Correspondence. Surname, 'Chalmers'

Contributors

The Wellcome Trust Centre for the History of Medicine at UCL

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 11 February 2004 12:52
To: Tilli Tansey
Cc: Wendy
Subject: FW: Prenatal corticosteroids for reducing morbidity and mortality ass ociated with preterm birth

Did you reply to this? I can't find a copy for the files. Thanks, Daphne

-----Original Message-----
From: Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 04 February 2004 22:11
To: d.christie
Subject: RE: Prenatal corticosteroids for reducing morbidity and mortality ass ociated with preterm birth

as you can see this came to me anyway. I'll try to reply tomorrow - feeling very unwell still

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 04 February 2004 11:40
To: Tilli Tansey
Subject: FW: Prenatal corticosteroids for reducing morbidity and mortality ass ociated with preterm birth

Will you reply or would you like me to? thanks, daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 04 February 2004 11:21
To: Daphne Christie (E-mail); Tilly Tansey (E-mail)
Cc: Mark Walport (E-mail)
Subject: Prenatal corticosteroids for reducing morbidity and mortality ass ociated with preterm birth

Dear Tilly and Daphne

At my meeting with Mark Walport yesterday, we noted that Professor Graham Liggins had been in receipt of a grant from the Trust for his research on parturition in sheep during the 1960s. His observations led directly to the first randomised controlled trial of prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth (which was published in 1972.

Mark asked me to suggest to you that this would be a good topic for a Witness Seminar, hence this note. In all sorts of ways, it's an important story, not least because only when a systematic review of the RCTs was done did a consensus emerge that it was a lifesaving and cost-effective intervention. Unsurprisingly, it forms the basis of the Cochrane logo.

If you need any further input from me, I'd be happy to try to help.

With best wishes, Iain

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 12 February 2004 14:34
To: Iain Chalmers
Cc: Wendy; Mark Walport (E-mail)
Subject: witness seminar Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Dear Iain
Thank you for passing on the suggestion of 'Prenatal corticosteroids for reducing morbidity and mortality' as a suitable topic for a witness seminar. As you heard from Tilli, we are very enthusiastic about developing a witness seminar on this subject. I have asked Wendy to check room availability over the next few months, and will get back to you as soon as I have some possible dates.
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With best wishes
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Fax 020 7679 8193
Mobile 07810 541812
E-mail d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed

Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 12 February 2004 15:25
To: 'd.christie'; Iain Chalmers
Cc: Wendy; Mark Walport (E-mail)
Subject: RE: witness seminar Prenatal corticosteroids for reducing morbid ity and mortality associated with preterm birth

Dear Daphne

Thanks very much. It seems that the time scale for organising this is going to be quite tight.

I think Dr Edmund Hey, a retired paediatrician based in Newcastle, would be a good chairman.

It may also be helpful for me to mention at this very early stage that I think there are two witnesses from overseas whom I regard as essential to this story. Sir Graham Liggins made the initial discovery in the late 1960s and early 1970s in New Zealand, and he had been in receipt of Trust support for his animal work. It was nearly two decades later that Professor Patricia Crowley (who lives in Dublin) made clear to the world how strong the evidence of the beneficial effects of prenatal corticosteroids had become when she prepared and published a systematic review of the relevant RCTs. Only after her review had been published did patients begin to benefit from the discovery. You may know already that this is the point made in the Cochrane Collaboration's logo (http://www.cochrane.org/resources/brochure.htm#LOGO)

I have pasted below contact details for the three people I have mentioned, and I look forward to discussing this with you.

With best wishes, Iain

IAIN CHALMERS
Editor, James Lind Library
The James Lind Initiative
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Oxford OX2 7LG, UK
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+44 (0)1865 517635
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Email: ichalmers@jameslindlibrary.org
Website: www.jameslindlibrary.org

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Tel. 0191 284 3219
Fax. 0191 213 6181
shey@easynet.co.uk

Prof Sir Graham Liggins
Department of Obstetrics & Gynaecology
University of Auckland
National Women's Hospital
Claude Road, Epsom, Auckland 3
New Zealand
Tel. 0064 9 638 9919
Fax. 0064 9 630 9858

Professor Patricia Crowley
Dept of Obstetrics and Gynaecology
Coombe Women's Hospital

Dublin 8
Eire
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Fax. 00353 1 454 9866
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www.ucl.ac.uk/histmed

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 13 February 2004 09:24
To: Iain Chalmers
Cc: Wendy
Subject: RE: witness seminar Prenatal corticosteroids for reducing morbid ity and mortality associated with preterm birth

Dear Iain
Thanks for your e-mail and useful suggestions. Dr Hey attended Maternal Care in June 2000 so will be familiar with the witness meetings.
As you may be aware we have little funds to assist with travel for overseas participants. Dublin is not a problem but NZ sounds difficult. We thought we might fax a letter to Sir Graham to see if he will be in the UK anytime soon, and if he was coming over, that would determine when we could hold the meeting.
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I look forward to hearing from you. I work tues - fri, often in early and gone by 4.30pm. Wendy works mon-thurs.
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National Women's Hospital
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New Zealand
Tel. 0064 9 638 9919
Fax. 0064 9 630 9858

Professor Patricia Crowley
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Sent: 13 February 2004 10:11
To: Iain Chalmers
Cc: Wendy
Subject: RE: witness seminar Prenatal corticosteroids for reducing morbid ity and mortality associated with preterm birth

Many thanks - I'll follow up your suggestions and let you know how I get on.
Best wishes, Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 13 February 2004 10:10
To: 'd.christie@ucl.ac.uk'; Iain Chalmers
Cc: Wendy
Subject: RE: witness seminar Prenatal corticosteroids for reducing morbid ity and mortality associated with preterm birth

Thanks for the discussion, Daphne. Here are contact details for Janet Darbyshire and Miranda Mugford. Looking forward to hearing from you. Best wishes, Iain

Prof Janet Darbyshire
Director
MRC Clinical Trials Unit
222 Euston Road
London
NW1 2DA
Tel. 020 7670 4700
Fax. 020 7670 4818
j.darbyshire@ctu.mrc.ac.uk

Professor Miranda Mugford
School of Medicine, Health Policy and Practice
University of East Anglia
Norwich
NR4 7TJ
Tel. 01603 593583
Fax. 01603 593604
m.mugford@uea.ac.uk

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 13 February 2004 12:02
To: Wendy
Subject: FW: witness seminar Prenatal corticosteroids for reducing morbid ity and mortality associated with preterm birth

Follow Up Flag: Follow up
Flag Status: Flagged

Please can you set up a grid for this meeting and insert Iain's suggestions (contact details given in his e-mail). Thanks Daphne

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 13 February 2004 12:38
To: Wendy
Subject: FW: witness seminar Prenatal corticosteroids for reducing morbid ity and mortality associated with preterm birth

Hi Wendy
This follows a telephone call this morning. Please add Miranda Mugford to the grid.
The following was discussed with Iain:

1. Iain believes Sir Graham is crucial to the success of this meeting. [In brief: Liggins was interested in the onset of labour. He used sheep as a model for his studies. He was able to induce labour by injecting steroids, and studied steroid effects on premature lambs with air in lungs. Work followed on rct of the steroid effect on the immature fetus [Liggins GC, Howie RN. (1972) A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics. Oct;50(4):515-25]. A landmark discovery which was taken up 2 decades later.]

2. Iain would know if Liggins intended to visit the UK in the near future. He hasn't done so for a long time. He suggested that we write and ask him if in principle he would be able to participate (even though he is such a long way away) if funds could be raised. Iain suggested two ways we might achieve this:
ask the RCOG if they might share the expense of bringing him across, as a great opportunity to document an obstetric success story, etc. He suggested I ask James Drife. (Iain resigned as a Fellow of the RCOG in protest of xxxx, so will not be able to contact the RCOG)
other option is to set up a video link - we could use this as a pilot for future occasions? I think you made enquiries for a previous meeting. Let's discuss.

3. Iain suggested we check the following venues for future witness meetings:
The RCOG new conference suite
The MRC Clinical Trials Unit rooms. Prof Janet Darbyshire might be able to help, and we may get this free [contact details below].

Please can you make necessary enquiries regarding use of these venues/facilities?

I will first ask Alan about funds for Liggins and tell him about Iain's suggestion of contacting the RCOG.

Note that Iain will be away from 2 July until the 24th, so that rules out the first week of July. He is available for most of June.
I think that's everything...

Let's discuss on Monday. Thanks, Daphne

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Prof Janet Darbyshire
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MRC Clinical Trials Unit
222 Euston Road
London
NW1 2DA
Tel. 020 7670 4700
Fax. 020 7670 4818
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Professor Miranda Mugford
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Dear Iain
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Meanwhile we can perhaps start thinking about who to invite as Witnesses, as chairman etc. and what main themes should, and which can, be addressed. As

you know all the routine administration is done by this office.
I look forward to working with you on this project.
With best wishes
Daphne

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

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Wendy Kutner

Subject: FW: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesdsay 15th June 2004

Follow Up Flag: Follow up
Flag Status: Flagged

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You may also like to know that Professor Farquhar has informed us that Sir Graham's wife died last year. We look forward to hearing from you. Best wishes, Wendy

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

Dear Ms Kutner,

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

Graham Liggins

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

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

Wendy Kutner

To: ucgachr@ucl.ac.uk
Subject: FW: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesdsay 15th June 2004

Follow Up Flag: Follow up
Flag Status: Flagged

having now had a response from Iain Chalmers, even though he is going to write to Sir Graham himself, we ought to acknowledge his reply ... What about something along the lines of - we obviously disappointed that he is unable to travel to London for the meeting and that Sir Iain will be contacting him direct about his part in the meeting? Also, should I send the invitations letters to Hey and the other people Iain suggested we invited?

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Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 18 February 2004 13:56
To: 'w.kutner@ucl.ac.uk'
Cc: ucgachr@ucl.ac.uk; Cindy Farquhar (E-mail)
Subject: RE: Witness Seminar: Prenatal corticosteroids for reducing morbid ity and mortality associated with preterm birth - Tuesdsay 15th June 2004

Thanks, Wendy. I'd forgotten the time difference, and I can see now that that would indeed be a problem. Accordingly, I think we should proceed on the basis that Sir Graham won't be able to contribute to the seminar 'in real time'.

As you say, one possibility is for the chair to read out a statement from him. Another may be to begin the seminar with a video of Sir Graham recalling the events that led to the discovery. It is possible that such a video already exists; but even if it doesn't, perhaps this is the moment for one to be made. I will copy this message to Cindy Farquhar, to ask for her further help in this respect.

I will also write to Sir Graham, both to offer belated condolences to him on his bereavement, and to make contact so that we can make the most of good lines of communication.

Best wishes, Iain

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 18 February 2004 10:28
To: ichalmers@jameslindlibrary.org
Cc: ucgachr@ucl.ac.uk
Subject: FW: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth - Tuesdsay 15th June 2004

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--
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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 18 February 2004 14:38
To: Iain Chalmers
Cc: Wendy
Subject: RE: Witness Seminar: Prenatal corticosteroids for reducing morbid ity and mortality associated with preterm birth - Tuesdsay 15th June 2004

Dear Iain
Thank you for this. Shall we go ahead and send letters to Dr Edmund Hey [chair], Professor Patricia Crowley and Professor Miranda Mugford, as you suggested?
Best wishes, Daphne

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Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 25 February 2004 16:26
To: 'd.christie@ucl.ac.uk'; Iain Chalmers
Cc: Wendy
Subject: RE: Dr Edmund Hey

Thanks, Daphne. Iain

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 24 February 2004 15:03
To: Iain Chalmers
Cc: Wendy
Subject: Dr Edmund Hey

Dear Iain
This is just to let you know the good news that Dr Hey has accepted to chair the proposed witness meeting on 15 June. I'll put a copy of his letter in the post to you.
Best wishes
Daphne

Dr Daphne Christie
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine at UCL
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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 02 March 2004 12:52
To: Wendy
Subject: FW: witness seminar prenatal corticosteroids 15 June

for the files
-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 02 March 2004 10:55
To: Iain Chalmers
Subject: witness seminar prenatal corticosteroids 15 June

Dear Iain
This is just to let you know that Professor Miranda Mugford has replied to say that she is able to attend the witness meeting. She has suggested inviting Dr John Gabbay (University of Southampton)as a witness. Please confirm that you agree with this. I have sent you a copy of her letter. Please can we have some names of other witnesses. Wendy is back and can send invitations this week.
Thank you.
With best wishes,
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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 03 March 2004 16:11
To: Iain Chalmers
Cc: Wendy
Subject: RE: witness seminar prenatal corticosteroids 15 June

Dear Iain
That's great news that she is able to attend. I'll check with Wendy what address she used and send a copy of correspondence if necessary.
Best wishes, Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 03 March 2004 15:55
To: 'd.christie@ucl.ac.uk'
Subject: RE: witness seminar prenatal corticosteroids 15 June

I spoke to Patricia Crowley just now. She can come and has the date in her diary. Her email service provider has been having problems, so if your invitation used that medium, that may explain why she doesn't appear to have received it. Best wishes, Iain C

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 03 March 2004 08:40
To: Iain Chalmers
Subject: RE: witness seminar prenatal corticosteroids 15 June

Dear Iain
We haven't heard from Patricia Crowley. I'll let you know as soon as we do.
Best wishes, Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 02 March 2004 18:54
To: d.christie@ucl.ac.uk
Cc: Edmund Hey (E-mail)
Subject: RE: witness seminar prenatal corticosteroids 15 June

Dear Daphne, Excellent that Miranda can come. I'd be delighted if John Gabbay comes. Has Patricia Crowley responded. She's crucially important. I'll discuss other witnesses with Ed Hey and get back to you. Best wishes, Iain

This e-mail contains information which is intended for the addressee only. If you receive this e-mail in error, please contact the sender and delete the original from your system. We cannot guarantee that any attachments to this e-mail are free of software viruses, and we recommend that you check for viruses before opening any attachments.

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Subject: witness seminar prenatal corticosteroids 15 June

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Key ISSUES - [Liggins]

Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 03 March 2004 18:39
To: 'd.christie@ucl.ac.uk'; g.liggins
Cc: Iain Chalmers; Wendy; Cindy Farquhar (E-mail); Edmund Hey (E-mail)
Subject: RE: Witness Seminar

Dear Mont

I'm sorry that it's taken me a few days to get back to you, and to say how delighted I am that you will be contributing to this witness seminar. As the key witness, it really would have been far from satisfactory without your input. Needless to say, however, I quite understand that you don't feel able to travel to the UK for it. Is there any video-recording of you being interviewed about the early days of your discovery? If not, shouldn't there be? I'll copy this message to Cindy because I think I raised that question with her a couple of weeks ago.

There are a number of issues I'd love you to cover in your contributions. Here are some of them:

- An account of the ?serendipitous observations in lambs (in research which I gather was supported partly by Wellcome). Might we be able to reproduce a relevant page in the lab book in the printed record of the seminar?

- Your decision, after the initial observations in lambs, to proceed directly to a randomised experiment in humans; that the first woman to be given steroids for this purpose was part of a well designed experiment, not an uninterpretable, uncontrolled case series, as is so often the case for innovations in medicine. Were research ethics committees involved, and if so, what did they have to say about the proposal?

- The integration of the trial within usual clinical care, with rather modest resources for the research.

- Reactions to your results: rejection of the report by the Lancet; reactions in the US and UK; ?jealousy among other perinatal researchers; subsequent, statistically less powerful trials that confused the picture; data dredging the in US Collaborative Study, leading to the bizarre notion that it was only black female infants born at particular gestations who benefited, a mistaken inference promulgated by Cliff Roberton, among others, in a BMJ editorial.

- The consequences of the fact that no pharmaceutical company could make much money out of the discovery.

These are some pointers for starters. And we'll rely on you not only to make the input that you're the best person to make as a first hand witness, but also your thoughts on other aspects that shouldn't be forgotten among other witnesses. Patricia Crowley and Miranda Mugford are both signed up, and their contributions about the systematic reviews and the cost –effectiveness analyses, respectively, are certainly crucial. It occurs to me that we might try to get a statement from John Ferguson (director c the NIH Office of Medical Applications of Research), who chose the topic for a Consensus Development Conference in the earl 1990s.

Ed Hey has kindly agreed to chair the seminar, so I'll copy this message to him as well as Daphne Christie and her colleagues at the Wellcome Trust.

I'm delighted to be working on this with you, Mont, even if it would be even nicer if we were face to face.

With best wishes, Iain

SIR IAIN CHALMERS
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The James Lind Initiative
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+44 (0)1865 517635
Fax:+44 (0)1865 516311
Email: ichalmers@jameslindlibrary.org
Website: www.jameslindlibrary.org

Wendy Kutner

To: ucgatlt@ucl.ac.uk
Cc: Daphne Christie
Subject: Meeting Rooms at the RCOG and MRC

Just to let you know that Sir Iain Chalmers has spoken with Daphne about availability of a conference suite at the RCOG and The MRC Clinical Trials Unit rooms.

Professor Janet Darbyshire is delighted we are considering the use of the MRC rooms, for which there may be no charge. I haven't spoken with the MRC as I felt it might be better to have dates available.

