I think the data might be there and we need to know the answer to a question that you hadn't asked at the time'.

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

Hey: The answer for Gill Gyte was that the data was there but, 20 years later, it had still not even been analysed. Who can put their hands up and say that, of a

[81] Liggins and Howie (1973).

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]

Not a very long time! Or is he referring to the time since the data was collected?

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.

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

[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.

What 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,

Chalmers: The MRC has a working party under the chairmanship of Peter Dukes, which is creating circumstances through which it would be possible for anyone receiving an MRC grant to archive their data.[90] So biomedicine is catching up with the social scientists.

Dr Dino Giussani: I wanted to draw together some of many comments, in particular one made by Iain Chalmers as to how do we translate evidence that we find in animal studies to the human situation. We haven't talked about many of the more subtle effects of antenatal glucocorticoid therapy that may prove detrimental in the long term to the adult. In the animal, there is overwhelming evidence now accumulated that antenatal steroid therapy, in the doses and dose intervals, used in human clinical practice today, have detrimental effects on the development of the adrenal gland. For example, fetuses that have been treated by steroids have an overreactive adrenal function, which may lead to long-term consequences in adult life. We have not talked about maturational effects on other systems, such as the cardiovascular system. We know that glucocorticoids in fetal life increase blood pressure in a sustained manner, at a time that mechanisms that are going to control the blood pressure of the individual in adult life are being programmed, such as baroreceptors. We have evidence that antenatal glucocorticoid therapy reset the arterial baroreceptors to run or to maintain blood pressure at a greater level. And of course we don't know whether that would lead eventually to detrimental effects. We all agree that glucocorticoids are life-savers, but we have to begin to think as to whether some of these more fine-tuned side-effects may become detrimental in later life.

I was also wondering whether we will talk later about refining some of the dosing of the regimens of glucocorticoid therapy today, in an effort to

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the Joint Information Systems Committee (JISC) of the Higher Education Funding Councils and the University of Essex.

[90] Iain, any update on this?

maintain the beneficial effects, but to 'weed out' the unwanted, adverse side-effects.

Harding: If I can make a very brief comment about that? This is another example of a new question for which the old data already had the answers. The blood pressure of the six-year-old children was recorded, but never analysed and published, and it will be published very shortly in *Paediatrics*.[91] We found the archives in the roof of the hospital, dragged them down, and said, 'Would you mind if we analysed these and published them?' There is no difference in blood pressure at six years or, incidentally, at 30 years, but I think the issue for this conference again is one of new questions to which old data actually has the answer.

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

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

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[91] Dalziel S R, Liang A, Parag V, Rodgers A, Harding J E. (2004) Blood pressure at six years of age after prenatal exposure to betamethasone: follow-up results of a randomized, controlled trial. *Pediatrics* 114: e(lectronic)373–7.

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

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[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 costs 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).

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

? True ? It was not in 1962

[99] Chalmers (1999).

[100] Glass (1976).

[101] Chalmers (1979).

fetal monitoring should replace intermittent auscultation using fetal stethoscopes. I set about analysing three published reports of RCTs comparing different methods of intrapartum fetal monitoring, and the findings from one unpublished RCT, which were kindly made available to me by the investigators. About 2000 babies had been born to the women who had been entered into these four trials: 13 of their babies had had neonatal convulsions. With the help of a medical statistician – Klim McPherson – I analysed the distribution of these babies among the comparison groups in the RCTs.[102] This revealed that the pattern was very unlikely to have occurred by chance (less than 1 in a 100): the analysis suggested that continuous electronic fetal heart rate monitoring with scalp sampling might reduce the risk of neonatal convulsions.

I was very impressed by this observation (which had not been picked up in any of the individual RCTs), and it influenced the design of a very large RCT (in which over 13 000 women and their babies participated), done at the National Maternity Hospital, Dublin, while Patricia Crowley was working there.[103] The results of the Dublin trial of fetal monitoring confirmed the hypothesis generated by my systematic review and meta-analysis. That seemed to me to provide encouraging evidence that systematic reviews and meta-analyses could be useful for generating and testing hypotheses about the effects of healthcare interventions. Furthermore, it was becoming clear that this approach was regarded as promising in other fields, particularly in cancer and cardiovascular disease.[104]

As has already been noted by Patricia Crowley, hundreds of people volunteered during the following decade to collaborate in helping to prepare systematic reviews of RCTs assessing the effects of interventions during pregnancy, childbirth and early infancy. For example, to identify relevant studies for a

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[102] See, for example, McPherson (1990).

[103] MacDonald *et al.* (1985).

[104] Stjernsward *et al.* (1976); Chalmers *et al.* (1977); Anonymous (1980).

register of RCTs,[105] some of these people helped to hand-search over 70 obstetric and paediatric journals back to their 1950 issues,[106] while others developed an agreed methodology for analysing the data from these studies.[107] Some of the resulting systematic reviews were published in journals (we were encouraged particularly by Frank Hytten, David Paintin and Sheila Duncan at the *British Journal of Obstetrics and Gynaecology*), and all of them were published in books[108] as well as electronically, so that the analyses could be kept up to date.[109] It was very important that an institutional base for this work existed – the National Perinatal Epidemiology Unit (NPEU). The Unit was funded by the Department of Health, which recognized that systematic reviews of existing evidence were a relevant way of identifying priorities for new research.

So what about the logo of the Cochrane Collaboration? The publications that had come from this 'pilot study' in the perinatal field were quite widely well received. Importantly, an oncologist, Michael Peckham, who had been appointed in 1991 to establish a new NHS research and development programme, commented favourably on our work in a *Lancet* article about his plans for the new programme.[110] He also responded encouragingly in that year when I suggested that a centre might be established to facilitate extension of the methods we had used to other areas of health care. His advisors subsequently agreed that it was worth giving the proposal three years to see whether we could make anything of it. As I have never had a contract for

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[105] National Perinatal Epidemiology Unit (1985).

[106] Chalmers *et al.* (1986).

[107] Chalmers *et al.* (1989).

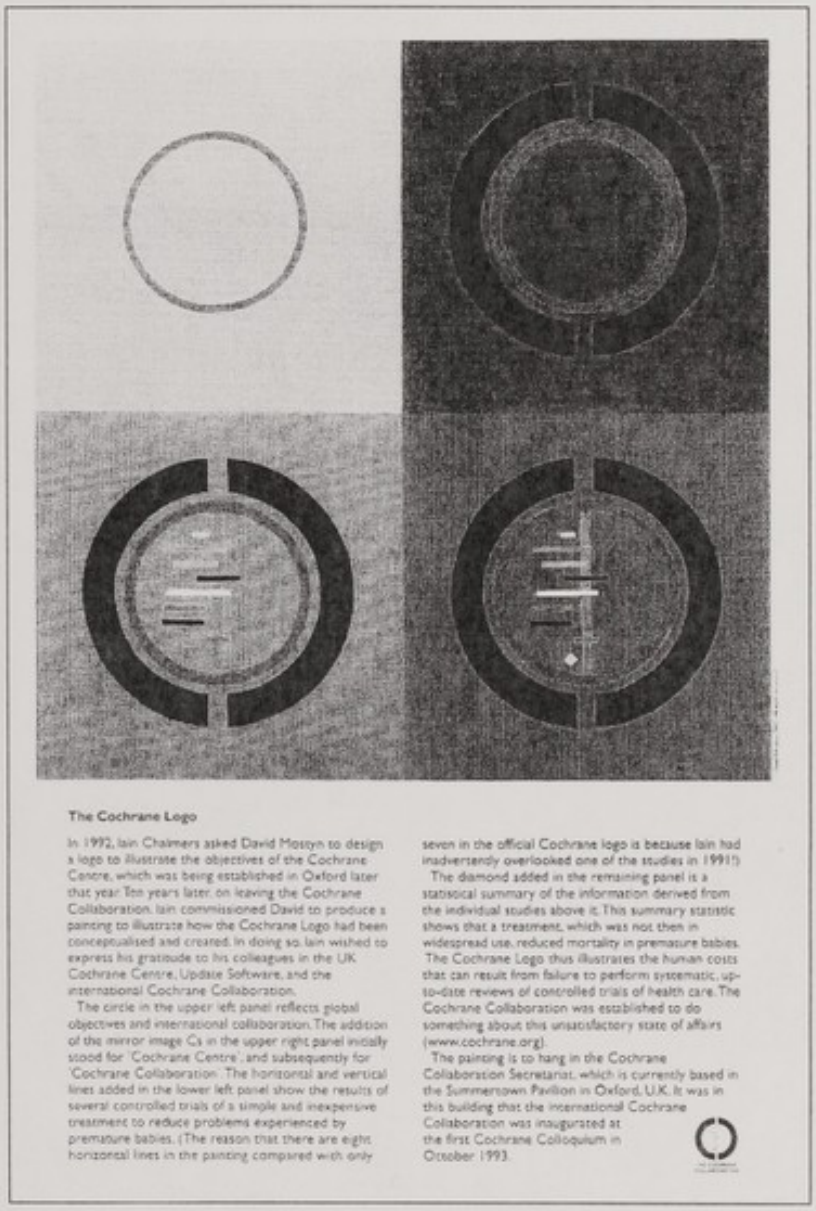
[108] Chalmers *et al.* (eds) (1989); Enkin *et al.* (1989); Sinclair and Bracken (1992).

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

[110] Peckham (1991).

longer than a few years, I accepted this challenge, and the (UK) Cochrane Centre was opened in 1992.[111]

[111] Chalmers (2003). See www.cochrane.org/docs/orderformarchiecochranebacktothefront.doc (visited 1 June 2005).



The Cochrane Logo

In 1992, Iain Chalmers asked David Mostyn to design a logo to illustrate the objectives of the Cochrane Centre, which was being established in Oxford later that year. Ten years later, on leaving the Cochrane Collaboration, Iain commissioned David to produce a painting to illustrate how the Cochrane Logo had been conceptualised and created. In doing so, Iain wished to express his gratitude to his colleagues in the UK Cochrane Centre, Update Software, and the international Cochrane Collaboration.

The circle in the upper left panel reflects global objectives and international collaboration. The addition of the mirror image Cs in the upper right panel initially stood for 'Cochrane Centre', and subsequently for 'Cochrane Collaboration'. The horizontal and vertical lines added in the lower left panel show the results of several controlled trials of a simple and inexpensive treatment to reduce problems experienced by premature babies. (The reason that there are eight horizontal lines in the painting compared with only seven in the official Cochrane logo is because Iain had inadvertently overlooked one of the studies in 1991!)