I telephoned the RCOG to find out how much they charge and for a meeting room for 40 people the cost would be £330 + a room for catering (The Collegiate Room) at £495. Tea is charged at £1.55 per head. I assume these costs would have VAT on top.

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Key Witnesses

Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 09 March 2004 14:52
To: Tilly Tansey (E-mail); Daphne Christie (E-mail)
Cc: Marc Keirse (E-mail); Edmund Hey (E-mail)
Subject: Witness seminar on prenatal corticosteroids

Witness seminar on prenatal st...

Dear Daphne and Tilly

Following a recent discussion with Ed Hey, I have drafted an outline programme and listed people who I think should be invited (see attached).

I have spoken to Marc Keirse and he is prepared to consider making a trip to Europe to enable him to participate. As he has been a sheep researcher as well as a clinical researcher, and knows Mont Liggins well, he would be an ideal person to introduce Mont's work (as I have suggested in the outline programme). I have suggested some other speakers for the programme, whose names have not been mentioned previously.
I have pasted contact details for all these key people, below, because invitations should probably go out to them quite promptly.

I hope this is helpful, and look forward to hearing from you about next steps.

With best wishes, Iain

Prof Marc Keirse
Dept of Obstetrics & Gynaecology
Flinders Medical Centre
Bedford Park
SA 5042
Australia
Tel. 0061 8 8204 4471
Fax. 0061 8 8204 5454
Email: marc.keirse@flinders.edu.au

Prof Sir Liam Donaldson
Chief Medical Officer Richmond House
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Prof Richard Lilford
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Fax. 0121 414 2752
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Dr Steve Hanney
Health Economics Research Group
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Prof Peter Brocklehurst
National Perinatal Epidemiology Unit
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Wellcome Witness seminar on 'Prenatal corticosteroids', pm Tuesday, 15 June 2004

Chair: Dr Edmund Hey

Introduction:	Dr Edmund Hey
From ewes and lambs to women and babies:	Professor Sir Graham Liggins (? represented by Professor Marc Keirse)
The systematic review of RCTs and the NIH consensus conference:	Professor Patricia Crowley
Cost-effective analyses:	Professor Miranda Mugford
The Cochrane Collaboration Logo:	Sir Iain Chalmers

? TEA at this point

Getting research into practice:	Professor Sir Liam Donaldson Professor Richard Lilford
Assessing payback from research:	Dr Stephen Hanney
Recent and current research on prenatal corticosteroids:	Professor Peter Brocklehurst

Suggested additional invitees:
Dr Mary Ellen Avery, retired paediatrician, Boston
Prof Martin Buxton, health economist, Uxbridge
Prof Geoffrey Chamberlain, retired obstetrician, Cardiff
Dr Pamela Davies, retired paediatrician, London
Prof James Drife, obstetrician, Leeds
Prof Peter Dunn, retired paediatrician, Bristol
Dr Harold Gamsu, retired paediatrician, London
Dr Jonathan Grant, RAND Europe, Cambridge
Dr Muir Gray, public health specialist, Oxford
Dr Selina Gray, public health specialist, Bristol
Dr Gill Gyte, formerly National Childbirth Trust, Poulton-le-Fylde
Dr Aidan Halligan, deputy chief medical officer, DH, London
Dr John Hayward, public health specialist, London
Dr Nick Hicks, public health specialist, Oxford
Dr Alison Hill, public health specialist, Oxford
Prof Frank Hytten, retired perinatal physiologist, London
Dr Jerold Lucey, Editor in Chief, *Pediatrics*
Prof Sally Macintyre, medical sociologist, Glasgow
Dr Jonathan Mant, general practitioner, Birmingham
Prof Jim Neilsen, obstetrician, Liverpool
Prof Ann Oakley, medical sociologist, London
Dr Sandy Oliver, formerly National Childbirth Trust, London
Dr David Paintin, retired obstetrician, London
Prof Osmund Reynolds, retired paediatrician, London
Dr Cliff Roberton, retired paediatrician, Cardiff
Dr Sam Richmond, paediatrician, Tyne and Wear
Ms Barbara Stocking, Chief Executive, Oxfam
Mr Derek Tacchi, retired obstetrician, Newcastle
Dr Roger Verrier Jones, retired paediatrician, Cardiff
Prof Jonathan Wigglesworth, retired paediatrician, Cardiff
Mr John Williams, obstetrician, Chester

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 09 March 2004 15:01
To: w.kutner
Subject: FW: Witness seminar on prenatal corticosteroids



Witness seminar on prenatal st...

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 09 March 2004 14:52
To: Tilly Tansey (E-mail); Daphne Christie (E-mail)
Cc: Marc Keirse (E-mail); Edmund Hey (E-mail)
Subject: Witness seminar on prenatal corticosteroids

Dear Daphne and Tilly

Following a recent discussion with Ed Hey, I have drafted an outline programme and listed people who I think should be invited (see attached).

I have spoken to Marc Keirse and he is prepared to consider making a trip to Europe to enable him to participate. As he has been a sheep researcher as well as a clinical researcher, and knows Mont Liggins well, he would be an ideal person to introduce Mont's work (as I have suggested in the outline programme). I have suggested some other speakers for the programme, whose names have not been mentioned previously.
I have pasted contact details for all these key people, below, because invitations should probably go out to them quite promptly.

I hope this is helpful, and look forward to hearing from you about next steps.

With best wishes, Iain

OS wrote 11/3/04

Prof Marc Keirse
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Dr Daphne Christie

(W)

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 09 March 2004 18:34
To: 'Edmund Hey'
Cc: Tilli Tansey (E-mail); Daphne Christie (E-mail)
Subject: RE: Witness seminar on prenatal corticosteroids

Have you added details on the guid (?)

Thanks, Ed. Some comments within your text. Iain

-----Original Message-----
From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 09 March 2004 16:16
To: Iain Chalmers
Subject: Re: Witness seminar on prenatal corticosteroids

Iain,

Just a few quick thoughts.

The whole thing has a slightly anglocentric feel to it at the moment.
Unsurprisingly, because there is no budget for bringing people from overseas. I have persuaded Marc Keirse to consider coming at his own expense. He can represent Belgium, the Netherlands (including the Amsterdam study) and the antipodes. I have mentioned the event to Jerry Lucey in the hope that he might be able to come, and listed Mary Ellen Avery to receive an invitation.

Can someone from across the water speak to the pivotal impact of the NIH consensus report ?
I hope that Patricia Crowley will do this if no Americans are there. She was at the consensus conference (as an invited speaker) and may well be aware of the impact assessments done subsequently.

What about the use of antenatal steroids down under? Was Mont a prophet without honour even in his own country?
Marc Keirse has been down under for a decade now, so he should be helpful on this score.

What was the motivation behind all the other trials after the first one ? How was the size of these studies justified ?
Harold Gamsu can provide some insights on this.

What plans (and funds) were there to follow the children ?
Mont can provide details of the follow up of the Auckland trial. Marc may be able to provide details of follow up of the Amsterdam trial. I know Harold Gamsu wanted to follow up his RCT children, but didn't/couldn't.

What about the propagation of this cheap life saving treatment in resource-poor countries ? Did the Maternal and Child Health branch of WHO ever take this up ?
Pass, but we could find out.

And can we please hear from industry and the CSM why the drug has still not been licensed for use for this well documented indication ?
We could ask Liam Donaldson to come prepared to cover that.

Cliff Roberton was based in Cambridge, not Cardiff, and has now retired to the Isle of Skye. Jonathan Wigglesworth worked at th Hammersmith would have called himself a perinatal pathologist and has retired to Somerset. It might be wise to check how well Derek Tacchi is before sending an invitation there.
Thanks for these corrections

Is Peter Brockelhurst a Professor yet ?
Yes (as I think I indicated in the draft and in covering email)

Dr Peter Stutchfield, a Paediatrician in Glan Cywyd, has been quietly plodding away for years now on a megerly funded trial looking at the effect of giving betamethasone antenatally to mothers haveing a planned section at 37+ weeks gestation, and I hear o the grape vine that the outcome of that study is due to be presented at the RCPCH meeting in York in April. Better check with Pete Brockelhurst what his perception is as to the quality of this trial, and try and find out what the take home message might be. Stutchfield might, however, have something to say about the use of betamethasone for a wider range of women, rather than the use of potentially dangerous repeat dosing to mothers facing preterm delivery.
Sounds as if he ought to be invited too

There is also a RCOG guideline on this topic that might be worth looking at. I gather (though I have not yet had time to look at it) that it decries use in mothers expecting to deliver before 24 weeks gestation but I am not quite sure why.
We should be able to rely on the invited obstetricians (particularly Richard Lilford) to bring us up to date on that.

Hope these random thoughts are some help.
Yes indeed, thanks. Now go off and have a good holiday in Florida with your daughter!!

E

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 10 March 2004 09:26
To: Iain Chalmers
Cc: w.kutner
Subject: RE: Witness seminar on prenatal corticosteroids

Thank you. Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 09 March 2004 17:19
To: 'd.christie@ucl.ac.uk'
Subject: RE: Witness seminar on prenatal corticosteroids

I told Marc that we had no money to bring him here, and that he could stay with us in Oxford. Obviously if you are able to make a contribution to his travel costs that would be very nice, but he's not expecting it. I am just hoping that giving him such a prominent and important role will ensure that he firms up his tentative agreement to try to come. Best wishes, Iain

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 09 March 2004 15:26
To: Iain Chalmers
Subject: RE: Witness seminar on prenatal corticosteroids

Dear Iain
Thank you for the draft programme and list of people who you think should be invited. We will send out invitations asap.
It's very good news that Marc Keirse is prepared to make a trip to Europe to participate - can I please check whether he is happy to fund his travel to the meeting or does he expect help from ourselves?
Thank you for your help. Tilli's e-mail says it all.
Best wishes, Daphne

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From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 09 March 2004 14:52
To: Tilly Tansey (E-mail); Daphne Christie (E-mail)
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With best wishes, Iain

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--
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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 11 March 2004 09:43
To: Iain Chalmers
Cc: Wendy
Subject: RE: Witness seminar on prenatal corticosteroids

Dear Iain
We've found contact addresses for the listed people who you think should be invited and are ready to send out letters. Please can you let me know if we should invite everyone on the list or separate the list into A (key participants) and B (members of the audience), As will receive an invitation and Bs will receive a publicity flyer. Prof Keirse, Sir Liam Donaldson, Prof Lilford, Dr Hanney, Prof Brocklehurst, Dr Avery, Dr Gamsu and Dr Robertson are all on the A list (+ Chalmers, Hey, Crowley, Mugford).
I'd also be very grateful if you could help draft a couple of paragraphs for a publicity flyer which we can then distribute to all the people.
Thank you for your help.
With best wishes
Daphne

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Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 12 March 2004 16:16
To: Graham Liggins (E-mail)
Cc: Cindy Farquhar (E-mail); Marc Keirse (E-mail); Tilli Tansey (E-mail); Daphne Christie (E-mail); Edmund Hey (E-mail)
Subject: Material for witness seminar on prenatal steroids

Dear Mont

Your wonderful letter, with three relevant slides, arrived here today. Thank you so much for this initial contribution to the witness seminar. I see that it was Nature that initially rejected your report, not the Lancet, as I suggested in the outline that I drafted and sent out yesterday.

A couple of things occurred to me during my first reading of your 3-page letter.

First, how sad that all your records were "consigned to the scrap heap" when you retired, and that you have never been interviewed on video about your experience. The records probably cannot now be retrieved from the scrap heap, but there is absolutely no reason why you shouldn't be interviewed on video. I'll copy this message to Cindy and Marc in the hope that they will ensure that this happens. Indeed, NZ TV ought to have made a programme about this whole story long ago, but better late than never. I hope they may be spurred on to do so by the news that a witness seminar is being organised thousands of miles away to celebrate a Kiwi discovery. Talk about a prophet not being recognised in his own land! Have New Zealanders no pride and sense of history outside rugby and Middle Earth?!

Second, would you be able to send me (signed) copies of your key papers in the story, up to and including the papers published in the early 1970s, and also the reference to the paper by DeLemos and Avery.

I am very glad to be involved in this exercise, and look forward to continuing to work with you towards an account of the whole story with which you will be pleased.

With best wishes

Aye, Iain

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Dr Daphne Christie

From: Dr Tilli Tansey [ucgatlt@ucl.ac.uk]
Sent: 14 March 2004 12:54
To: Iain Chalmers
Cc: Daphne Christie (E-mail)
Subject: RE: Material for witness seminar on prenatal steroids

Dear Iain,
thank you for this information.
I'll be discussing this meeting with Daphne on Tuesday (as she only works part-time and will not be in until then).
I'm particularly interested in the fact that the Trust supported this work from 1967-1977, clearly of critical importance in establishing the basic physiological parameters that could feed into clinical research and trials. I would like to include physiologists/endocrinologists from this period, and also if possible someone from the Trust. Looking at the (very tiny) staff lists from that period, the only immediately obvious person to inivite seems to be Peter Williams. Stan Peart was one of the Trustees then, and the one with the most obvious clinical input, although it is interesting that Henry Barcroft was a Trustee from 1966-1975 - one wonders whether Liggins' research would have immediate resonance with him, because of his father's work?
this is therefore a quick query for advice about suitable scientists/administrators. If recommendations don't immediately come to mind, please don't trouble about it - Daphne will be doing literature searches etc for others to include, and the meeting's publicity will also generate interest amongst likely contributors.
bets wishes, tilli

Dr Tilli Tansey
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http://www.ucl.ac.uk/histmed

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Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 14 March 2004 13:59
To: ucgatlt@ucl.ac.uk
Cc: Daphne Christie (E-mail); Graham Liggins (E-mail); Edmund Hey (E-mail); Marc Keirse (E-mail); Iain Chalmers
Subject: RE: Material for witness seminar on prenatal steroids

Dear Tilli

On the basis of the memorandum he has sent to me, Mont Liggins regards Mary Ellen Avery as the most important person in replicating the animal work, and she is on the list of potential invitees I sent. Don't underestimate the importance of our chair, Ed Hey, who was working with the physiologist Kenneth Cross on neonates at the time. Mont also mentions the grant support he received from the Trust through Peter Williams, so he should probably be invited. Does the Trust keep records of how that decision was taken. If so, other names might suggest themselves. I think the key people in this country were probably Geoffrey Dawes, Anne Anderson and Alec Turnbull, all of whom died some time ago. However, Mont, Ed or Marc Keirse may be able to help with additional names, so I'll copy these messages to them for comment.

Aye, Iain

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From: Dr Tilli Tansey [ucgatlt@ucl.ac.uk]
Sent: 14 March 2004 15:38
To: Iain Chalmers
Cc: Daphne
Subject: RE: Material for witness seminar on prenatal steroids

Thanks Iain,
I was wondering about Cross et al, and hadn't realised that Hey had been a member of that team. But as you say, people like Dawes, Comline, Turnbull are no longer with us. I'll ask Daphne to add Peter to the list, and might give him a call about Trust procedures at the time. I'll also make some enquiries about th e original application and referees.
thanks for your help,
tilli

Please add to list + draft letter

Dr Tilli Tansey
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deceased

deceased

Dear Tilli

On the basis of the memorandum he has sent to me, Mont Liggins regards Mary Ellen Avery as the most important person in replicating the animal work, and she is on the list of potential invitees I sent. Don't underestimate the importance of our chair, Ed Hey, who was working with the physiologist Kenneth Cross on neonates at the time. Mont also mentions the grant support he received from the Trust through Peter Williams, so he should probably be invited. Does the Trust keep records of how that decision was taken. If so, other names might suggest themselves. I think the key people in this country were probably Geoffrey Dawes, Anne Anderson and Alec Turnbull, all of whom died some time ago. However, Mont, Ed or Marc Keirse may be able to help with additional names, so I'll copy these messages to them for comment.

(d)

Aye, Iain

This e-mail contains information which is intended for the addressee only. If you receive this e-mail in error, please contact the sender and delete the original from your system. We cannot guarantee that any attachments to this e-mail are free of software viruses, and we recommend that you check for viruses before opening any attachments.

-----Original Message-----
From: Dr Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 14 March 2004 12:54
To: Iain Chalmers
Cc: Daphne Christie (E-mail)
Subject: RE: Material for witness seminar on prenatal steroids

Dear Iain,

thank you for this information.
I'll be discussing this meeting with Daphne on Tuesday (as she only works part-time and will not be in until then).
I'm particularly interested in the fact that the Trust supported this work from 1967-1977, clearly of critical importance in establishing the basic physiological parameters that could feed into clinical research and trials. I would like to include physiologists/endocrinologists from this period, and also if possible someone from the Trust. Looking at the (very tiny) staff lists from that period, the only immediately obvious person to inivite seems to be Peter Williams. Stan Peart was one of the Trustees then, and the one with the most obvious clinical input, although it is interesting that Henry Barcroft was a Trustee from 1966-1975 - one wonders whether Liggins' research would have immediate resonance with him, because of his father's work?
this is therefore a quick query for advice about suitable scientists/administrators. If recommendations don't immediately come to mind, please don't trouble about it - Daphne will be doing literature searches etc for others to include, and the meeting's publicity will also generate interest amongst likely contributors.
bets wishes, tilli

Dr Tilli Tansey
Historian of Modern Medical Sciences/Convenor of the History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine,
UCL, 24 Eversholt St, LONDON NW1 1AD
tel 020 7679 8124 (sec 8106); fax 020 7679 8193
http://www.ucl.ac.uk/histmed

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 12 March 2004 16:16
To: Graham Liggins (E-mail)
Cc: Cindy Farquhar (E-mail); Marc Keirse (E-mail); Tilli Tansey (E-mail); Daphne Christie (E-mail); Edmund Hey (E-mail)
Subject: Material for witness seminar on prenatal steroids

Dear Mont

Your wonderful letter, with three relevant slides, arrived here today. Thank you so much for this initial contribution to the witness seminar. I see that it was Nature that initially rejected your report, not the Lancet, as I suggested in the outline that I drafted and sent out yesterday.

A couple of things occurred to me during my first reading of your 3-page letter.

First, how sad that all your records were "consigned to the scrap heap" when you retired, and that you have never been interviewed on video about your experience. The records probably cannot now be retrieved from the scrap heap, but there is absolutely no reason why you shouldn't be interviewed on video. I'll copy this message to Cindy and Marc in the hope that they will ensure that this happens. Indeed, NZ TV ought to have made a programme about this whole story long ago, but better late than never. I hope they may be spurred on to do so by the news that a witness seminar is being organised thousands of miles away to celebrate a Kiwi discovery. Talk about a prophet not being recognised in his own land! Have New Zealanders no pride and sense of history outside rugby and Middle Earth?!

Second, would you be able to send me (signed) copies of your key papers in the story, up to and including the papers published in the early 1970s, and also the reference to the paper by DeLemos and Avery.

I am very glad to be involved in this exercise, and look forward to continuing to work with you towards an account of the whole story with which you will be pleased.

With best wishes

Aye, Iain

IAIN CHALMERS
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The James Lind Initiative
Summertown Pavilion
Middle Way
Oxford OX2 7LG, UK
Tel: +44 (0)1865 517636 (direct)
+44 (0)1865 517635
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Email: ichalmers@jameslindlibrary.org
Website: www.jameslindlibrary.org

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--
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Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 24 March 2004 15:50
To: Graham Liggins (E-mail)
Cc: Edmund Hey (E-mail); Marc Keirse (E-mail); Daphne Christie (E-mail)
Subject: Thanks

Dear Mont

Thank you very much for the bundle of goodies that arrived here today. I gather from the Wellcome Trust that preparations for the June meeting are proceeding satisfactorily. I hope that Marc Keirse - as a sheep and clinical researcher, like you - has been able to arrange to come to the UK to kick off the proceedings.

With best wishes, Iain

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 25 March 2004 08:34
To: Wendy
Subject: FW: Thanks

copy for the files. thanks, daphne
-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 24 March 2004 15:50
To: Graham Liggins (E-mail)
Cc: Edmund Hey (E-mail); Marc Keirse (E-mail); Daphne Christie (E-mail)
Subject: Thanks

Dear Mont

Thank you very much for the bundle of goodies that arrived here today. I gather from the Wellcome Trust that preparations for the June meeting are proceeding satisfactorily. I hope that Marc Keirse - as a sheep and clinical researcher, like you - has been able to arrange to come to the UK to kick off the proceedings.

With best wishes, Iain

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 25 March 2004 11:44
To: Wendy
Subject: FW: WELLCOME MEETING

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 25 March 2004 11:31
To: 'Lynne Roberts'
Cc: Daphne Christie (E-mail)
Subject: RE: WELLCOME MEETING

Thanks, Lynne. That's great news. Iain

-----Original Message-----
From: Lynne Roberts
[mailto:lynne.roberts@perinatal-epidemiology.oxford.ac.uk]
Sent: 25 March 2004 09:24
To: ichalmers@jameslindlibrary.org
Subject: WELLCOME MEETING

Dear Iain

Peter has the invitation to speak at the Wellcome meeting, which probably explains why I couldn't find it. He has e-mailed me to say that he will definitely be speaking at the meeting and hopes to leave his training session in the morning early.

With best wishes

Lynne

****

Lynne Roberts
PA to the Director
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Old Road
Headington
Oxford
OX3 7LF

Tel: 01865 226966
Fax: 01865 227004
web: http://www.npeu.ox.ac.uk

****
--
Virus scanned by edNET.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 25 March 2004 11:59
To: Iain Chalmers
Cc: Wendy
Subject: Witness Seminar

Dear Iain
Thank you for yesterday's very useful discussion regarding key participants. Dr Jonathan Mant has replied that he is unable to join us as he is examining on that day. He has sent me three papers regarding increasing uptake of the therapy, which I'll keep on file.
I'll keep you posted on other developments.
Best wishes
Daphne

Dr Daphne Christie
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www.ucl.ac.uk/histmed

Wendy Kutner

To: Chalmers, Sir Iain
Cc: Daphne Christie
Subject: FW: Witness Seminar: Prenatal corticosteroids - 15 June 2004 2pm/6pm

Plesae see e-mail below, as mentioned in my e-mail to you today

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

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

-----Original Message-----
From: Lynne Roberts
[mailto:lynne.roberts@perinatal-epidemiology.oxford.ac.uk]
Sent: 30 March 2004 11:32
To: w.kutner
Subject: Re: Witness Seminar: Prenatal corticosteroids - 15 June 2004 2pm/6pm

Dear Wendy

Many thanks for contacting me. I will forward your e-mail to Peter Brocklehurst so that he knows that something will be on its way to him. It would be useful if his talk could be in he latter half of the afternoon as he is attending a course in Oxford in the morning, and hopes to leave this early in order to be with you.

With best wishes

Lynne Roberts
PA to Peter Brocklehurst

****

Lynne Roberts
PA to the Director
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Old Road
Headington
Oxford
OX3 7LF

Tel: 01865 226966
Fax: 01865 227004
web: http://www.npeu.ox.ac.uk

****

>>> "Wendy Kutner" <w.kutner@ucl.ac.uk> 30/03/2004 11:22:33 >>>
Thank you for your reply on behalf of Dr Brocklehurst. We are delighted he

is able to attend. We are in the process of drafting a programme and will
let Dr Brocklehurst know further details in due course. Yours sincerely,
Wendy Kutner

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

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w.kutner@ucl.ac.uk
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Wendy Kutner

To: Chalmers, Sir Iain
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - Attendance list 30.3.04


CORTIattendancelst.doc


CORTIpubFLYER_whk.doc

Please find attached an up to date draft attendance list. We have received a reply from Dr Mary Ellen Avery that she has great pleasure in accepting the invitation and confirms that she will pay her travel expenses. She has also kindly sent several papers and lecture notes. This is very good news.

Dr Peter Brocklehurst, Professor Martin Buxton and Professor Osmund Reynolds have also accepted. Dr Brocklehurst's secretary has sent an e-mail (forwarded to you separately) that Dr Brocklehurst will be attending a course in Oxford in the morning; hopes to leave early to attend the Witness Seminar and would like to speak in the latter half of the programme (according to your draft programme, he is already listed as the last 'Witness').

Professor Harold Gamsu has also accepted and would like to discuss the Witness Seminar with you. He has asked us to give him your contact details. His telephone number is 0208693 9920. Is it ok for us to give him your e-mail/telephone/address details?

Professor Sally Macintyre is away on sick leave until early May. Professor Ann Oakley is away on leave until mid-April.

In your e-mail with Dr Hey the following paragraph was listed: 'Dr Peter Stutchfield, a Paediatrician in Glan Cywyd, has been quietly plodding away for years now on a megerly funded trial looking at the effect of giving betamethasone antenatally to mothers haveing a planned section at 37+ weeks gestation, and I hear on the grape vine that the outcome of that study is due to be presented at the RCPCH meeting in York in April'. Do you want us to send him a flyer or an invitation?

We are almost ready to send out the flyers for the meeting. Can you please send me Mrs Gill Gyte's address so that I can send her a flyer in the general mailing.

We have edited the flyer, copy attached. Please confirm you agree the changes. We have also sent a copy of the draft flyer to Dr Hey, together with a draft attendance list.

Professor Frank Hytten and Barbara Stocking are unable to attend.

Mrs Wendy Kutner
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w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 31 March 2004 10:16
To: 'w.kutner@ucl.ac.uk'
Cc: Daphne Christie; Edmund Hey (E-mail)
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Dear Wendy

Thanks for your message. I have made further changes to the flyer, some of them in the light of information sent to me by Mont Liggins, particularly information relevant to the excellent news that Mel Avery will be attending. Professor Avery should now replace Professor Keirse on the draft programme I sent you. I have spoken to Professor Keirse. In the light of the news that Professor Avery will be attending, he has decided that he will not now attend.

Please send an invitation to Dr Peter Stutchfield, and to Gill Gyte, whose contact details I have pasted below. By all means give my contact details to Harold Gamsu.

Let me know if I have overlooked anything

Best wishes

Iain

Mrs Gill Gyte
'Oldfield'
159 Hardhorn Rd
Poulton-Le-Fylde
Lancashire
FY6 8ES
Tel. 01253 899030
Fax. 01253 899030
Email: ggyte@cochrane.co.uk

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 30 March 2004 13:55
To: Chalmers, Sir Iain
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - Attendance list 30.3.04

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Dr Peter Brocklehurst, Professor Martin Buxton and Professor Osmund Reynolds have also accepted. Dr Brocklehurst's secretary has sent an e-mail (forwarded to you separately) that Dr Brocklehurst will be attending a course in Oxford in the morning; hopes to leave early to attend the Witness Seminar and would like to speak in the latter half of the programme (according to your draft programme, he is already listed as the last 'Witness').

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Ann Oakley is away on leave until mid-April.

In your e-mail with Dr Hey the following paragraph was listed: 'Dr Peter Stutchfield, a Paediatrician in Glan Cywyd, has been quietly plodding away for years now on a megerly funded trial looking at the effect of giving betamethasone antenatally to mothers haveing a planned section at 37+ weeks gestation, and I hear on the grape vine that the outcome of that study is due to be presented at the RCPCH meeting in York in April'. Do you want us to send him a flyer or an invitation?

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We have edited the flyer, copy attached. Please confirm you agree the changes. We have also sent a copy of the draft flyer to Dr Hey, together with a draft attendance list.

Professor Frank Hytten and Barbara Stocking are unable to attend.

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

To: Iain Chalmers
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Dear Sir Iain, Thank you for your e-mail and for Mrs Gyte's address. You told me in an earlier e-mail that you had forwarded the invitation I sent to your offices to her, therefore I am uncertain whether to send her a further invitation directly. We usually send out reminder invitations when we have not received replies and I will also be sending out flyers, so will send her a reminder letter and copy original invitation with the flyer if I haven't heard from her before then.
As you requested, I have marked Professor Keirse as 'NO' on the grid and under apologies on the draft attendance list, and have replaced his name with that of Dr Avery on the draft programme.
Please note that Dr Paintin has accepted and replied as follows:
'Thank you for inviting me to take part in this Witness Seminar. I am pleased to accept - but as an interested observer rather than as someone who can make a significant contribution. I was an obstetrician during the relevant period but had no academic involvement in feto-maternal medicine - apart from as part of the editorial team of the British Journal of O & G. (My particular academic interest was the provision of induced abortion - I took part in the Witness Seminar on the history of the Abortion Act). Obstetricians who it would be worth inviting are:
Professor Richard Beard, 64 Elgin Crescent, London W11 2JJ
Professor Phillip Steer, 48 Langley Ave, Surbiton, Surrey, KT6 4QR
and the paediatrician:
Professor Rodney Rivers, 53 Loftus Rd, London, W12 7EH'.
All names will be entered on the grid and the above suggested participants will be sent flyers unless you wish them to receive invitations.
We are still following up scientists who might be able to attend.
I will send an invitation to Dr Peter Stutchfield, as you requested and have just telephoned Professor Gamsu with your contact details.
Unfortunately your edited flyer does not seem to have arrived with your e-mail, so I would be very grateful if you could send me the edited flyer once again.
Wtih best wishes, Wendy

Mrs Wendy Kutner
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-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 31 March 2004 10:16
To: 'w.kutner@ucl.ac.uk'
Cc: Daphne Christie; Edmund Hey (E-mail)
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Dear Wendy

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Please send an invitation to Dr Peter Stutchfield, and to Gill Gyte, whose contact details I have pasted below. By all means give my contact details to Harold Gamsu.

Let me know if I have overlooked anything

Best wishes

Iain

Mrs Gill Gyte
'Oldfield'
159 Hardhorn Rd
Poulton-Le-Fylde
Lancashire
FY6 8ES
Tel. 01253 899030
Fax. 01253 899030
Email: ggyte@cochrane.co.uk

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 30 March 2004 13:55
To: Chalmers, Sir Iain
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - Attendance list 30.3.04

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We have edited the flyer, copy attached. Please confirm you agree the changes. We have also sent a copy of the draft flyer to Dr Hey, together with a draft attendance list.

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Mrs Wendy Kutner
Secretary to Dr Tilli Tansey

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--
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Wendy Kutner

To: Iain Chalmers
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Dear Sir Iain, you didn't attach the amended flyer, so I haven't seen the further amendments. Could you please send it to me.

Re. scientists, I'm sorry to have been so vague. Tilli is keen to invite some physiologists/endocrinologists who were possibly around at the time, and this is what we are following up. Daphne wrote to Dr Saffron Whitehead, a Physiologist at St George's, who recommended we wrote to Professor Brian Cooke, Dr Joe Herbert and Professor Gavin Vinson. Professor Vinson has responded so far, suggesting we contacted Professor John Coghlan and Professor Marelyn Wintour-Coghlan in Australia. I e-mailed yesterday and have received a reply today from Professor Wintour-Coghlan listing 2 physiologists at Cambridge (Professor Abigail Powden and Dr Dino Guissani (who both "know much of the action of glucocorticoids on in utero maturation") and as for 'oldies' writes "I don't quite know wo is still around - there were some at the Mordun at Cardiff, and Mark Hanson at Cardiff might be able to help". I am in the process of writing to Mark Hanson asking whether he can suggest names. We also asked Dr Hey if he had any names to suggest. Hope this clears up any confusion I may have caused. Wendy

Mrs Wendy Kutner
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-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 31 March 2004 13:30
To: 'w.kutner@ucl.ac.uk'
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Thanks, Wendy. Am I right to assume that my suggested amendments to the flyer are acceptable?

I wasn't very clear to whom you were referring when you wrote "We are still following up scientists who might be able to attend." Many (if not most) of the people already involved are scientists. Who did you have in mind?

Best wishes, Iain

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 31 March 2004 11:46
To: Iain Chalmers
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Dear Sir Iain, Thank you for your e-mail and for Mrs Gyte's address. You told me in an earlier e-mail that you had forwarded the invitation I sent to your offices to her, therefore I am uncertain whether to send her a further invitation directly. We usually send out reminder invitations when we have not received replies and I will also be sending out flyers, so will send her a reminder letter and copy original invitation with the flyer if I haven't

heard from her before then.
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Please note that Dr Paintin has accepted and replied as follows:
'Thank you for inviting me to take part in this Witness Seminar. I am pleased to accept - but as an interested observer rather than as someone who can make a significant contribution. I was an obstetrician during the relevant period but had no academic involvement in feto-maternal medicine - apart from as part of the editorial team of the British Journal of O & G. (My particular academic interest was the provision of induced abortion - I took part in the Witness Seminar on the history of the Abortion Act).
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Mrs Wendy Kutner
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Sent: 31 March 2004 10:16
To: 'w.kutner@ucl.ac.uk'
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Please send an invitation to Dr Peter Stutchfield, and to Gill Gyte, whose contact details I have pasted below. By all means give my contact details to Harold Gamsu.

Let me know if I have overlooked anything

Best wishes

Iain

Mrs Gill Gyte

'Oldfield'
159 Hardhorn Rd
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-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 30 March 2004 13:55
To: Chalmers, Sir Iain
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - Attendance list 30.3.04

Please find attached an up to date draft attendance list. We have received a reply from Dr Mary Ellen Avery that she has great pleasure in accepting the invitation and confirms that she will pay her travel expenses. She has also kindly sent several papers and lecture notes. This is very good news.

Dr Peter Brocklehurst, Professor Martin Buxton and Professor Osmund Reynolds have also accepted. Dr Brocklehurst's secretary has sent an e-mail (forwarded to you separately) that Dr Brocklehurst will be attending a course in Oxford in the morning; hopes to leave early to attend the Witness Seminar and would like to speak in the latter half of the programme (according to your draft programme, he is already listed as the last 'Witness').

Professor Harold Gamsu has also accepted and would like to discuss the Witness Seminar with you. He has asked us to give him your contact details. His telephone number is 0208693 9920. Is it ok for us to give him your e-mail/telephone/address details?

Professor Sally Macintyre is away on sick leave until early May. Professor Ann Oakley is away on leave until mid-April.