The diamond added in the remaining panel is a statistical summary of the information derived from the individual studies above it. This summary statistic shows that a treatment, which was not then in widespread use, reduced mortality in premature babies.

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

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

Figure 5: The story of the Cochrane Logo, 1992.

Part of the Centre's logo shows the results of the first seven trials of prenatal corticosteroids (I overlooked, inadvertently, an eighth trial that had been published during this time period. It happened to have exactly the same confidence interval as one of the others, and I had thought that we might have been double counting). The reason that we used the steroid trials was that we wanted to show that within ten years of the Liggins and Howie trial,[112] there had been crystal clear evidence that this was a very important way of reducing neonatal deaths. In launching the Cochrane Centre, we wanted to make the point that this very important information had been available more than a decade earlier, yet it was still not being acted upon sufficiently, in practice. In the brochures we produced and the talks we gave to introduce the objectives of the Centre to others, we made the point that tens of thousands of babies had suffered and died unnecessarily (and cost health services more than they need have done) because information had not been assembled in a systematic review, and meta-analysis used to show the strength of the evidence. In 1993, a year after the Cochrane Centre had opened for business, we convened the meeting at which the International Cochrane Collaboration was founded, and the Centre's logo was adopted by the new organization.[113] [See Figure 5]

I want to end with a statement that may sound rather carping, but I am keen that it should be on the record, given that this seminar is [also] supported by the Wellcome Trust. Although the Trust supports clinical trials in some other parts of the world, it has always discouraged applications for support of clinical trials in the UK. In addition, I have it on good authority that some of the governors of the Trust have not only been unsupportive, but actually dismissive of the kind of research I have described here – RCT registration, systematic reviews and meta-analysis. Indeed, the Trust's website declares unambiguously that it will not support systematic reviews of clinical trials.[114] Given that those

[112] Liggins and Howie (1972).

[113] Chalmers (1993); Chalmers *et al.* (1997).

[114] See the Wellcome Trust Funding for Clinical Trials at www.wellcome.ac.uk/doc%5Fwtx022708.html (accessed 5 August 2005).

assessing payback from research and others recognize the crucial importance of systematic reviews of clinical trials for patient benefit, I and others continue to resent the Trust's unwillingness to engage in discussion with outsiders about the scientific rationale for its attitudes to clinical trials and systematic reviews.[115] It is time that the Trust and other funders of biomedical research assessed more rigorously and transparently the cost-effectiveness of their research funding decisions.[116]

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: It's a great honour to be here today to say a few words about moving knowledge into clinical practice. I was plucked from obscurity in 1991, I think it was, by the then President of the Royal College of Obstetricians and Gynaecologists, Stan Simmons. He called me into his office and said that he wanted me to take over the Audit Committee. I had not been on the committee before I went down to the first meeting as their Chair. It was a very boring meeting; it didn't seem to go anywhere. The idea of guidelines was coming into people's consciousness at around this time and on the train back home the idea came into my head that what I should do with the committee

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[115] Hanney *et al.* (2005).

[116] Chalmers (2000).

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.

Journal on the use of steroids, although, as we shall see, his was an euological [???] 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

Is the NHS letter reference correct?

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[118] Donaldson (1992).

[119] British Association of Perinatal Medicine (???Toschke AM, Ehlin AG, von Kries R, Ekbom A, Montgomery SM. (2003) Maternal smoking during pregnancy and appetite control in offspring. J Perinat Med. 2003;31(3):251-6.???) zxxx. (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/ExecutiveLetters/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 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*, 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 Bromholtz 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 why embark on all these activities? That was what our study was designed to find out. We took four guidelines: the Ventouse, stitching up of the perineum using the correct materials, antenatal steroids, and antibiotics in preterm labour. Then we added one on the hoof, because during the course of the study, Lelia Duley and her colleagues published a spectacular trial – it must be *the* trial of the 1990s – which showed that magnesium was the optimum treatment for eclampsia.[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 [??was the proportion??] of women receiving steroids (a) who were recognized to be in preterm labour; (b) in whom birth was not so imminent as to negate any possible benefit; and (c) 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 attack on admission, such as raised ST segments on the ECG. The clot busting drug can have some nasty side-effects (brain haemorrhage) and it is properly withheld in these cases. So you need to look at people who have presented with clear features of heart attack, not those coded as having had a heart attack.

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.

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.

[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.

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

The second part is that not only has there been a change in the hearts and minds of practitioners, but there has also been a change, in a societal sense, in how we organize ourselves to receive new evidence. Back in the 1970s and 1980s many trials were done (the idea of doing trials had to be sold). Those ideas were coming, but what we didn't have was a method, a societal method, to assimilate the results of the trials. Trials would be done and that would be that. No one knew what to do with the results. How do you react to these trials? When is trial evidence sufficient for a guideline to be developed? So what I did back in those early days of 1992 was to start to provide some kind of societal mechanism to pick up the results of research. It's not surprising that it took us a while to learn how to do this, and, of course, that's now been formalized much more, some would say too much, with organizations such as the National Institute for Clinical Excellence (NICE) and its equivalents in other parts of the world.[133]

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[133] NICE was established in 1999 to give guidance on the use of new and existing medicines and treatments; the appropriate treatment and care of people with specific diseases and conditions; whether interventional procedures used for diagnosis or treatment are safe enough and work well enough for routine use. From 1 April 2005 it joined with the Health Development Agency to become the new National Institute for Health and Clinical Excellence, still known as NICE. See http://www.nice.org.uk/ (visited 29 June 2005).