In your e-mail with Dr Hey the following paragraph was listed: 'Dr Peter Stutchfield, a Paediatrician in Glan Cywyd, has been quietly plodding away for years now on a megerly funded trial looking at the effect of giving betamethasone antenatally to mothers haveing a planned section at 37+ weeks gestation, and I hear on the grape vine that the outcome of that study is due to be presented at the RCPCH meeting in York in April'. Do you want us to send him a flyer or an invitation?

We are almost ready to send out the flyers for the meeting. Can you please send me Mrs Gill Gyte's address so that I can send her a flyer in the general mailing.

We have edited the flyer, copy attached. Please confirm you agree the changes. We have also sent a copy of the draft flyer to Dr Hey, together with a draft attendance list.

Professor Frank Hytten and Barbara Stocking are unable to attend.

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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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: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 31 March 2004 14:42
To: 'w.kutner@ucl.ac.uk'; Iain Chalmers
Cc: Daphne Christie
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04



CORTIpubFLYER_whk-IC.doc

Thanks for the clarification, Wendy, and apologies for not attaching the flyer with my suggested amendments. Here it is. Iain

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 31 March 2004 13:11
To: Iain Chalmers
Cc: Daphne Christie
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Dear Sir Iain, you didn't attach the amended flyer, so I haven't seen the further amendments. Could you please send it to me.

Re. scientists, I'm sorry to have been so vague. Tilli is keen to invite some physiologists/endocrinologists who were possibly around at the time, and this is what we are following up. Daphne wrote to Dr Saffron Whitehead, a Physiologist at St George's, who recommended we wrote to Professor Brian Cooke, Dr Joe Herbert and Professor Gavin Vinson. Professor Vinson has responded so far, suggesting we contacted Professor John Coghlan and Professor Marelyn Wintour-Coghlan in Australia. I e-mailed yesterday and have received a reply today from Professor Wintour-Coghlan listing 2 physiologists at Cambridge (Professor Abigail Fowden and Dr Dino Guissani (who both "know much of the action of glucocorticoids on in utero maturation") and as for 'oldies' writes "I don't quite know wo is still around - there were some at the Mordun at Cardiff, and Mark Hanson at Cardiff might be able to help". I am in the process of writing to Mark Hanson asking whether he can suggest names. We also asked Dr Hey if he had any names to suggest. Hope this clears up any confusion I may have caused. Wendy

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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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: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 31 March 2004 13:30
To: 'w.kutner@ucl.ac.uk'
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Thanks, Wendy. Am I right to assume that my suggested amendments to the

flyer are acceptable?

I wasn't very clear to whom you were referring when you wrote "We are still following up scientists who might be able to attend." Many (if not most) of the people already involved are scientists. Who did you have in mind?

Best wishes, Iain

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 31 March 2004 11:46
To: Iain Chalmers
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Dear Sir Iain, Thank you for your e-mail and for Mrs Gyte's address. You told me in an earlier e-mail that you had forwarded the invitation I sent to your offices to her, therefore I am uncertain whether to send her a further invitation directly. We usually send out reminder invitations when we have not received replies and I will also be sending out flyers, so will send her a reminder letter and copy original invitation with the flyer if I haven't heard from her before then.
As you requested, I have marked Professor Keirse as 'NO' on the grid and under apologies on the draft attendance list, and have replaced his name with that of Dr Avery on the draft programme.
Please note that Dr Paintin has accepted and replied as follows:
'Thank you for inviting me to take part in this Witness Seminar. I am pleased to accept - but as an interested observer rather than as someone who can make a significant contribution. I was an obstetrician during the relevant period but had no academic involvement in feto-maternal medicine - apart from as part of the editorial team of the British Journal of O & G. (My particular academic interest was the provision of induced abortion - I took part in the Witness Seminar on the history of the Abortion Act).
Obstetricians who it would be worth inviting are:
Professor Richard Beard, 64 Elgin Crescent, London W11 2JJ
Professor Phillip Steer, 48 Langley Ave, Surbiton, Surrey, KT6 4QR
and the paediatrician:
Professor Rodney Rivers, 53 Loftus Rd, London, W12 7EH'.
All names will be entered on the grid and the above suggested participants will be sent flyers unless you wish them to receive invitations.
We are still following up scientists who might be able to attend.
I will send an invitation to Dr Peter Stutchfield, as you requested and have just telephoned Professor Gamsu with your contact details.
Unfortunately your edited flyer does not seem to have arrived with your e-mail, so I would be very grateful if you could send me the edited flyer once again.
Wtih best wishes, Wendy

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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www.ucl.ac.uk/histmed

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 31 March 2004 10:16
To: 'w.kutner@ucl.ac.uk'
Cc: Daphne Christie; Edmund Hey (E-mail)
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - At tendance list 30.3.04

Dear Wendy

Thanks for your message. I have made further changes to the flyer, some of them in the light of information sent to me by Mont Liggins, particularly information relevant to the excellent news that Mel Avery will be attending. Professor Avery should now replace Professor Keirse on the draft programme I sent you. I have spoken to Professor Keirse. In the light of the news that Professor Avery will be attending, he has decided that he will not now attend.

Please send an invitation to Dr Peter Stutchfield, and to Gill Gyte, whose contact details I have pasted below. By all means give my contact details to Harold Gamsu.

Let me know if I have overlooked anything

Best wishes

Iain

Mrs Gill Gyte
'Oldfield'
159 Hardhorn Rd
Poulton-Le-Fylde
Lancashire
FY6 8ES
Tel. 01253 899030
Fax. 01253 899030
Email: ggyte@cochrane.co.uk

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 30 March 2004 13:55
To: Chalmers, Sir Iain
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15 June 2004 - Attendance list 30.3.04

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In your e-mail with Dr Hey the following paragraph was listed: 'Dr Peter Stutchfield, a Paediatrician in Glan Cywyd, has been quietly plodding away for years now on a megerly funded trial looking at the effect of giving betamethasone antenatally to mothers haveing a planned section at 37+ weeks gestation, and I hear on the grape vine that the outcome of that study is due to be presented at the RCPCH meeting in York in April'. Do you want us to send him a flyer or an invitation?

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general mailing.

We have edited the flyer, copy attached. Please confirm you agree the changes. We have also sent a copy of the draft flyer to Dr Hey, together with a draft attendance list.

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April 6, 2004

Sir Iain Chalmers
James Lind Library
Summertown Pavilion
Middle Way
Oxford OX2 7LG, UK

Dear Iain,

As you say, it would be nice to be fit enough to do this face-to-face.I will do my best to answer your queries. There is no video-recording of an appropriate interview. Nor can I provide pages from a lab book. Lacking your sense of history, All my records were consigned to the scrap heap when I retired. The best I can do is enclose a slide of a photo taken of those very first lungs showing partial inflation after fetal infusion with cortisol at 118 days of gestation The lamb had delivered during the night.To my great surprise, I found it still alive in the morning, gasping but surviving. I was fully occupied with studies of parturitional physiology and was not inclined to pursue it further at that time. However, I did tell Mel Avery who was visiting NZ soon afterwards. She got on the phone and called one of her Fellows in her lab and told him to give cortisol to some fetal sheep. Our observation was published in 1969 was soon followed by DeLemos and Avery in 1970 which confirmed the finding as well as providing direct evidence of accelerated appearance of surfactant as we had postulated.
When I returned to a position as Senior Lecturer in O & G at National Women's Hospital in 1959 after 6 years of clinical work and no research in the UK, I realised that my academic appointment required me to do some research. I asked my friend, Bill Liley, of fetal transfusion fame how to choose a topic. He said to look for a major problem which was potentially soluble. The major problem was easy. Prematurity stood out above everything else. I naively thought that all I had to do was solve the ancient question of what controlled the onset of labour at term and the reason for premature onset would become apparent. I thought it might be a fetal activity although at the time it was generally believed maternal activity via release of oxytocin from her pituitary. But I had some

4/8/05.
Scanned + sent to IC asking for permission

circumstantial evidence to support my idea.The second slide enclosed shows two sheep brousing on veratrum californicum or skunk cabbage in the mountains. They don't like it bit will eat it in times of drought. Binns et al in 1960 described how the lambs were cyclopian and had prolonged pregnancies.At autopsy they found defective pituitaries. With this titbit I set out to hypopyhsectomise fetal sheep.Having no money and no animal lab I called on friends at Ruakura Animal Research Station 80 miles south of Auckland. They generously provided everything I needed. So over the next sheep season I worked out how to do fetal hypophysectomies and adrenalectomies. The following year I had a sabbatical and went off to the Vet School at Davis, California and put the techniques to the test. The results were dramatically successful.Pregnancies continued on and on after hypophysectomy.

Back in Auckland I needed a lab and money, The Hospital gave me an abandoned shed [see slide 3] and the Wellcome Trust courtesy of that wonderful man, Peter Williams, gave me money. My first experiments were to test the idea that the effects of the pituitary were mediated by the fetal adrenal. Infusion of cortisol or ACTH caused premature delivery at any gestational age.With that lengthy background we have arrived at the subject of the seminar although there is plenty more to the parturition story.

When I saw the inflated lungs and correctly guessed that cortisol had induced one or more enzymes responsible for surfactont synthesis and/or release, it seemed very likely that this was not a species specific response since cortisol was well known to induce a variety of enzymes in a variety of species.So no time was lost in enlisting the collaboration of my neonatal colleague, Ross Howie, who I knew to be meticulous almost to a fault. We worked out what we thought was a rigorous protocol but as simple in design as possible. An immediate problem was what to give the mothers and how much of it. It happened that I had been studying the effects of corticosteroids on human fetal adrenal function by measuring urinary oestriol excretion which is a product of the fetal zone of the fetal adrenal. So I knew the dose of corticosteroid required to cause marked inhibition of adrenal function. To simplify administration to the mothers in the trial a once daily dose was desirable so we chose a mixture of a long acting and a short acting corticosteroid. This created a problem since all long acting preparations are insoluble and in suspension. The placebo had to be identical in appearance. We finally chose cortisone acetate which is a suspension but one seventieth of the potency of our active agent.The choice of active agent came down to what Drug company was willing to supply the active and placebo ampoules. Glaxo, originally a NZ company,came up trumps and the trial soon began.Glaxo could

see that no profit was to be made but were happy to do it for goodwill. It was by chance then our choice of agent has turned out to be the best. Ethics committee hadn't arrived in 1969 but all clinical studies had to be submitted to the Senior Hospital Medical Committee for approval. The main purpose was to let the staff know what was going on and to enlist their cooperation. There were no conditions. We had told them that verbal consent would be obtained. The staff gave their full support so that 287 mothers were recruited in 22 months. The trial ran within the clinical care of each mother and no funding was required .
We offered our manuscript first to Nature which promptly rejected it without sending it out for review on the grounds that it lacked general interest.
Judging by the number of trials that soon followed there was a lot of interest amongst obstetricians particularly in US. I got the impression on visits to the UK that paediatricians there were luke warm perhaps because there was a perception that their territory was being encroached on. Judging by the 20 years that it took the RCOG to come out in favour despite your constant nagging there was a problem with British obstetricians too though I don't understand it.
Iain, please regard this as a trial run, to be amended as you wish.

Best wishes, Mont

Mont.

Wendy Kutner

From: Tilli Tansey [ucgatlt@ucl.ac.uk]
Sent: 07 April 2004 11:05
To: wendy kutner
Subject: FW: Lancet rejection of Liggins and Howie (not Nature)

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 07 April 2004 09:05
To: 'ucgatlt@ucl.ac.uk'; Iain Chalmers
Subject: RE: Lancet rejection of Liggins and Howie (not Nature)

To follow up, Tilli: Mont wrote in a letter to me dated 16 March 2004: "My memory played me tricks. It was the Dawes/Liggins paper reporting fetal breathing that was turned down by Nature. You are correct in citing Lancet." Aye, Iain

-----Original Message-----
From: Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 06 April 2004 19:01
To: Iain Chalmers
Subject:

dear Iain,

Not the repressive hand of dogmatic censorship - simply an acknowledgement that mere words are inadequate to herald your own presentation at the meeting.
But then, of course, you may wish to re-insert it - if you make enough space elsewhere!!
best wishes,
tilli

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 06 April 2004 18:53
To: ucgatlt
Subject: RE:

Thanks, Tilli. Almost all your edits are improvements! As the Wellcome Trust has steadfastly refused to provide moral or any other form of support to the Cochrane Collaboration I'm not surprised that my insertion of more details about the basic science has survived in the redraft while reference to the Cochrane Collaboration has been deleted completely! The divisive effect of reductionist snobbery rears its ugly head yet again!

I have a feeling that in one of his communications with me, Mont remembered that Nature had rejected his sheep paper, and that it was indeed the Lancet that had rejected the report of the RCT. I've checked my emails from him (I'm at home now); but I'll have a look at his letters when I go in tomorrow and let you know if that needs changing.

Best wishes, Iain

-----Original Message-----
From: Dr Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 06 April 2004 13:45
To: Iain Chalmers
Subject:

Dear Iain,

Many thanks for your time yesterday - it was very useful for Richard to meet both you and Irvine .

I think we got quite a bit of useful business done. I'll get back to you after my next lot of students, about the D'Arcy Hart meeting. I've had a first go at editing the overlong publicity flyer for the Corticosteroids meeting. I attach two copies - one with all the editing marks retaines, and one without. I have cut fairly drastically - it must fit on one page as shown, and too much text usually deters rather than attracts the eye. I know I will have cut some things, particularly the logo, which you will not like. Perhaps you would like to have a look at it now?
The Wellcome Trust have found the original Liggins file for me. I am going to e-mail Sir Graham (I can hardly call him Mont) and ask for his permission to view his application and reports, which might smooth the way through concerns about the Data Protection Act. I may not be able to see referee reports however (although in those daysm, there may not have been any - everything was much more informal).

Did you see the obituary in today's Guardian for Reggie Saxton?

best wishes, tilli

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Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 11 April 2004 12:02
To: Edmund Hey
Cc: Patricia Crowley (E-mail); James P Neilson (E-mail); Peter Brocklehurst (E-mail); John Sinclair; Daphne Christie (E-mail)
Subject: RE: Wellcome meeting

Dear Ed

Just a reminder that, because I left the perinatal field more than a decade ago, I am relying on others who are still part of that world, and you as chair of the 15 June Seminar, to ensure that the post-1990 scene will be well covered. For example, if you want to check that Dr Stutchfield has been invited, or if you feel that people involved in the follow-up of the Auckland trial or Laura Leviton should be invited (as implied by Jack), please let Daphne Christie know (d.christie@ucl.ac.uk).

Aye, Iain

This e-mail contains information which is intended for the addressee only. If you receive this e-mail in error, please contact the sender and delete the original from your system. We cannot guarantee that any attachments to this e-mail are free of software viruses, and we recommend that you check for viruses before opening any attachments.

-----Original Message-----
From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 10 April 2004 14:34
To: Iain Chalmers; John Sinclair
Cc: Patricia Crowley (E-mail); James P Neilson (E-mail); Peter Brocklehurst (E-mail)
Subject: Re: Wellcome meeting

Iain
If any of the people you passed your last message to remain unsure as to why Jack was concerned about the lack of good follow up data on the antenatal use of steroids they merely need to look at the lastest isue of NEJM on the long term consequence of its post natal use (NEJM 2004;350:1304-13) although, admittedly, in this trial, full dose treatment started at birth (0.5 mg/kg a day for 7 days) was followed by a slow tappering of that dose over a further 21 days.

E

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 09:48
To: Wendy
Subject: FW: Wellcome meeting, 15 June

Let's discuss on Tuesday... did you update Hey before Easter. Thanks, Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 14 April 2004 11:06
To: 'Edmund Hey'
Cc: Daphne Christie (E-mail)
Subject: RE: Wellcome meeting, 15 June

Dear Ed,

As you will have seen from another message, I have put the Auckland people in touch with Daphne Christie, so I hope they will receive an invitation.

You ask what direction I want you to run in. Please don't regard me as the planner of this seminar. I simply tried to respond to Tilli Tansey's and Daphne Christie's request to help get things off the ground by producing a draft agenda and invitation list. They needed something to be done quite urgently, given the very short notice that was available for organising the meeting.

Unlike you, I have very little pre-1972 and post-1990 knowledge about this topic. Indeed, there can be few (if any) people in the world whose knowledge about pre-natal steroids is as extensive as yours. That is why I recommended to Wellcome that you should be invited to chair the Seminar. In my view, that means that your views should count more than anyone else's about the shape and content of the meeting.

If a direct line of communication has not already been established between you and Daphne, I think it should be. I will continue to do my best to respond to her and your requests for assistance.

With best wishes, Iain

-----Original Message-----
From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 14 April 2004 07:13
To: Iain Chalmers
Subject: Fw: Wellcome meeting

Iain,

With my historian's hat on I guess we need to find some way of getting this amazing piece of news (that is the 30 year follow up) fed into the 'record' during that meeting on June 15. How do we do that ? There are so many who excuse the lack of 'follow through' information in most trials of this nature by saying that 'it can't be done'. This gives the lie to that.