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).

was the basis for his opposition. If you have seen someone have a haemorrhagic stroke after you have given streptokinase,[139] 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.

Just to clarify the experience in St David's Hospital in Cardiff, because John Gabbay misunderstood what had happened. They had adopted steroids on the basis of the trials. The study that Roger Verrier Jones did was a retrospective assessment.[140] The staff at St David's had taken up steroids to a greater extent than the University Hospital of Wales based on the Liggins and Howie trial.

Hayward: I wonder whether it might be useful to describe briefly an intervention that I led over a two-year period, which was partly triggered by Richard's list of suggested effective interventions that should be used for prospective audit by obstetricians under the banner of the RCOG.[141] I am Director of Public Health in Newham, but I am here because in 1994 I was a public health specialist in training at Camden and Islington Health Authority. I have also known Iain for years, because I married his sister.

It took me ten years to get a grip on what Iain had been going on about evidence-based treatment. But there's nothing like a convert late in life to become a passionate advocate, and this made me very interested to know why other people were having equivalent problems. A number of things happened to coincide, as is usually the way when you start an initiative, and someone who had seen the draft of those clinical audit suggestions was on the Maternity Services Liaison Committee (MSLC) for Camden and Islington that covered three maternity units – the Whittington, the Royal Free and University College Hospital (UCH), just round the corner here. We hatched an idea over a beer in

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

[140] Jones R V. (xxxx) XXXX

[141] Royal College of Obstetricians and Gynaecologists, Scientific Advisory Committee (1992).

one of the local pubs that it would be interesting to look at four of those interventions,[142] and to take them around three units, using the MSLC. What made it uniquely different was that there would be women, the users of services, involved and at the centre of the work. Out of that a two-year project emerged called the Effective Care Project, subsequently published in *Quality of Health Care* in 1997.[143] My guess is that nobody would have read it, and it certainly isn't on Richard's reference list. Like most of these things, it didn't get into the *British Medical Journal* either. It was advocated as an example of good practice for MSLCs nationally, but my guess that a very few of them have been able to do what we did, because we had an unusually committed bunch of users who were really passionate to get into it, and we also had three units to deal with. Most MSLCs only deal with one. It's much easier to deal with three, because you can compare your information automatically.

What we did was to visit each of the units, asking them to share with us their policies on these four interventions, giving them an advance section of what was later going to be the Cochrane library, but in those days was the Cochrane Pregnancy and Childbirth Database, and we still referred to ECPC – *Effective Care in Pregnancy and Childbirth*.[144] All our users had already received the users copies, I may say.

We took the evidence that was in the actual trials, and made certain that every unit had them so they knew what information we were using. We used the blobograms, and it's nice to see four different varieties of those blobograms from Patricia Crowley's original work.[145] I remember ringing Patricia in Dublin at the beginning of this project and you were extremely helpful. We reserved the right that we might ask a statistician to help us resolve complex issues about

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[142] The four interventions were: use of steroids prior to likely preterm delivery; prophylactic antibiotcs for caesarean section; management of perineal repair; and external cephalic version for breech presentation at term.

[143] Berrow *et al.* (1997).

[144] See note 43.

[145] See Figure 4, page xx.

odds ratios or whatever, but we never needed one. The women understood it instinctively, because blobograms graphically are so striking. You immediately see the effect size, and the size of the wings on the aircraft, as it were, give you an idea of the confidence level, about the precision of the results. They understood that instantly. [See Figure 5]

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

We ran into less trouble with steroids than we did with the others and I want to say that we did persuade one hospital to introduce vicryl for the midwives to repair the perineum, whereas otherwise only the doctors were [??had been??] given these expensive sutures, never mind the outcomes. [146] That was a

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

dramatic change. One hospital that used antibiotics for caesarean section had realized, of course, that it's the anaesthetist who tended to give it, but when the anaesthetists had audited it, actually only 60 or 70 per cent of women who should have been getting antibiotics actually did. That was changed. And, the most difficult thing was ECV, where the baby is presented breech, and there's an opportunity to turn the baby round *in utero* before labour, provided it is done close to term, with an operating theatre available and consent for an emergency section obtained. You can, if necessary, bail out by doing an emergency section if anything goes wrong.

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

Apart from power, I think that vested interests, empire building and struggles and political competition between trusts were barriers – this was the time of the purchaser–provider split and market competition was a really important issue around 1995/6. The main barrier was fear of something going horrendously wrong. People would then distort their perception of the evidence and vigorously resist 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. 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).

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

Richard [Lilford] raised the interesting analysis from Rogers' work on the diffusion of innovations.[151] From the analysis that I have, I agree with you that on the whole the profession is much more now receptive. One of the things that Everett Rogers did say was that often when an innovation gets to between 10 and 20 per cent uptake, in fact diffusion becomes almost impossible to stop, it tends to escalate.[152] What I find interesting in this case is that it is clear that the bottom level of where take-off should be impossible to stop, was achieved and then it just didn't take off for quite a long time. There was stalling at exactly the point when Rogers suggested that usually there would be this take-off. So what was it that gave it the nudge to start going again? This is where the systematic review comes in as being very important. It was published in 1989–90, we have heard, and perhaps particular attention was focused on this systematic review for several reasons.[153] The link, as explained earlier with the logo of the Cochrane Collaboration and Miranda's subsequent cost-effective [?cost–benefit??] studies, showed that this was one of the few areas where there had been economic cost savings as well as health gains.