I am prepared to make some of the running in this as I realise you still have another 'day job' - unlike me - but I do need to know what direction you want me to run in.

E

----- Original Message -----

From: Stuart Dalziel
To: 'Iain Chalmers' ; James P Neilson

Cc: John Sinclair ; Patricia Crowley (E-mail) ; Peter Brocklehurst (E-mail) ; Edmund Hey (E-mail) ; Devender Roberts (E-mail) ; Devender Roberts (E-mail 2) ; Jane Harding (E-mail)
Sent: 14 April 2004 06:06
Subject: RE: Wellcome meeting

Dear Jim and Iain,

Thank you for passing on the messages. These will be a great help for the review.

It maybe of interest to everyone that we have just completed the thirty year follow-up of 534 participants from the original trial by Liggins and Howie. The initial data has been presented in abstract form over the last month at SGI, and to our local Australasian Perinatal meeting and will be presented at SPR in a few weeks. We have looked at socio-economic, reproductive, cardiovascular (BP, body size), endocrine (HPA & glucose/insulin axes), and lung endpoints in the main group. With ongoing work in a geographical cohort of 180-190 involving psychological and bone density endpoints nearing completion.

Kind regards,

Stuart.

Dr Stuart Dalziel

Research Fellow
Clinical Trials Research Unit
University of Auckland
Private Bag 92019
Auckland
Ph: +64 9 3737599 ext. 84722
Fax:+64 9 3671710
e-mail: s.dalziel@ctru.auckland.ac.nz
http://www.ctru.auckland.ac.nz

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-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: Wednesday, 14 April 2004 6:43 a.m.
To: James P Neilson; Iain Chalmers
Cc: John Sinclair; Patricia Crowley (E-mail); Peter Brocklehurst (E-mail); Edmund Hey (E-mail); Devender Roberts; Stuart Dalziel

Subject: RE: Wellcome meeting

Thanks, Jim. Iain

This e-mail contains information which is intended for the addressee only. If you receive this e-mail in error, please contact the sender and delete the original from your system. We cannot guarantee that any attachments to this e-mail are free of software viruses, and we recommend that you check for viruses before opening any attachments.

-----Original Message-----
From: James P Neilson [mailto:jneilson@liverpool.ac.uk]
Sent: 13 April 2004 18:26
To: Iain Chalmers
Cc: John Sinclair; Patricia Crowley (E-mail); Peter Brocklehurst (E-mail); Edmund Hey (E-mail); Devender Roberts; Stuart Dalziel
Subject: RE: Wellcome meeting

Dear Iain et al

I'll pass on this and subsequent messages to Devender Roberts & Stuart Dalziel who are, with Patricia, taking the lead on updating the review.

Unfortunately, I can't make the meeting in London.

Best wishes
Jim

--On 09 April 2004 23:54 +0100 Iain Chalmers <ichalmers@jameslindlibrary.org> wrote:

> Thanks, Jack. I'll copy your message to Patricia Crowley, Jim Neilson, Peter Brocklehurst and Ed Hey, so that they can take account of your suggestions/comments for the Cochrane review. Have a good time with the mosquitoes when the time comes. Best wishes, iain
>
> -----Original Message-----
> From: John Sinclair [mailto:sinclair@mcmaster.ca]
> Sent: 09 April 2004 18:21
> To: ichalmers@jameslindlibrary.org
> Subject: Wellcome meeting
>
> Dear Iain,
>
> Thank you for your phone call and the very kind invitation to this meeting on the antenatal corticosteroid story. I am grateful you understand the reason behind my regrets -- we are so firmly attached to

> our rustic cottage up north and the Canadian summer cottage season is so
> short (even if the mosquito season seems long!)
>
>
>
> Anything useful I had to contribute (and I haven't done anything new on
> this since) was published as part of the series of reports of the NIH
> consensus exercise. My report is in AJOG 1995;173:335-344.
>
>
>
> Looking at that in retrospect, I think several issues I raised are still
> relevant:
>
> i) The issue of post-randomization deletions of
> babies born at term who were thus not at risk for RDS (what I called
> "destined for non-event"). The extent to which this occurred in the
> various trials was uncertain to me then, and may still need to be nailed
> down (in an update of the Cochrane review?). To the extent it did occur,
> it can affect the validity of the various measures of treatment affect.
> If the treatment is effective but only in preterm babies, and if we
> assume that all who were excluded because they were born at term truly
> did not have the event of interest, the reported absolute risk difference
> will be too high and the NNT too low, compared to an analysis based on
> all randomized. I noted that in my Discussion at the time, but what I
> didn't note was the effect of this sort of exclusion on other treatment
> effect estimators: there is no effect on relative risk, but the odds
> ratio will be too low, ie depart further from one, compared with an
> analysis based on all randomized. (As an aside, I have wondered to what
> extent this problem is generic among reports of trials of other antenatal
> interventions for reducing adverse outcomes in preterm infants. It could
> be interesting to survey trials in this field to document the extent of
> this problem -- maybe someone has already done this).
>
>
>
> ii) The issue of subgroup analyses by gestational age.
> The clinically applicable subgroup analyses, ie reflecting the evidence
> relevant to the time of the treatment decision, would be subgroup
> analyses based on gestational age at randomization and treatment. I
> assumed at the time (maybe incorrectly) that this was the way the data
> were reported and analyzed in Crowley's subgroup analyses by gestational
> age. But now I suspect it was by gestational age at delivery. If so, this
> also could be re-examined in an update of the Cochrane review.
>
>
>
>
>
> iii) Long term follow-up. I flagged this as the weak
> point in the evidence at the time, given the paucity of trials that had
> undertaken this, and the large loss-to-follow-up rates in some of those
> trials. I called for renewed effort to trace the survivors in all trials
> to ascertain long term outcomes. Ten years later, I don't know whether in
> the interim that has been done by anybody, or indeed whether later

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 12:29
To: Wendy
Subject: FW: Wellcome meeting

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 11 April 2004 12:02
To: Edmund Hey
Cc: Patricia Crowley (E-mail); James P Neilson (E-mail); Peter Brocklehurst (E-mail); John Sinclair; Daphne Christie (E-mail)
Subject: RE: Wellcome meeting

Dear Ed

Just a reminder that, because I left the perinatal field more than a decade ago, I am relying on others who are still part of that world, and you as chair of the 15 June Seminar, to ensure that the post-1990 scene will be well covered. For example, if you want to check that Dr Stutchfield has been invited, or if you feel that people involved in the follow-up of the Auckland trial or Laura Leviton should be invited (as implied by Jack), please let Daphne Christie know (d.christie@ucl.ac.uk).

Aye, Iain

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-----Original Message-----
From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 10 April 2004 14:34
To: Iain Chalmers; John Sinclair
Cc: Patricia Crowley (E-mail); James P Neilson (E-mail); Peter Brocklehurst (E-mail)
Subject: Re: Wellcome meeting

Iain
If any of the people you passed your last message to remain unsure as to why Jack was concerned about the lack of good follow up data on the antenatal use of steroids they merely need to look at the lastest isue of NEJM on the long term consequence of its post natal use (NEJM 2004;350:1304-13) although, admittedly, in this trial, full dose treatment started at birth (0.5 mg/kg a day for 7 days) was followed by a slow tappering of that dose over a further 21 days.

E

--
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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 10:23
To: Wendy
Subject: FW: Wellcome meeting, 15 June

we need to send letters as a matter of urgency... let's discuss on Tuesday.
Thanks, Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 14 April 2004 08:01
To: Stuart Dalziel
Cc: Daphne Christie (E-mail); Edmund Hey (E-mail)
Subject: RE: Wellcome meeting, 15 June

Dear Stuart

This is very impressive. It's clearly very important that the Wellcome Trust Witness Seminar on the afternoon of 15 June records this achievement. It would be splendid if you and Jane Harding could attend and contribute to the seminar. You will have learned already from Mont that he felt unable to accept the invitation to attend, but he has sent a helpful memorandum, copies of some of the key papers and a few slides. Mary Ellen Avery has accepted an invitation to attend.

Unfortunately, there is no budget to meet the cost of international travel. However, I am copying these messages to Dr Daphne Christie, who is convening the seminar, so that you and she can discuss your and Jane's possible participation, and to Edmund Hey, who will be chairing the afternoon's proceedings.

I do hope that we will have a delegation from Auckland after all!

With best wishes

Iain

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-----Original Message-----
From: Stuart Dalziel [mailto:s.dalziel@ctru.auckland.ac.nz]
Sent: 14 April 2004 06:07
To: 'Iain Chalmers'; James P Neilson
Cc: John Sinclair; Patricia Crowley (E-mail); Peter Brocklehurst (E-mail); Edmund Hey (E-mail); Devender Roberts (E-mail); Devender Roberts (E-mail 2); Jane Harding (E-mail)
Subject: RE: Wellcome meeting

Dear Jim and Iain,

Thank you for passing on the messages. These will be a great help for the review.

It maybe of interest to everyone that we have just completed the thirty year follow-up of 534 participants from the original trial by Liggins and Howie. The initial data has been presented in abstract form over the last month at SGI, and to our local Australasian Perinatal meeting and will be presented at SPR in a few weeks. We have looked at socio-economic, reproductive, cardiovascular (BP, body size), endocrine (HPA & glucose/insulin axes), and lung endpoints in the main group. With ongoing work in a geographical cohort

of 180-190 involving psychological and bone density endpoints nearing completion.

Kind regards,

Stuart.

Dr Stuart Dalziel

Research Fellow
Clinical Trials Research Unit
University of Auckland
Private Bag 92019
Auckland
Ph: +64 9 3737599 ext. 84722
Fax:+64 9 3671710
e-mail: s.dalziel@ctru.auckland.ac.nz
http://www.ctru.auckland.ac.nz

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-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: Wednesday, 14 April 2004 6:43 a.m.
To: James P Neilson; Iain Chalmers
Cc: John Sinclair; Patricia Crowley (E-mail); Peter Brocklehurst (E-mail); Edmund Hey (E-mail); Devender Roberts; Stuart Dalziel
Subject: RE: Wellcome meeting

Thanks, Jim. Iain

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-----Original Message-----
From: James P Neilson [mailto:jneilson@liverpool.ac.uk]
Sent: 13 April 2004 18:26
To: Iain Chalmers
Cc: John Sinclair; Patricia Crowley (E-mail); Peter Brocklehurst (E-mail); Edmund Hey (E-mail); Devender Roberts; Stuart Dalziel
Subject: RE: Wellcome meeting

Dear Iain et al

I'll pass on this and subsequent messages to Devender Roberts & Stuart Dalziel who are, with Patricia, taking the lead on updating the review.

Unfortunately, I can't make the meeting in London.

Best wishes
Jim

--On 09 April 2004 23:54 +0100 Iain Chalmers <ichalmers@jameslindlibrary.org> wrote:

> Thanks, Jack. I'll copy your message to Patricia Crowley, Jim Neilson, Peter Brocklehurst and Ed Hey, so that they can take account of your suggestions/comments for the Cochrane review. Have a good time with the mosquitoes when the time comes. Best wishes, iain
>
> -----Original Message-----
> From: John Sinclair [mailto:sinclair@mcmaster.ca]
> Sent: 09 April 2004 18:21
> To: ichalmers@jameslindlibrary.org
> Subject: Wellcome meeting
>
> Dear Iain,
>
> Thank you for your phone call and the very kind invitation to this meeting on the antenatal corticosteroid story. I am grateful you understand the reason behind my regrets -- we are so firmly attached to our rustic cottage up north and the Canadian summer cottage season is so short (even if the mosquito season seems long!)
>
> Anything useful I had to contribute (and I haven't done anything new on this since) was published as part of the series of reports of the NIH consensus exercise. My report is in AJOG 1995;173:335-344.
>
> Looking at that in retrospect, I think several issues I raised are still relevant:
>
> i) The issue of post-randomization deletions of babies born at term who were thus not at risk for RDS (what I called "destined for non-event"). The extent to which this occurred in the various trials was uncertain to me then, and may still need to be nailed down (in an update of the Cochrane review?). To the extent it did occur, it can affect the validity of the various measures of treatment affect. If the treatment is effective but only in preterm babies, and if we assume that all who were excluded because they were born at term truly did not have the event of interest, the reported absolute risk difference will be too high and the NNT too low, compared to an analysis based on all randomized. I noted that in my Discussion at the time, but what I didn't note was the effect of this sort of exclusion on other treatment effect estimators: there is no effect on relative risk, but the odds ratio will be too low, ie depart further from one, compared with an analysis based on all randomized. (As an aside, I have wondered to what extent this problem is generic among reports of trials of other antenatal interventions for reducing adverse outcomes in preterm infants. It could be interesting to survey trials in this field to document the extent of this problem -- maybe someone has already done this).
>
> ii) The issue of subgroup analyses by gestational age. The clinically applicable subgroup analyses, ie reflecting the evidence relevant to the time of the treatment decision, would be subgroup analyses based on gestational age at randomization and treatment. I assumed at the time (maybe incorrectly) that this was the way the data were reported and analyzed in Crowley's subgroup analyses by gestational age. But now I suspect it was by gestational age at delivery. If so, this also could be re-examined in an update of the Cochrane review.
>

> iii) Long term follow-up. I flagged this as the weak
> point in the evidence at the time, given the paucity of trials that had
> undertaken this, and the large loss-to-follow-up rates in some of those
> trials. I called for renewed effort to trace the survivors in all trials
> to ascertain long term outcomes. Ten years later, I don't know whether in
> the interim that has been done by anybody, or indeed whether later
> follow-up has been reported for those trials that did report some
> follow-up data. Again, an opportunity in updating the Cochrane review.
>
>
>
> Best wishes for a stimulating conference. If you think any of these
> thoughts are useful, please feel free to make use of them as you see fit,
> including passing them on to the Cochrane reviewers who will be doing
> future updates of the review. It was very nice to talk with you.
>
>
>
> Best regards,
>
> Jack
>
>
>
>
> --
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>

Jim Neilson
Professor of Obstetrics & Gynaecology,University of Liverpool;
Co-ordinating Editor, Cochrane Pregnancy & Childbirth Group;
Co-Chair, Cochrane Collaboration Steering Group.

Liverpool Women's Hospital
Crown Street
Liverpool L8 7SS, UK.
Tel: (44) 151 702 4100

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Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 17 April 2004 18:24
To: Edmund Hey (E-mail)
Cc: Tilli Tansey (E-mail); Daphne Christie (E-mail)
Subject: Mont Liggins JY Simpson Lecture

Dear Ed

Tidying up some of my untidy things at home today I came across an audio recording 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. He 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. Mont states that his own work in fetal physiology began in 1965 with hypophysectomy ablation experiments in fetal lambs, which showed that this prevented the onset of spontaneous labour.

He deals with management of Rhesus disease at some length, mentioning that Denis Liley got the idea of intraperitoneal blood transfusions in anaemic fetuses from a visitor from Africa who mentioned that he used such transfusions in severely anaemic African children. Mont ranges quite widely in his lecture, including stressing the importance of recognising the need for partnership with women/parents; but he actually touches only very briefly on antenatal corticosteroids, and even then not mentioning his key role in that story!

At one point in his talk he says:

"A major advance in perinatal medicine that receives too little acknowledgement has been the replacement of uncontrolled trials - or indeed, no trials - by well controlled trials of new and old remedies. Much of the credit for this must go to Iain Chalmers, director of the National Perinatal Epidemiology Unit, who has been persistently insistent on the need for controlled trials."

Now I know the reason I kept a copy of the tape!! Vanity, vanity; all is vanity!!

I'll post the tape to you next week. You can pass it on to Tilli Tansey and Daphne Christie at the Witness Seminar, so that it can be archived with other material that they seem likely to assemble in the course of organising the seminar.

Best wishes, Iain

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Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 18 April 2004 20:27
To: ucgatlt@ucl.ac.uk
Cc: Edmund Hey (E-mail); Daphne Christie (E-mail); Iain Milne (E-mail); Cindy Farquhar (E-mail); Graham Liggins (E-mail); j.harding@auckland.ac.nz
Subject: Liggins audiotape & D'Arcy Hart videotape

Dear Tilli

The quality of the audiotape of Mont's James Young Simpson Lecture is fine. I'll send the master to you after making a copy to send to Ed Hey. I don't know whether the lecture has been published, so I'll copy this message to Mont so that he can let us know. I continue to hope that his colleagues in Auckland will make a videotape of Mont in time for the witness seminar (I'm copying these messages to two of them).

Please would you post the D'Arcy Hart tapes directly to Iain Milne (Librarian, Royal College of Physicians, 9 Queen Street, Edinburgh EH2 1JE). He's going to arrange to put the excerpt about the patulin trial on the James Lind Library.

Best wishes, Iain

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-----Original Message-----
From: Dr Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 18 April 2004 18:08
To: Iain Chalmers; Edmund Hey (E-mail)
Cc: Daphne Christie (E-mail)
Subject: RE: Mont Liggins JY Simpson Lecture
Importance: High

Dear Iain,

Before you post it - PLEASE make (and keep) a copy!!!