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[151] Rogers E. (1995) *Diffusions of Innovations*, 4th edn. New York, NY: The Free Press. See page 259 for the S-shaped curve.

[152] Hanney *et al.* (2005): 938.

[153] Crowley *et al.* (1990).

A few years later there were several policy statements advocating the use, in the form of clinical guidelines from professional bodies and, as is said in the paper [??which paper?? Hanney *et al.* 2005??], these did cite the systematic review, again emphasizing the importance of this particularly review.[154] I hadn't realized until he spoke quite how explicitly Richard [Lilford] looked through systematic reviews to produce the clinical guideline on that, and clearly the systematic review there influenced the policy guidelines. There were also these important implementation initiatives. There's one that's been mentioned. All these factors seem to have resulted in quite a dramatic increase in uptake during the 1990s. There's the figures from your study, Richard, and figures in 1997, from your survey, Peter [Brocklehurst], which shows a very large uptake by the end of the 1990s. Miranda's analysis suggested that with 75 per cent uptake there would be more than 400 deaths averted annually in England and Wales. So clearly, there has been quite a big health gain. The problem though, as has already been mentioned, without putting a precise figure on this, is that with the use of surfactant and the improvement of the neonatal care, it is not clear of course that all these deaths would have actually happened if there hadn't been the use of steroids. But nevertheless as has been said there is also evidence that even if some of them would never have happened, surfactant wouldn't have stopped all of them. What I think is unclear, is whether there is an actual measure of how many. So definitely this has had substantial health gain as well as impact on policy, knowledge gain, impact on further research.

Mention has been made of the US NIH consensus conference.[155] This was broadly endorsed by the American College of Obstetricians and Gynecologists and it is claimed that this consensus statement had more impact than most of them.[156] An implementation project found that after a year of passive

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

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

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

dissemination, implementation of the guidelines went up to 58 per cent, which is quite substantial.[157] But following active dissemination it went up from 33 to 68 per cent. So it does seem that there are many elements of this whole stream of research that have produced benefits. Perhaps the key thing from our work on this stream of research that is different from some other perspectives in the debate about research utilization, is that our work has been concentrated on showing that benefits have been achieved even when the uptake level has been less than optimum.

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

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

in full

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

Chalmers: We keep on talking about benefits in terms of the baby, but what about the parents? The reduced exposure to the terrible courses that babies would go through before death, and indeed before surviving – and the accompanying anxiety –those things haven't been made explicit. We had hoped that there would be a woman here who had received prenatal

[157] Leviton *et al.* (1999).

corticosteroids.[158] I was impressed by Barbara Stocking, now chief executive of OXFAM, saying that in her first pregnancy she had delivered prematurely and her son went through a really rough time. After she read Patricia's systematic review before her second pregnancy, she insisted that she should have steroids if she went into preterm labour again. She became a big advocate of prenatal steroids when she was a senior manager in the NHS. I have come across more than one mother – maybe Gill Gyte can enlighten us here – who has lobbied to have this. Obviously, as parents, they think this is important, because they are worried about their children. But possibly also so that they have less to worry about themselves.

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

Oakley: This is slightly beside the point, or perhaps not, because I think this issue of the role of the users of health services and the extent to which they are demanding evidence is a very important one and it's something that we need to know more about. But of course one of the problems with that, or one of the issues in that area, is that first of all the user needs to be dissuaded from the belief that experts know what they are doing. I remember one of the early projects that I worked on in 1974 involved an observational study of an antenatal clinic at a hospital in London that, of course, has got to be nameless, and I hung around this clinic for about a year observing what the doctors were doing. I was absolutely astonished. In my second week, there was a changeover in junior doctors, and two of them came to me and they asked me what Consultant X would recommend in a particular case, because they didn't know what they were supposed to be doing because they hadn't met their consultant yet. I didn't realize that the eight different consultants who ran this clinic all

[158] More about patient???

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.

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[159] May we have a date on this?

[160] Dr Hey, could you elaborate?

[161] Prof Mugford, could you provide a reference here?

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

A very interesting paper has been published in the *American Journal of Obstetrics and Gynecology* by Alan Jobe and Roger Soll,[162] which looked at the available trials and separated them into those have used dexamethasone and those that have used betamethasone. The interesting thing is there have been no head-to-head comparisons of dexamethasone versus betamethasone, which have looked at substantive neonatal outcomes.[163] There have been trials that look at antenatal fetal heart rate tracings, which seems to be irrelevant if they are not related to the outcome for the baby.[164] Jobe and Soll suggest that

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[162] Jobe and Soll (2004).

[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-α-fluoro 16-α methyl prednisolone; betamethasone is 9-α-fluoro 16-β methyl prednisolone)[Sweetman (2002): 1063 and 1067]. In the usual pharmacological tests of corticosteroid potency, they are equivalent. In general, the mode of action (pharmacodynamics) seem similar, so they should be therapeutically equivalent.' E-mail to Dr Daphne Christie, 10 January 2005.

[164] See for example, Senat MV, Minoui S, Multon O, Fernandez H, Frydman R, Ville Y. (1998) Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm

Is this true? Is it confirmed in other studies? If so, why is dexamethasone so widely used?

betamethasone is preferable to dexamethasone, because the betamethasone trials, compared with placebo, have a marked reduction in the incidence of death, and [while?] dexamethasone has no statistically significant effects on neonatal death. Although one of the things they reported is the fact that the number of trials using betamethasone is substantially larger than the number of trials using dexamethasone, and the numbers of participants in each trial of betamethasone are larger.[165] However, they have suggested some biological plausibility for this, and I am sure we are going to see a lot more about what agent we should be using. One of the issues that they raised is the availability of the drug, because no drug companies hold a licence for steroids for antenatal indications, the ability to get hold of dexamethasone and betamethasone in the US is becoming more and more difficult, because no company is producing it, because it doesn't have a licence. So people are using all sorts of other steroids, some of which clearly do not cross the placental barrier and may not be effective at all. They also raise issues about whether oral steroids may be as good as intramuscular steroids and also discuss different ways of giving steroids to the baby, whether you can give it into the intra-amniotic fluid, or give it directly intramuscularly into the fetal thigh, which seems a little bit more invasive than a quick intramuscular injection into the mother's thigh. I suspect we are going to see a lot more about the choice of the agent in the future.

We have heard a lot about long-term follow up after a single dose of antenatal steroids and the 30-year follow up of the original Liggins and Howie trial will be extremely useful. I think we probably need to do more follow up, much longer-term follow up of the other trials that have been done to try to strengthen the evidence base on the long-term effects, if only to be reassured

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labour: a randomized study. *British Journal of Obstetrics and Gynaecology* **105**: 749–55. Subtil D, Tiberghien P, Devos P, Therby D, Leclerc G, Vaast P, Puech F. (2003) Immediate and delayed effects of antenatal corticosteroids on fetal heart rate: a randomized trial that compares betamethasone acetate and phosphate, betamethasone phosphate, and dexamethasone. *American Journal of Obstetrics and Gynecology* **188**: 524–31.

[165] See note 75, Liggins to Howie, 11 Jan 2005.

that there are no adverse effects, even though the death rate has decreased and therefore one might expect a worse outcome in the steroid arm.

Another issue is the one of twins and there is an ongoing debate about what you should do with twins and higher-order births. I was very interested when I saw the title of a paper in the *American Journal of Obstetrics and Gynecology* in 2002 looking at twins.[166] Unfortunately it was comparing prophylactic multiple doses of steroids with a single course of 'rescue' steroids when the women presented in preterm labour and which showed no difference. But it certainly didn't elucidate whether the dose that they were using was appropriate or whether it was benefiting twins. Studies of individual patient data meta-analysis of the existing trials may well take us forward on that issue, if we can ever get the data or the money to do it.

Finally, I want to touch briefly on the issue of repeated doses of antenatal steroids that has been brought up time and time again today. I think here there are lessons to be learnt. As Patricia said, within a very short space of time of us beginning to use steroids, we were liberally splashing them around and giving them to everybody we possibly could, often on a weekly basis, to the point where we were giving prophylactic steroids weekly to twins from 20 weeks. Certainly lots of clinicians were giving it to their triplets weekly from 20 weeks, until they got to 34 weeks or when the risk of preterm delivery was no longer thought to be present. Because of this a great deal of effort went into designing a number of trials around the world to compare a single course of steroids and multiple courses of steroids to look at the outcome for the baby. When we originally thought about this, following our survey of practice in 1997, there were five trials designed that would have added up to a total of 10 000 women randomized.[167] Five trials around the world, one of which we have already

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[166] Murphy D J, Caukwell S, Joels L A, Wardle P. (2002) Cohort study of the neonatal outcome of twin pregnancies that were treated with prophylactic or rescue antenatal corticosteroids. *American Journal of Obstetrics and Gynecology* 187: 483–8. Is this satisfactory?

[167] Brocklehurst (1999).

heard about in Australia, two in the US, one in Canada and one in the UK, and in Europe, which I was going to be leading from the NPEU.[168]

I 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. Ours was the largest of those trials, the Trial of the Effects of Antenatal Multiple courses of Steroids (TEAMS) trial, which was going to include 4000 women and would have measured the primary outcome at age two.[169] We did undertake a pilot trial, but unfortunately we went to the MRC at the time when the MRC had no money – you may remember that event – so despite achieving the highest grade that we could possibly get for the quality of our trial, there was no money to fund it. That trial would almost have been finished now if we had got the funding. The Canadian trial, which aimed to recruit over 1900, is still recruiting. It was due to finish several years ago, but has currently enrolled 900 women. I don't know whether it will ever get to 1900 because it might take as long again to reach the target. The Australian trial is getting close to the 980 it wanted to recruit, although 980 is too small to look at long-term outcomes. The US trial aimed to recruit 1000 was stopped early by the Data Monitoring Committee (DMC) at 500, because they decided it was futile to continue as they wouldn't be able to detect the short-term benefit.[170] The other large trial of 2500, run by the Maternal and Fetal Medicine's Unit Network, was also stopped by the DMC at 500, because they found a slightly lower birthweight in the group receiving

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[168] Details of 5 trials, please. Is this described on your website?

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

[170] Guinn *et al.* (2001).

multiple courses of steroids. So it looks likely that we may end up with about 3000 women recruited around the world in trials on multiple courses of steroids versus the a single course, instead of the 10 000 women. I am very sceptical whether in five years time we will actually have enough information to answer the question of the long-term outcomes. The short-term respiratory outcomes look as if they may be favourable for multiple courses of steroids, but clearly that is only part of the question. So the fact that we didn't get the original trials into practice very quickly has not necessarily taught us to improve on past performance when it comes to antenatal corticosteroids.