Is any of it suitable for inclusion at the meeting? If the Chairman is agreeable, we could try to edit a short recording that could be played? Has the lecture been published? If not, it might be worth transcribing this tape? I would need to listen to it myself to check the quality, but on the whole our transcriber is very skilled at dealing with even poor quality recordings. Please let me know, and if you and Dr Hey are agreeable to trying to include Professor Liggins' voice, we will need to have a copy (or preferably the master) of the tape here.

I'll finish the D'Arcy Hart piece for you in the next couple of days, before I head up to Sheffield for a few days' filial duties. Shall I post the video-tapes back to you?

best wishes,
tilli

Dr Tilli Tansey
Historian of Modern Medical Sciences/Convenor of the History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine,
UCL, 24 Eversholt St, LONDON NW1 1AD
tel 020 7679 8124 (sec 8106); fax 020 7679 8193

http://www.ucl.ac.uk/histmed

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 17 April 2004 18:24
To: Edmund Hey (E-mail)
Cc: Tilli Tansey (E-mail); Daphne Christie (E-mail)
Subject: Mont Liggins JY Simpson Lecture

Dear Ed

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I'll post the tape to you next week. You can pass it on to Tilli Tansey and Daphne Christie at the Witness Seminar, so that it can be archived with other material that they seem likely to assemble in the course of organising the seminar.

Best wishes, Iain

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Dr Daphne Christie

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 19 April 2004 04:23
To: g.liggins@auckland.ac.nz
Cc: Tilli Tansey (E-mail); Daphne Christie (E-mail); Edmund Hey (E-mail)
Subject: RE: Liggins audiotape & D'Arcy Hart videotape

Thanks, Mont. Much appreciated. Aye, Iain

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-----Original Message-----
From: Graham Liggins [mailto:g.liggins@auckland.ac.nz]
Sent: 18 April 2004 23:48
To: 'Iain Chalmers'
Subject: RE: Liggins audiotape & D'Arcy Hart videotape

Dear Iain,
I don't think the Simpson lecture was published.I will expect my colleagues to act on the video you want.I will send by mail the abstract of a paper about to be submitted which may possibly interest you.
Regards, Mont

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: Monday, 19 April 2004 7:27 AM
To: ucgatlt@ucl.ac.uk
Cc: Edmund Hey (E-mail); Daphne Christie (E-mail); Iain Milne (E-mail); Cindy Farquhar (E-mail); Graham Liggins (E-mail); j.harding@auckland.ac.nz
Subject: Liggins audiotape & D'Arcy Hart videotape

Dear Tilli

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-----Original Message-----
From: Dr Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 18 April 2004 18:08
To: Iain Chalmers; Edmund Hey (E-mail)
Cc: Daphne Christie (E-mail)
Subject: RE: Mont Liggins JY Simpson Lecture
Importance: High

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I'll finish the D'Arcy Hart piece for you in the next couple of days, before I head up to Sheffield for a few days' filial duties. Shall I post the video-tapes back to you?

best wishes,
tilli

Dr Tilli Tansey
Historian of Modern Medical Sciences/Convenor of the History of Twentieth Century Medicine Group Wellcome Trust Centre for the History of Medicine, UCL, 24 Eversholt St, LONDON NW1 1AD tel 020 7679 8124 (sec 8106); fax 020 7679 8193 http://www.ucl.ac.uk/histmed

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 17 April 2004 18:24
To: Edmund Hey (E-mail)
Cc: Tilli Tansey (E-mail); Daphne Christie (E-mail)
Subject: Mont Liggins JY Simpson Lecture

Dear Ed

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Now I know the reason I kept a copy of the tape!! Vanity, vanity; all is vanity!!

I'll post the tape to you next week. You can pass it on to Tilli Tansey and Daphne Christie at the Witness Seminar, so that it can be archived with other material that they seem likely to assemble in the course of organising the seminar.

Best wishes, Iain

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Wendy Kutner

From: Dr Tilli Tansey [ucgatlt@ucl.ac.uk]
Sent: 20 April 2004 12:32
To: w.kutner
Subject: RE: Lancet rejection of Liggins and Howie (not Nature)

the revised version, and correspondence with Iain, post 8th April, went to Daphne. please check with her

Dr Tilli Tansey
Historian of Modern Medical Sciences/Convenor of the History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine,
UCL, 24 Eversholt St, LONDON NW1 1AD
tel 020 7679 8124 (sec 8106); fax 020 7679 8193
http://www.ucl.ac.uk/histmed

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 20 April 2004 12:25
To: ucgatlt
Subject: FW: Lancet rejection of Liggins and Howie (not Nature)

I don't have the attachments. Please can you send me the version we are using of the flyer. Thanks, Wendy

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

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

-----Original Message-----
From: Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 07 April 2004 11:05
To: wendy kutner
Subject: FW: Lancet rejection of Liggins and Howie (not Nature)

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 07 April 2004 09:05
To: 'ucgatlt@ucl.ac.uk'; Iain Chalmers
Subject: RE: Lancet rejection of Liggins and Howie (not Nature)

To follow up, Tilli: Mont wrote in a letter to me dated 16 March 2004: "My memory played me tricks. It was the Dawes/Liggins paper reporting fetal breathing that was turned down by Nature. You are correct in citing Lancet." Aye, Iain

-----Original Message-----
From: Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]

Sent: 06 April 2004 19:01
To: Iain Chalmers
Subject:

dear Iain,

Not the repressive hand of dogmatic censorship - simply an acknowledgement that mere words are inadequate to herald your own presentation at the meeting.
But then, of course, you may wish to re-insert it - if you make enough space elsewhere!!
best wishes,
tilli

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 06 April 2004 18:53
To: ucgatlt
Subject: RE:

Thanks, Tilli. Almost all your edits are improvements! As the Wellcome Trust has steadfastly refused to provide moral or any other form of support to the Cochrane Collaboration I'm not surprised that my insertion of more details about the basic science has survived in the redraft while reference to the Cochrane Collaboration has been deleted completely! The divisive effect of reductionist snobbery rears its ugly head yet again!

I have a feeling that in one of his communications with me, Mont remembered that Nature had rejected his sheep paper, and that it was indeed the Lancet that had rejected the report of the RCT. I've checked my emails from him (I'm at home now); but I'll have a look at his letters when I go in tomorrow and let you know if that needs changing.

Best wishes, Iain

-----Original Message-----
From: Dr Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 06 April 2004 13:45
To: Iain Chalmers
Subject:

Dear Iain,

Many thanks for your time yesterday - it was very useful for Richard to meet both you and Irvine .

I think we got quite a bit of useful business done. I'll get back to you after my next lot of students, about the D'Arcy Hart meeting. I've had a first go at editing the overlong publicity flyer for the Corticosteroids meeting. I attach two copies - one with all the editing marks retaines, and one without. I have cut fairly drastically - it must fit on one page as shown, and too much text usually deters rather than attracts the eye. I know I will have cut some things, particularly the logo, which you will not like. Perhaps you would like to have a look at it now?
The Wellcome Trust have found the original Liggins file for me. I am going to e-mail Sir Graham (I can hardly call him Mont) and ask for his permission to view his application and reports, which might smooth the way through concerns about the Data Protection Act. I may not be able to see referee reports however (although in those daysm, there may not have been any - everything was much more informal).

Did you see the obituary in today's Guardian for Reggie Saxton?

best wishes, tilli

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 22 April 2004 08:39
To: Iain Chalmers
Cc: Wendy
Subject: RE: Howie address

thanks, daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 22 April 2004 06:53
To: Daphne Christie (E-mail)
Cc: Edmund Hey (E-mail)
Subject: FW: Howie address

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-----Original Message-----
From: Graham Liggins [mailto:g.liggins@auckland.ac.nz]
Sent: 22 April 2004 00:29
To: ichalmers@jameslindlibrary.org
Subject: Howie address

Dear Iain..
How nice to talk to you. Ross has moved house recently. His new address is 2 Mtata St.
Blockhouse Bay, Auckland
Regards, Mont

--
Virus scanned by edNET.

Wendy Kutner

To: Edmund Hey; Chalmers, Sir Iain
Cc: Daphne
Subject: Witness Seminar: Prenatal corticosteroids - 15 June 2004



CORTInon-reply,dates,adds.doc

Dear Sir Iain and Dr Hey, Further to Sir Iain's e-mail to Daphne, I attach a list of those from whom we are awaiting replies and a list of suggestions for flyers to be sent (hopefully today). Professor Howie is unable to attend and Mr John Williams has accepted. Please let me know if either of you have any comments or suggestions. Yours sincerely, 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

Witness Seminar: Prenatal corticosteroids – 15th June 2004

27/4/04

Attending

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

Apologies

Professor Sir Robert Boyd
Dr Pamela Davies
Professor Sir Liam Donaldson
Professor Peter Dunn
Professor Aidan Halligan
Professor Mark Hanson
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

Awaiting replies

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

Professor Geoffrey Chamberlain FRCS FRCOG Sycamores, Llanmadoc, Gower, SwanseaWest Glamorgan SA3 1DB	Dr Stuart Dalziel, Research Fellow, Clinical Trials Research Unit, University of Auckland, Private Bag 92019, Auckland, NEW ZEALAND (f) 00 649 373 7481

Dr Jonathan Grant Research Leader and Associate Programme Director RAND Europe Grafton House 64 Maids Causeway Cambridge CB5 8DD	Dr Selina Gray FFPHM FRCP, Research & Development Directorate, Westward House, Lime Kiln Close, Stoke Gifford, BRISTOL BS34 8SR
Professor Jane Harding FRACP FRSNZ, Dept of Neonatology, University of Auckland, Private Bag 91029, Auckland, NEW ZEALAND (f) 00 649 3737497 (e) j.harding@auckland.ac.nz	Dr John Hayward, Brent & Harrow Health Authority, Harovian Business Village, Bessborough Road, Harrow, Middx HA1 3EX
Dr Nick Hicks, Upper Dolcoppice Farm, Whitwell, Ventnor P038 20B	Dr Alison Hill, Buckinghamshire Health Authority, Vernley House, Gatehouse Road, Aylesbury HP19 8ET
Dr Sandy Oliver, Reader in Public Policy, Institute of Education, University of London 20 Bedford Way London WC1H 0AL	Mr Derek Tacchi TD FRCOG, 2 Oakfield Road, Gosforth, Newcastle upon Tyne NE3 4HS
Dr Roger Verrier Jones, FRCP Ed., FRCP, Hon. FRCPCH, Greenfields, Newport Road, St Mellons, Cardiff CB3 5TW	Professor Jonathan Wigglesworth FRCPath FRCPCH, Wason House, Upper High Street, Castle Cary BA7 7AT

Other suggestions (to be sent flyers today)

Professor Richard Beard, 64 Elgin Crescent, London W11 2JJ (Obstetrician) **suggested by (sb)** Paintin, Boyd	Dr Clive Dash FFPM, 8 Bluebird Way, Bricket Wood, St Albans AL2 3UH (office) Bio Products Lab, Dagger Lane, Elstree, Herts WD63 BX (Worked at Glaxo was Med Dir Glaxo Gp. Rsch.) **sb** Gamsu
Mr Paul Donnai FRCOG, Dept of Obstetrics & Gynaecology, St Mary's Hospital, MANCHESTER M13 0JH (Consultant Obstetrician) **sb** Gamsu	Professor Denys Fairweather, 37 Lyndhurst Avenue, Mill Hill, LONDON NW7 2AD

	sb Walters
Dr Alison Hislop, Developmental Vascular Biology & Pharmacology Unit, Great Ormond Street Hospital NHS Trust, Great Ormond Street, LONDON WC1N 3JH **sb** Walters	Sir David Hull (Dept of Child Health, University of Nottingham) **sb** Sir Robert Boyd
Mrs Brenda Mullinger, Larches, Green Road, Shipbourne, Tonbridge, Kent TN11 9PL **sb** Gamsu	Professor Colin Normand FRCP 23 St Thomas Street WINCHESTER Hampshire SO23 9JH **sb** Sir Robert Boyd
Professor Richard Olver, Maternal & Child Health Sciences, Ninewells Hospital & Medical School, University of Dundee, Dundee DD1 9SY **sb** Boyd, Walters	Professor Rodney Rivers, 53 Loftus Rd, London, W12 7EH (Paediatrician) **sb** Paintin
Professor Charles Rodeck, Department of Obstetrics & Gynaecology, University College London Medical School, 86-96 Chenies Mews, LONDON WC1E 6HX **sb** Walters	Professor Phillip Steer, 48 Langley Ave, Surbiton, Surrey, KT6 4QR **sb** Paintin
Professor Andrew Whitelaw FRCP FRCPCH, Neonatal Intensive Care Unit, Southmead Hospital, Southmead Road, Westbury-on-Trym, BRISTOL BS10 5NB **sb** Gamsu	Professor Charles Whitfield FRCP (Glas) FRCOG, 7 Grange Road, Bearsden, Glasgow G61 3PL **sb** Gamsu

Wendy Kutner

To: Edmund Hey; Chalmers, Sir Iain
Cc: Daphne
Subject: Witness Seminar: 15th June 2004 - Prenatal corticosteroids



CORTInon-reply,da
tes,adds.doc

Dear Sir Iain and Dr Hey, Further to my e-mail and attached list which I sent you both this morning, I attach another list which I have updated to include those attending and apologies, which you requested. Please note that Mrs Brenda Mullinger, a suggestion by Professor Gamsu, was not on the previous list I sent you. I hope to send flyers later today or tomorrow. Wendy

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

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w.kutner@ucl.ac.uk
www.ucl.ac.uk/histmed

Wendy Kutner

To: Edmund Hey
Cc: Tilli; Daphne; Chalmers, Sir Iain
Subject: Witness Seminar: Prenatal corticosteriods - 15 June 2004

We have today sent faxed invitation letters to Professor Jane Harding and Dr Stuart Dalziel.

I attach the final edited meeting flyer for your information. We hope to circulate it to everyone on the attached list and relevant university departments tomorrow, so please let us know if there are any further changes you wish to incorporate. Please note that we have received a reply from Dr Peter Stutchfield informing us that he will be away on leave at the time of the meeting.

Wendy

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

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

Wendy Kutner

To: Chalmers, Sir Iain
Cc: Daphne
Subject: Prenatal Corticosteriods Wit Sem



CORTInon-reply,dates,adds.doc

Dear Sir Iain, As requested, I attach an updated attendance list and list of those who have not yet responded, updated from the previous list I sent you on 27 April. Professor Geoffrey Chamberlain is unable to attend, as is Clive Dash. Professor Richard Beard will be attending. Daphne is in correspondence with Jane Harding and is hoping that she will be attending. Please note that I will be away on leave after today, returning to work on Wednesday 2nd June and that Daphne will be at work during this time. Wendy

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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for the History of Medicine at UCL
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Sir Iain Chalmers
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James Lind Library
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Fax: +44 (0) 20 7679 8193

26 April 2004

Dear Sir Iain

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

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

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

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

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

Yours sincerely

Wendy Kutner

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

enc.

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

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 05 May 2004 10:48
To: Iain Chalmers
Cc: Wendy; Edmund Hey
Subject: prenatal corticosteroids witness seminar 15 june 2004



CORTI280404NAME D-PROG.doc

Dear Iain

Please find attached a draft programme with the names of key witnesses, as you suggested in an earlier e-mail. Are there any changes/additions you would like made? We haven't had a reply from either Professor Jane Harding/Dr Stuart Dalziel, who might speak on Mont's behalf and also update everyone as to the latest spin-offs and follow-up findings. Is there still the possibility of obtaining a short extract of Mont speaking in person at the Witness Seminar?

We will send 'start-the-ball rolling' letters to key witnesses and circulate the draft programme, once we have received the go ahead from you and Edmund.

With best wishes,

Daphne Christie

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

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

Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 05 May 2004 11:26
To: 'd.christie@ucl.ac.uk'
Cc: Wendy; Edmund Hey
Subject: RE: prenatal corticosteroids witness seminar 15 june 2004

Thanks, Daphne. I feel I should probably defer to Ed at this stage, but I think we should assume that Jane Harding will be with us, and that, if so, she should kick off the proceedings on behalf of Liggins and Howie, mentioning the 30-year follow up of their trial which she and others are conducting. Mel Avery would then follow her.

I think that the best way of obtaining an audio recording would be to let Jane Harding know what you would like, and ask her to record a message from Mont Liggins and Ross Howie specially for the seminar. The tape of Mont Liggins' RCOG Silver Jubilee speech which I sent to you really doesn't do justice to his steroid research. Please would you try to reach Jane by phone to discuss these things with her directly.

Best wishes, Iain

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 05 May 2004 09:48
To: Iain Chalmers
Cc: Wendy; Edmund Hey
Subject: prenatal corticosteroids witness seminar 15 june 2004

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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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London NW1 1AD

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Mobile 07810 541812
E-mail d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 05 May 2004 11:50
To: Iain Chalmers
Cc: Wendy; Edmund Hey
Subject: RE: prenatal corticosteroids witness seminar 15 june 2004

Dear Iain
Thanks. I'll wait to hear from Ed and also contact Jane Harding as you suggest.
I'll keep you informed.
Best wishes, Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 05 May 2004 11:26
To: 'd.christie@ucl.ac.uk'
Cc: Wendy; Edmund Hey
Subject: RE: prenatal corticosteroids witness seminar 15 june 2004

Thanks, Daphne. I feel I should probably defer to Ed at this stage, but I think we should assume that Jane Harding will be with us, and that, if so, she should kick off the proceedings on behalf of Liggins and Howie, mentioning the 30-year follow up of their trial which she and others are conducting. Mel Avery would then follow her.