The other thing to mention, I suppose, is that in the absence of trial evidence about long-term outcome, people will rely on observational studies of long-term outcome. The one observational study with repeated courses of steroids which has been published is from the Western Australian group, which suggested a statistically significantly decreased incidence of cerebral palsy with multiple courses of steroids versus a single course, but a statistically significant increase in significant behavioural problems among the children who survived to the age of six years.[171] I was discussing this with Jane [Harding] during the break this afternoon that in Australia and New Zealand the amount of steroid used is going down. I think it is going down in the UK when I talk to clinicians, because of these uncertainties and concerns about the harm associated with multiple courses of steroids. How we ever get people to interpret what we say correctly, I am not sure. Clearly the messages that are coming out at the moment are not that steroids are bad, but that we need to be more sophisticated in how we use them and how that information is interpreted appears to be to stop using them.

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

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[171] Is this the correct Western Australia group reference?? Ee L, Hagan R, Evans S, French N. (1998) Antenatal steroids, condition at birth and respiratory morbidity and mortality in very preterm infants. *Journal of Paediatrics and Child Health* 34: 377–83.

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

As to the gestational age at which to use steroids, what formulation, what dose, and what route of administration, I think these are questions that we will have to tackle in the future. What gestational age to give steroids? Nobody has mentioned yet the trial that has only been published in abstract that Peter Stutchfield did in Wales where they recruited women who were going for elective caesarean section at greater than 37 weeks.[172] They randomized nearly 1000 women to receive steroids or not and showed a significantly decrease in admissions to the neonatal unit with respiratory symptoms in the group given [receiving?] steroids. So even beyond 37 weeks, if you deliver electively by caesarean section, steroids seem to offer some advantages. The issue about whether there is a cut-off when you don't give them is going to be re-opened. The multiple course of steroids debate is, as I said, still wide open, although we will see more evidence about this over the coming years, and it may hopefully answer some of our questions.

A big lesson that has come out of the steroids trials – not only antenatal steroids, but postnatal steroids – is that with perinatal interventions we really, really have to look at the children, if not the mothers as well, in the longer term, because these babies don't stop developing the minute they are born, they go on and on and on.[173] I was reading in *Time Magazine* recently about a study where they had done serial MRI scans in teenagers and they are suggesting that the brain does not stop developing until age 25, which seems a

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[172] Where was the abstract printed?

[173] Dr Clive Dash wrote: 'The response by the delegates at the RCOG meeting in 1977 may also have been tempered by the anxiety, certainly among many clinicians with whom I spoke at that time, that the long-term effects might prove to be significant.' E-mail to Dr Daphne Christie, 10 January 2005. See also note 20.

perfectly reasonable justification for raising the age at which you can vote.[174] But babies develop, they develop for a long, long time and something like steroids has an enormously potent effect on all the systems of the body, and yet we think we can just look at RDS and ignore the potential long-term effects. I think we are beginning to realize that we cannot do that, that interventions which show short-term benefits, like neonatal dexamethasone, may be countered by long-term harm. Not that there is no benefit in the long term, but that the long-term effects may be in the opposite direction. This means that long-term follow up studies of these trial cohorts become essential and yet the current situation [?of funding??] in the UK, I would suggest, is making it more and more difficult and more and more expensive in terms of being able to follow-up people.

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

Brocklehurst: I think there is an issue here about preparations, because I remember [??who??, from??] the Canadian study got in touch with us about our TEAMS trial, and asked, 'How [?Where?] did you get a placebo for your betamethasone, because ours is cloudy?' We replied that ours was completely clear. The original trial doesn't specify what the betamethasone preparation was and we were using the betamethasone that was available in this country, and in the UK you can only buy betamethasone in a solution, not a suspension.

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[174] Wallis (2004).

Gamsu: This is why, of course, with the advice of Glaxo we chose the three-dose regimen of betamethasone phosphate to try to achieve the same sort of levels as the 12-hourly regime that was used in New Zealand and also the placebo that was used was the vehicle and has the same appearance as the steroid that was used. And of course there's a slight caveat about the use of cortisone acetate as the placebo in the Liggins trial, ~~in which way~~ and how it influenced things, 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 US NIH Collaborative Group trial, is seriously flawed because there were unblinding issues.

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

To come back to Peter Brocklehurst's point about how come they chose the best dose and the best drug, I don't think we know that they did. Nobody's looked and almost all of the issues that Peter has raised – the repeat steroids, which dose, which drug, how often, at what gestation, to which pregnancy – all

of those things were raised by Liggins and Howie in their original publications and said these were the things that needed work, including long-term follow up. When Stuart Dalziel, the key person in the 30-year follow up, presents this data, he starts off by saying, 'Why do we do this?' He then puts up a quotation from the original papers, and says, 'Because they told us we had to 30 years ago'.[175] To complete that story, recently at a meeting at the National Women's Hospital, Stuart said, 'I expect that it will be my PhD student in 20 years time who will have to do the 50-year follow up'.

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

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[175] Dalziel *et al.* (2005).

Appendix

If permission to reproduce is granted, appendices will include:

'Prenatal glucocorticoids in preterm birth: a paediatric view of the history of the original studies', a memoir by Roos N Howie, 2 June 2004, circulated at the meeting.

A letter from G C (Mont) Liggins to Iain Chalmers, 6 April 2004, with three slides.

A history of the Wellcome Trust grant support for G C Liggins research group at the Postgraduate School of Obstetrics and Gynaecology, University of Auckland, 1968–76

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*Biographical notes**

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

Dr Mary Ellen (Mel) Avery

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

Sir Joseph Barcroft

Kt CBE HonFRSE HonFRCOG FRS (1872–1947) was Reader (1919) and Professor of Physiology (1926–1937) in Cambridge, and was appointed Director of the Unit of Animal Physiology, Agricultural Research Council, in 1941. His research interests included studies of the properties of blood, especially blood gases and the oxygen-carrying function of haemoglobin, and studies on the physiology of the fetus. See, for example, *The Respiratory Function of the Blood* (1914) and *Researches on Prenatal Life* (1946). See also Roughton (1948–49).

Sir Christopher Booth

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

Dr Peter Brocklehurst

MBChB FRCOG MSc(Epidemiology) (b. 1962) trained as an obstetrician and gynaecologist, and an epidemiologist in London. He joined the National Perinatal Epidemiology Unit (NPEU), Oxford, as a Research Fellow in 1994, became consultant epidemiologist in 1996 and was appointed Director in 2002. See www.npeu.ox.ac.uk/npeu_home.php (visited 18 July 2005).

Sir Iain Chalmers

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

Professor Archie Cochrane

CBE MBE FRCP FFCM (1909–88), medical scientist and epidemiologist, whose first clinical trial was conducted as a prisoner of war in Salonika. Following the war he was appointed to the Medical Research Council's Pneumoconiosis Research Unit in 1948. In 1960 he was appointed David Davies Professor of Tuberculosis and Diseases of the Chest at the Welsh National School of Medicine, Cardiff, becoming Director of the Epidemiology Research Unit there in 1961 until his retirement in 1974. His papers are available for study at the Cochrane Archive, Llandough Hospital, Penarth, Cardiff. See Cochrane (1976); Cochrane [ALC] (1988). See also Ness *et al.* (2002).

Dr Patricia Crowley

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

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

Deputy Director. She has been Director of the Social Science Research Unit at the University of London Institute of Education since 1990 and Professor of Sociology and Social Policy there since 1991. She has been involved in health services research for many years, and has a particular interest in the evaluation of social interventions, methodology, and the experiences of health service users.

Dr Sam Richmond

FCRP FRCPCH (b. 1949) graduated MB BS at Newcastle upon Tyne in 1972. Worked for various Non-Governmental Organizations in maternal child health in North Africa and Arabia from 1974 before returning to Newcastle in 1979 to train in paediatrics and neonatology. He has been a Consultant neonatologist at Sunderland Royal Hospital [?Infirmary? District General Hospital??], since 1988. His research interests include the epidemiology of fetal abnormalities, neonatal screening and resuscitation at birth.

Professor Leonard Birnie Strang

FRCP (1925–97) trained in Newcastle, joined the Department of xxx at UCL in 19xx. His main research interest in clinical paediatrics was in the adaptation of the fetal lung to breathing air. He was President of the Neonatal Society from 19xx to 19xx and received the James Spence Medal of the Royal College of Paediatrics and Child Health. See Boyd (2000).

Dr Roger Verrier Jones

Xxx (b. 19xx) xxx

Professor Dafydd Walters

BSc FRCP FRCPCH (b. 1947) has been Professor of Child Health at St George's Hospital Medical School since 1994. He trained at UCL taking degrees in physiology and medicine. He worked later at University College Hospital Medical School in general paediatrics and neonatology from 19xx to 19xx, as well as undertaking research into the maturation of the fetal lung. For a short time he worked with Professor John Clements at the CRVRI [?in full??] in San Francisco on pulmonary surfactant composition. He was Chairman of the Executive of the Physiological Society for 2002–04 and has been chairman of the Historical and Archives Committee of the Physiological Society since xxxx.

Mr John Williams

Xxxx (b. 1945) has been Consultant Obstetrician [?and?] Gynaecologist at the ?Countess? of Chester Hospital, formerly Senior Registrar (Lecturer) at the University College Hospital of Wales, Cardiff, from xxxx to xxxx.

Professor Maureen Young

PhD (b. 1915) graduated in physiology from Bedford College for Women, where she worked from 1933 to 1938. She spent two years at a London Blood Transfusion Unit at the beginning of the Second World War and returned to teach at Bedford. Later she was one of the first women to join the staff of the Physiology Department at St Thomas' Hospital Medical School, London, after the war. She worked at the hospital for 36 years, later she was invited to join a research unit in Professor Philip Rhodes'

Department of Gynaecology, and was given a personal chair in Perinatal Physiology in 19xx. She was one of the founder members of the Neonatal Society and was President from 1984 to 1987. See Christie and Tansey (eds) (2001). A copy of her letter to Dr David Gordon, Professor Osmund Reynolds and Dr Tilli Tansey, dated 26 April 1999, describing the changes in physiology and clinical practice at St Thomas' Hospital and UCL during the 1960s and 1970s, has been deposited with the records of volume 9 in GC/253, Archives and Manuscripts, Wellcome Library, London.

Glossary
Note the use of bold for items in glossary