I think that the best way of obtaining an audio recording would be to let Jane Harding know what you would like, and ask her to record a message from Mont Liggins and Ross Howie specially for the seminar. The tape of Mont Liggins' RCOG Silver Jubilee speech which I sent to you really doesn't do justice to his steroid research. Please would you try to reach Jane by phone to discuss these things with her directly.

Best wishes, Iain

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 05 May 2004 09:48
To: Iain Chalmers
Cc: Wendy; Edmund Hey
Subject: prenatal corticosteroids witness seminar 15 june 2004

Dear Iain
Please find attached a draft programme with the names of key witnesses, as you suggested in an earlier e-mail. Are there any changes/additions you would like made? We haven't had a reply from either Professor Jane Harding/Dr Stuart Dalziel, who might speak on Mont's behalf and also update everyone as to the latest spin-offs and follow-up findings. Is there still the possibility of obtaining a short extract of Mont speaking in person at the Witness Seminar?
We will send 'start-the-ball rolling' letters to key witnesses and circulate the draft programme, once we have received the go ahead from you and Edmund.
With best wishes,
Daphne Christie

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Email: ichalmers@jameslindlibrary.org

11/5/04

Dear Tilli + Daphne
I had the impression from something one of you said to me that you might not be aware of just how much of a physiologist Ed Hay was in the 1960s + early 1970s. The attached should be of interest.
Iain

51 Alwinton Terrace,
Newcastle upon Tyne,
NE3 1UD

22nd February 2004

Dear Iain,

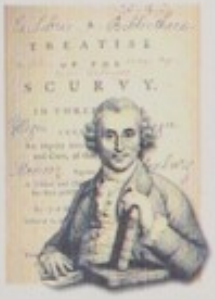
Just a note to say I have now had a note from the Wellcome people saying the meeting is scheduled for June 15th. You have moved fast. That date eats into a short break I was trying to take in France but it is a sufficiently important venture that I would certainly want to be there and, if the price of attendance is to earn my keep as Chairman, so be it.

I will need to do quite a bit of homework so I know about all the people who are attending and what it is that I am being asked to try and coax out of each of them. I would not recognise most of these people in the flesh even if I know all about their work, so that is another piece of preparatory work I am going to have to try and do. Do you have any mug shots I can sharpen my wits on. Could you, alternatively, for this proposed web site, get some decent mug shots of key people ahead of the meeting ?

I have just chanced on something I was asked to write for a book by RA McCance back in 1973 just as news of the 1972 paper was breaking. (I was an MRC Clinical Research Fellow working with Frank Hytten in Newcastle at the time.) The book had the somewhat gruesome title "The mammalian Fetus in vitro" and it was my task to provide a final chapter showing how such work might eventually inform and improve the care of the pre-term baby. It is interesting to look back and see what I said all those years ago !

removed + in file 20/3/07 LL

PS. I see the Lister speaks about their Witness Seminar being mainly about Bristol contributions. I am glad I hope they don't share that when they write to Mark Taggart!



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Fax: +44 (0) 1865 516311
Email: jli@jameslindlibrary.org

15 May 2004

Dr Daphne Christie
Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
24 Eversholt Street
London
NW1 1AD

Dear Daphne

Witness Seminar on Prenatal Corticosteroids, Tuesday 15 June 2004

Thank you for your letters of 26 April and 12 May. Plans for the seminar do indeed seem to be proceeding well. I am particularly glad that Jane Harding will be able to represent the Auckland team.

In response to you invitation to do so, I am sending you a supply of single page handouts in support of my two-pennyworth.

And thank you and Tilli for your invitation for supper after the event. I am pleased to accept.

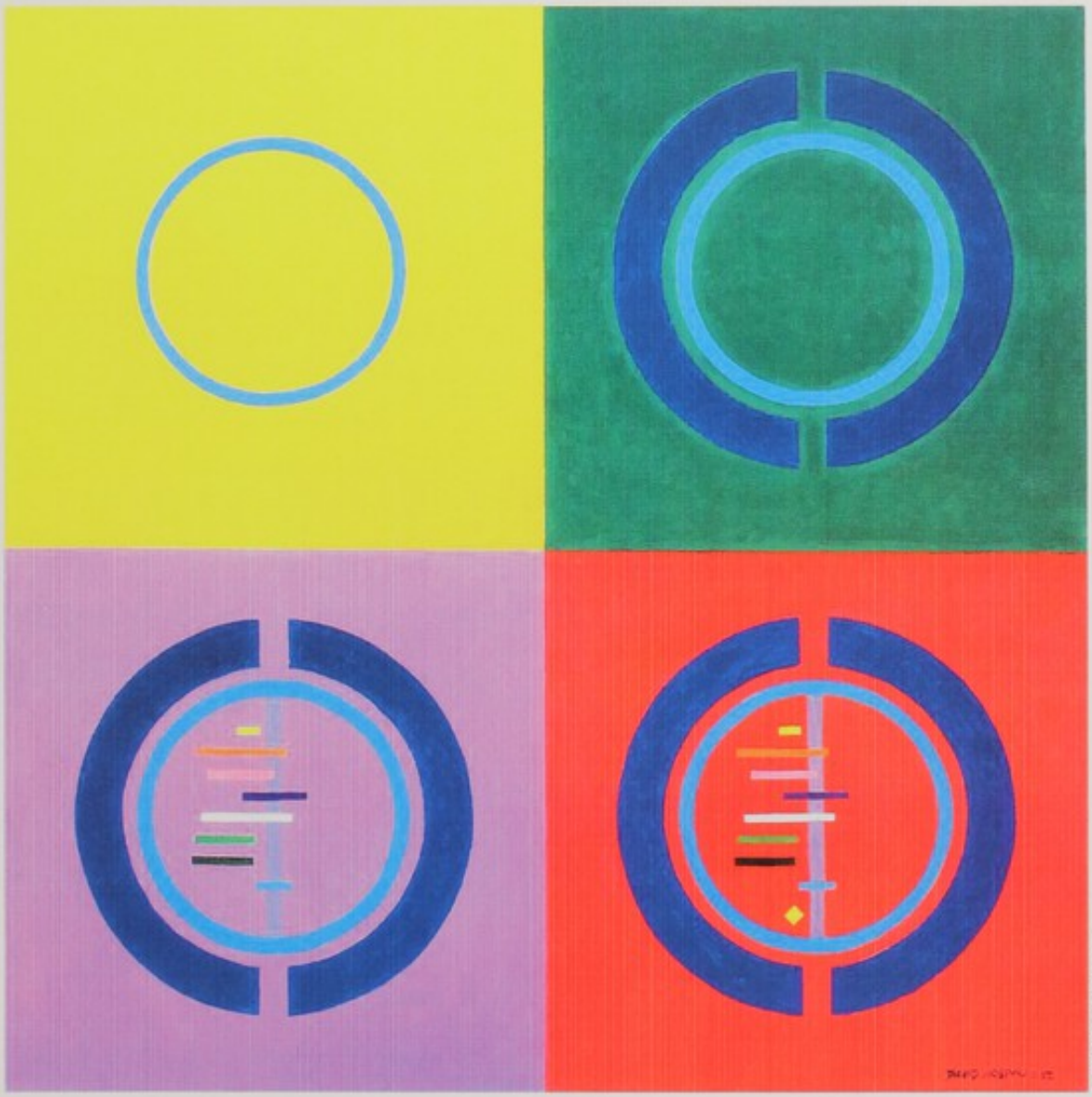
With best wishes

Yours sincerely

Iain

Sir Iain Chalmers

Encl.



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.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 20 May 2004 10:19
To: Iain Chalmers
Cc: Wendy
Subject: RE: witness meeting 15 June

Dear Iain
Thank you for your e-mail and useful suggestions. Daphne

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 20 May 2004 10:08
To: 'd.christie'
Cc: Wendy; Edmund Hey (E-mail); Tilli Tansey (E-mail)
Subject: RE: witness meeting 15 June

Dear Wendy

I'm sorry that Ed is unable to be there, and very sorry that he is having to fund travel to break his holiday to chair the meeting. In view of the fact that this seminar was a suggestion from Mark Walport himself, and was organised at very short notice (thus precluding the arrangements of less expensive travel for those coming from abroad), would it not be reasonable to ask Mark whether he could provide a supplement to your budget to recognise these features of this particular seminar?

I certainly think all the name presenters on the programme should be invited to diner. Beyond them, I think it would be unwise to invite anyone else, because those not invited might reasonably ask what criteria had been used to discriminate against them and in favour of non-programmed speakers who had been favoured.

Best wishes, Iain

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 19 May 2004 10:18
To: Iain Chalmers
Cc: Wendy
Subject: witness meeting 15 June

Dear Iain
Thank you for your letter dated 15 May, and supply of handouts for the meeting.
We are pleased that you able to accept our invitation to supper. You may like to know that Dr Hey, Professor Harding, Dr Avery and Dr Crowley have also been invited to supper. Unfortunately Ed is unable to attend. Please can you indicate who should be invited to the supper - key participants include Mugford, Lilford, Hanney and Brocklehurst? Anyone else?
With best wishes
Daphne

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 26 May 2004 12:27
To: Wendy
Subject: FW: Draft paper on predicting and measuring benefits from antenat al steroid research

please add this correspondence to the files, daphne

-----Original Message-----
From: Iain Chalmers [mailto: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

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-----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
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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
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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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James Lind Initiative
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Professor Patricia Crowley
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Coombe Women's Hospital
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Eire
Tel. 00353 1 453 7561
Fax. 00353 1 454 9866
patc@indigo.ie

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-----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

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-----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
Research Fellow
Health Economics Research Group (HERG)
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Middlesex, UB8 3PH, UK

Email: stephen.hanney@brunel.ac.uk
Tel: +44 (0)1895 274000 ext 3709
Fax: +44 (0)1895 203330

-----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

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-----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 are free of software viruses, and you are
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>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
>

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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 02 June 2004 09:43
To: Wendy
Subject: FW: Production of edited transcript of Witness Seminar on prenatal st eroids

for the files

-----Original Message-----
From: Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 01 June 2004 17:45
To: Iain Chalmers; Tilli Tansey (E-mail); Daphne Christie (E-mail)
Cc: Edmund Hey (E-mail)
Subject: RE: Production of edited transcript of Witness Seminar on prenatal st eroids

dear Iain,

That's absolutely correct. The level of involvement is up to the individual (s) concerned. We don't permit 'guest editors' (to quote a favourite bete noire of Stephen Lock's), but are very happy if people seriously become interested in the nitty gritty slog of doing this work. So far, there are not many people who have accepted that challenge.
It will be much easier to examine and discuss these issues after the meeting, and indeed after we have the first raw draft of the transcript. Please be re-assured that we not refuse or exclude genuine help!!
yours,
tilli
PS - I have now been through all the extant relevant Wellcome Trust records, relating to the support of Liggins and his team. sadly some material is missing.

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 01 June 2004 17:05
To: Tilli Tansey (E-mail); Daphne Christie (E-mail)
Cc: Edmund Hey (E-mail)
Subject: Production of edited transcript of Witness Seminar on prenatal st eroids

Dear Tilli and Daphne

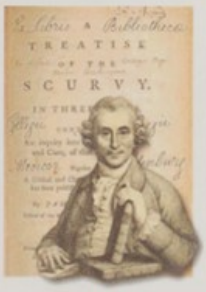
Some very interesting things are coming out of the woodwork as preparations are made for the seminar on 15 June, and I am very impressed with just how seriously Ed Hey is taking his preparatory work for chairing it. It seems to me that the published proceedings will be of great relevance to issues in the 21st century. Needless to say, therefore, I envisage the edited proceedings being of particular importance, and look forward to purchasing a supply of these and commending them to others.

I am fairly certain from my involvement in a previous witness seminar that you will be sending individuals drafts of their transcribed comments to check, and I am assuming that you will involve Ed Hey in the overall editing process. Please would you confirm that my understanding is correct.

With best wishes, Iain

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Email: ichalmers@jameslindlibrary.org

7/6/04

Dear Daphne
Before Ed Hey went off to France, he asked me to make these copies and to request that you arrange for them to be put on everyone's chairs before the seminar begins

'Promoting better controlled trials for better health care'

Best wishes, Iain.

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

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

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

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

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

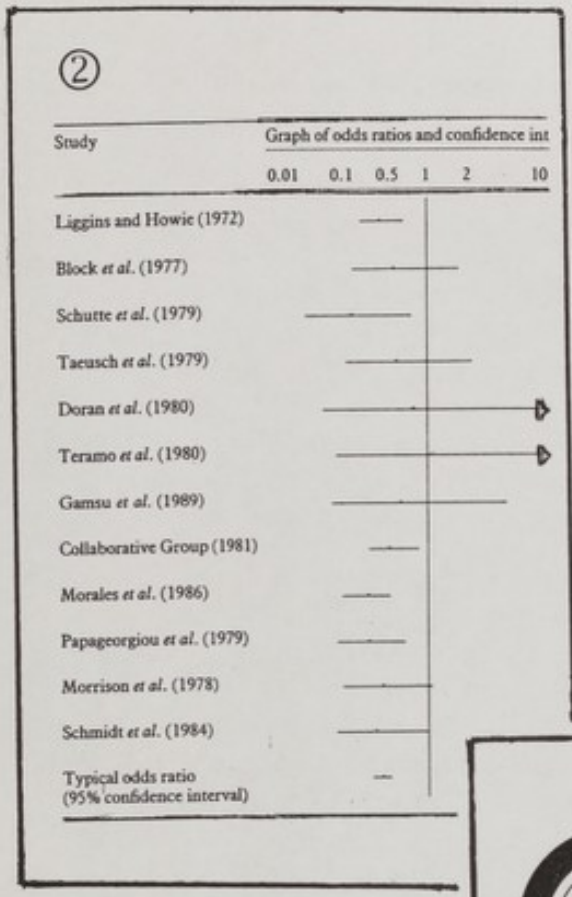
[4] A cumulative meta-analysis of the same 15 trials as in [3] incorporating each trial in turn by date of publication, taken from Jack Sinclair's commentary on the NIH Conference presentation, as published in July 1995 in the *American Journal of Obstetrics and Gynecology* 1995;173;335-44..

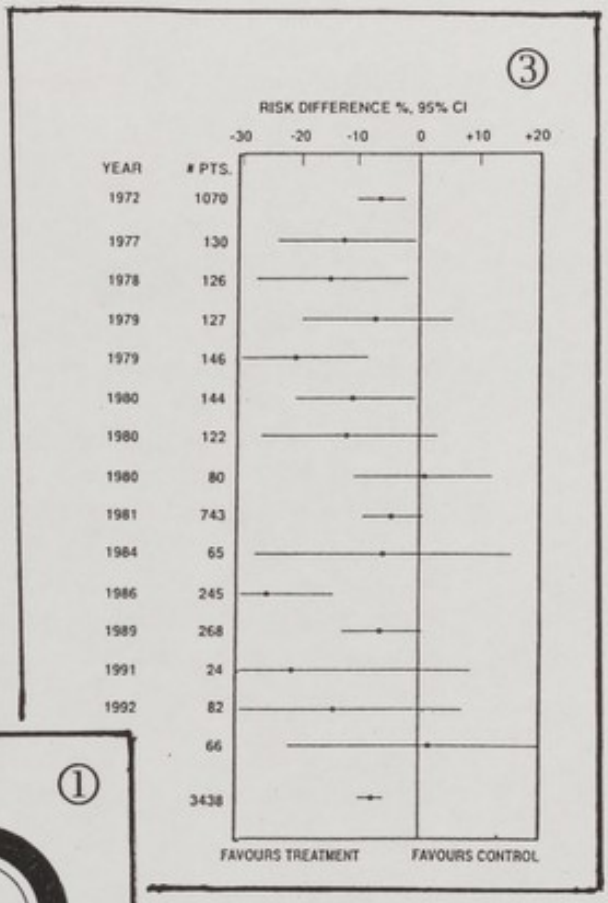
[5] The current version of Patricia Crowley's meta-analysis with data from 18 trials, as it appears in the latest version of the *Cochrane Library*, 2004 (CD000065).

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

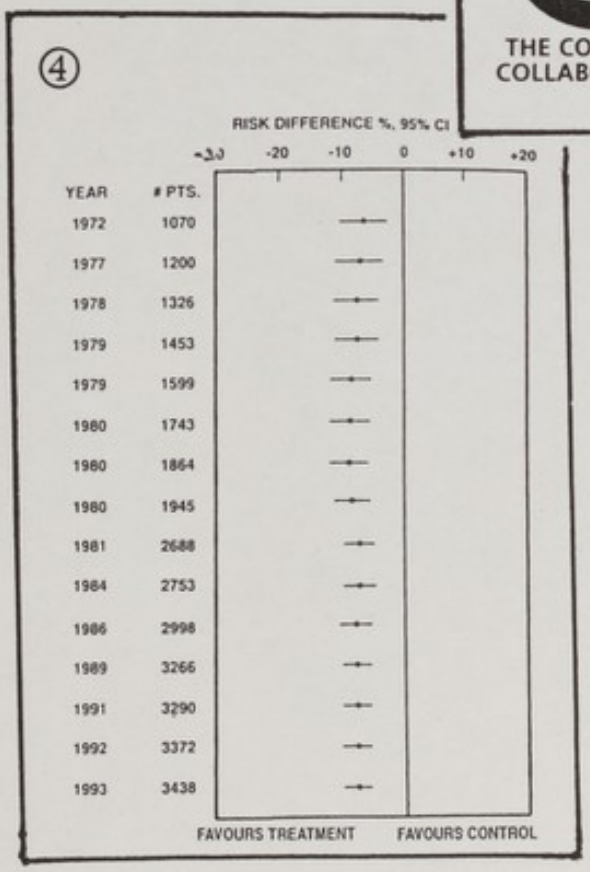
Table 45.3 Effect of corticosteroids prior to preterm delivery on respiratory distress following optimal treatment

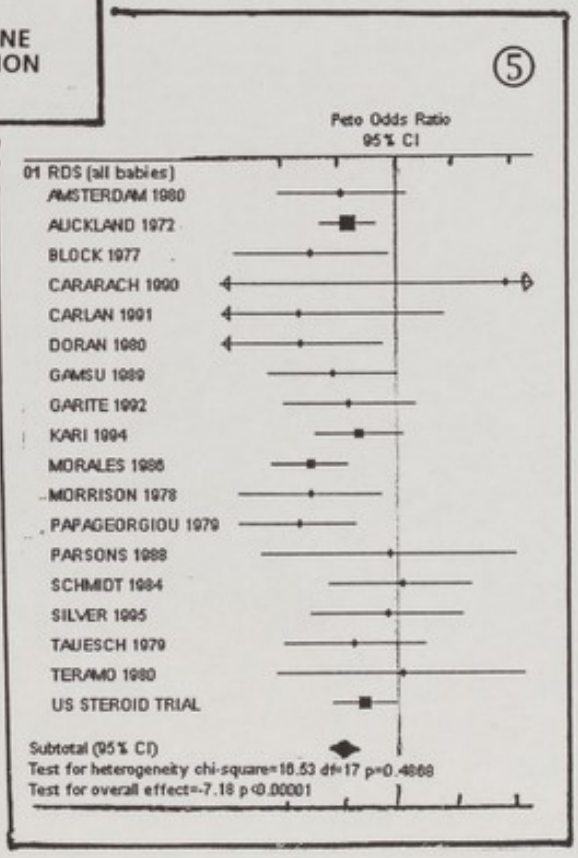
Study	EXPT		CTRL		Odds ratio	Graph of odds ratios and confidence intervals
	n	(%)	*n*	(%)	(95% CI)	0.01 0.1 0.5 1 2 10 100
Liggins and Howie (1972)	16/182	(8.79)	37/156	(23.72)	0.32 (0.18–0.58)	
Block *et al.* (1977)	4/36	(11.11)	6/29	(20.69)	0.48 (0.13–1.86)	
Schutte *et al.* (1979)	0/22	(0.00)	6/25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


②
Study
Graph of odds ratios and confidence int
0.01 0.1 0.5 1 2 10
Liggins and Howie (1972)
Block et al. (1977)
Schutte et al. (1979)
Taeusch et al. (1979)
Doran et al. (1980)
Teramo et al. (1980)
Gamsu et al. (1989)
Collaborative Group (1981)
Morales et al. (1986)
Papageorgiou et al. (1979)
Morrison et al. (1978)
Schmidt et al. (1984)
Typical odds ratio
(95% confidence interval)


③
RISK DIFFERENCE %, 95% CI
-30 -20 -10 0 +10 +20
YEAR # PTS.
1972 1070
1977 130
1978 126
1979 127
1979 146
1980 144
1980 122
1980 80
1981 743
1984 65
1986 245
1989 268
1991 24
1992 82
66
3438
FAVOURS TREATMENT
FAVOURS CONTROL


①
THE COCHRANE
COLLABORATION


④
RISK DIFFERENCE %, 95% CI
-30 -20 -10 0 +10 +20
YEAR # PTS.
1972 1070
1977 1200
1978 1326
1979 1453
1979 1599
1980 1743
1980 1864
1980 1945
1981 2688
1984 2753
1986 2998
1989 3266
1991 3290
1992 3372
1993 3438
FAVOURS TREATMENT
FAVOURS CONTROL


⑤
Peto Odds Ratio
95% CI
01 RDS (all babies)
AMSTERDAM 1980
AUCKLAND 1972
BLOCK 1977
CARARACH 1990
CARLAN 1991
DORAN 1980
GAMSU 1989
GARITE 1992
KARI 1994
MORALES 1986
MORRISON 1978
PAPAGEORGIOU 1979
PARSONS 1988
SCHMIDT 1984
SILVER 1995
TAUESCH 1979
TERAMO 1980
US STEROID TRIAL
Subtotal (95% CI)
Test for heterogeneity chi-square=16.53 df=17 p=0.4868
Test for overall effect=-7.18 p<0.00001

Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 09 June 2004 09:23
To: 'w.kutner'
Cc: Daphne; Edmund Hey; Nicholas Hicks (E-mail); Nicholas Hicks (E-mail); Alison Hill (E-mail)
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Thanks, Wendy.

I have just spoken to Roger Verrier Jones. He now understands why I suggested he should be invited (I have put documentation about this in the post to him and to Daphne), so you should soon receive a formal acceptance of your invitation from him.

I spoke to Nick Hicks on Monday. He is still trying to escape another commitment on that day, but hopes to be able to attend.

Alison Hill is away until next week, so I have not been able to chase her up, but I'll copy this message to her.

Ed Hey and I have both written to Pamela Davies urging her to attend, in spite of the fact that she has declined. So you may hear from her again if we have been successful.

I think Colin Normand's name should probably be deleted from the 'Other suggestions' list, because he is also listed as 'Attending'.

Best wishes, Iain

-----Original Message-----
From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 08 June 2004 10:48
To: Edmund Hey; Chalmers, Sir Iain
Cc: Daphne
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Please find attached an attendance list for the above meeting as of today.
With best wishes, 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

--
Virus scanned by edNET.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 09 June 2004 09:55
To: ucgawhk@ucl.ac.uk
Subject: FW: Witness Seminar: prenatal corticosteroids
Follow Up Flag: Follow up
Flag Status: Flagged

-----Original Message-----
From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 09 June 2004 08:49
To: Daphne Christie (E-mail)
Cc: William Silverman (E-mail); Edmund Hey (E-mail)
Subject: FW: Witness Seminar: prenatal corticosteroids

Dear Daphne

Thanks for sending me a copy of Ross Howie's very interesting account. I don't know the answer to his query about the origins of the term 'perinatal', but I am copying the paper to Bill Silverman, who may well do, and who anyway will be interested to read Ross's account. Indeed, please would you note Bill postal address (below) and arrange for him to be sent a copy of the report of the Witness Seminar in due course.

Best wishes, Iain

Dr William Silverman
501 Via Casitas/Apt 421
Greenbrae CA 94904-1947
USA
Tel. 001 415 464 1595
Email: fumer@aol.com

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 08 June 2004 08:18
To: Iain Chalmers; Edmund Hey
Subject: FW: Witness Seminar: prenatal corticosteroids

Please find enclosed piece from Howie for the Seminar. I'll make copies for all the participants. Can you help with his query? With best wishes and looking forward to Tuesday's meeting.
Daphne

-----Original Message-----
From: Howie [mailto:h.r.howie@xtra.co.nz]
Sent: 07 June 2004 07:44
To: d.christie
Subject: Witness Seminar: prenatal corticosteroids

Dear Dr Christie,

Sorry to have been so very long in getting in touch again but here at last is the piece I promised you. It is still too long for circulating - 6 pages - but it has been cut down from 13.

Writing it reminded me that there is a piece of history that I have long intended to ask experts, and your people may be in as good a position as anyone to answer it. It is my endnote 2: to

quote it -

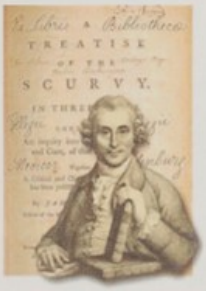
"On the history of the word 'perinatal', I wonder whether anyone in the Wellcome Trust Centre can enlighten us. The coining of the word was a landmark that surely deserves recognition. A quick check of the US NLM website PubMed for occurrences of the words 'perinatal' and 'perinatale' in titles of journal articles showed none earlier than 1952, when there were 3. I tentatively concluded that the first use of the word may have been in Europe in a language not English, French or German, but possibly Dutch, Scandinavian or Eastern European. At this point I found myself out of my depth and in need of more expert help."

Can anyone oblige?

Again, my best wishes for the seminar and apologies for being unable to attend in person. I look forward to seeing the transcript later.

Sincerely,
Ross Howie

ncd 11/6/04



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9/6/04.

Daphne
Documents relating to Roger Vernier-Jones contribution next Tuesday, for your collection.
Bye, Iain.

'Promoting better controlled trials for better health care'

Chalmers. Table 4, pg. 35
Verrier Jones: RDS+
dexamethasone

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Cyncoed Road East
Cardiff
CF1 9JZ
Tel: 0222 44141

SOUTH GLAMORGAN HEALTH AUTHORITY (TEACHING)
Awdurdod Iechyd De Morgannwg (Dysgu)

RVJ/GJ

24th November 1980.

Dr. Iain Chalmers,
National Perinatal Epidemiology Unit,
The Research Institute,
Churchill Hospital,
OXFORD.

Dear Iain,

We have just looked at two groups of babies, the mothers of one group had Dexamethasone and the others did not and, as you can see, the incidence of R.D.S. and the mortality rate is markedly different.

I would be most grateful if you could go over these statistics and tell me frankly (which I know you will) whether this is worth publishing. There seems to be a fair amount in the American literature, but not much in the British paediatric literature, i.e. B.M.J. or Archives.

Yours sincerely,

Roger Verrier Jones, MA, FRCP, DCH.,
Consultant Paediatrician.

St. David's Hospital
Cowbridge Road East
Cardiff
CF1 9TZ
Tel: 0222 44141

SOUTH GLAMORGAN HEALTH AUTHORITY (TEACHING)
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Yours sincerely,

Roger Verrier Jones, MA, FRCP, DCH.,
Consultant Paediatrician.

Period of Study - Jan. 1979 - Oct, 1980 (22 months)

Study Group. ≤ 35 wks.

Weight range - 800 g to 2100 g.

	STEROID (N=11)	CONTROL (N=36)
Sex (M:F)	8:3	22:14
Mean Gestational Age (Weeks)	32.1	32.3
Mean Birth Height (Kg)	1.630	1.590
Mean Apgar Score		
at 1 minute	5.8	5.5
5 minutes	8.2	7.9
Twin pregnancies	1	2
Mortality	0 (0%)	10 (28%) ($p < 0.001$)

clusions

Severe P.E.T

Congenital anomalies

Uncertain gestational age

Delivery within 24 hrs of steroid administration.

Mean "steroid administration to delivery interval"
= 65.3 hrs.

Range: 26 hrs to 11 days.

Criteria for diagnosis of RDS

(1) Respiratory problems developing within 4 hrs of delivery & lasting - ≥ more than 24 hrs -

(a) Grunting
(b) Tachypnoea, RR > 60/min
(c) Sternal or intercostal recession.

(2) Requiring F_1O_2 > 25% for more than 24 hrs.

(3) ± Radiographic

(4) ± Autopsy findings

Incidence Of RDS.

	STEROID (N=11)	CONTROL (N=36)	
RDS	2 (18%)	21 (59%)	
No RDS	9 (82%)	15 (41%)	($p < 0.001$)

Effect of prolonged rupture of membranes.
(P.R.O.M)

1. STEROID GROUP. (N = 11)

	P.R.O.M (N=4)	No P.R.O.M (N=7)
RDS	1 (25%)	1 (14%)
No RDS	3	6

2. CONTROL GROUP.

	(N = 10)	(N = 26)
RDS	6 (60%)	16 (62%)
No RDS	4	10

TOTAL

	(N = 14)	(N = 33)
RDS	7 (50%)	17 (51%)
No RDS	7	16

Details of deaths

Age	Wt	APGAR 1	APGAR 5	Notes	Age death
32	1·900	9	10	Em. LSCS for praevia. RDS → CPAP + IPPV. P.M → HMD (Hyaline membrane disease)	21 hrs
30	1·325	1	6	APH → Assisted breech delivery. Mild RDS. PM – (1) Intracranial haemorrhage (2) Tentorial tears (3) Lungs – firm & indurated + lobular haem	48hrs
29	1·300	7	9	Preterm labour (Previous preterm baby). RDS → IPPV ® pneumothorax. CXR – Ground glass appearance. No PM	5 hrs
33	1·500	6	8	P·R·O·M (36 hrs). RDS → IPPV. Bilateral pneumothoraces. Haem. influenzae (Blood culture). PM – HMD IVH	5hrs
28	1·050	4	9	APH. RDS → IPPV. Pneumothoraces. PM – HMD IVH	48hrs
32	1·925	9	9	APH. RDS → IPPV. Pneumothoraces. PM – HMD IVH	3 days
30	.850	7	9	P·R·O·M (11/7). No maternal infection (HVS – Neg). RDS → IPPV. PM – HMD IVH	3 days
30	.975	1	6	Neonatal asphyxia – Intubated. RDS → IPPV. No PM	12hrs
28	1·025	3	6	No RDS. DIC. PM – (1) Petechial haem – lungs & heart (2) Oedema of lungs (3) Post fossa subdural haem (4) Thrombosis (L) femoral vein.	21 hrs
33	1·750	5	8	P·R·O·M (72+ hrs). Assisted breech delivery. RDS → cPAP (→ IPPV). ?NEC at 10 hrs (Blood & meconium) Abdo XR – NAD. Sudden deterioration at 23 hrs → No response to IPPV. PM: (1) HMD (No IVH) (2) Sub pericardial haem (3) Congestion of liver, spleen, kidneys, meningeal vessels (4) ? [illegible]	26hrs

National Perinatal Epidemiology Unit

Radcliffe Infirmary
Oxford OX2 6HE

Tel: 0865 49891 Ext. 876

15th December 1980

Dr Roger Verrier Jones
Consultant Paediatrician
St David's Hospital
Cowbridge Road East
CARDIFF CF1 9TZ

(15g)

Dear Rog,

Thanks for sending me the data on Dexamethasone treatment in pre-term labour; there certainly is a marked difference in the mortality rate. I have to admit, though, that I find the data difficult to interpret.

Firstly, I am worried about the exclusions. Steroid treated babies delivered within twenty-four hours of administration were excluded. Was a similar allowance made in the case of the non-treated group - e.g. were those who delivered within 24 hours of admission (say) also excluded? You only supply detailed information about the babies who died, but certainly there would have been insufficient time to treat some of these. (I assume cases of severe PET were excluded because of the suggestion from Liggins' work that steriods may make the outcome worse in these cases). Were hospital transfers included?

Secondly, from the information which you have given me, it is difficult to assess the comparability of the two groups. I think mean gestational age and mean birth weight may be misleading particularly if no indication of the variability is given) It would be nice to see a full breakdown of thier distributions; in particular how many very low birth weight babies there were in each group. Similarly I am not happy about comparing the condition of the babies in the two groups at birth with mean apgar levels. The apgar score is not a true continuous variable. I think you need to look at the relative numbers which were asphyxiated (say scores less than 3 at one minute and/or less than 5½ at five minutes) because of the association of RDS with birth asphyxia.

Thirdly - this is an extension from the first two points - the treated PROM group all had ruptured membranes for at least 24 hours. Was this true for the untreated group?

Lastly but most important of all, on what basis was the treatment allocated anyway? Was there a definite hospital policy?

I have managed to identify ten randomised controlled trials of steroid treatment in labour as prophylaxis for RDS; only one of these was performed in the UK - at Queen Charlotte's Hospital - but I haven't been able to pin point the reference to the final report but it is referred to in Sims C A, Chamberlain G P, Boyd I G, Lewis P J - A comparison of Salbutamol and on the treatment of pre-term labour. British Journal of Obstetrics and Gynaecology 85 (10) 761-6 October 1978.

The references for the other nine are as follows:-

1. Liggins G C and Howie M B. Acontrolled trial of antepartum glucocorticoid treatment for prevention of respiratory distress syndrome in premature infants, Pediatrics 50:515, 1972.

2. Liggins G C. Prenatal glucocrticoid treatment: Prevention of respiratory distress syndrome, in Moore T D (editor): Lung maturation and the prevention of hyaline membrane disease. Report of the Seventieth Ross Conference on Pediatric Research, Columbus, Ohio, 1976, Ross Laboratories, pp 97-103.

3. Block M, King O R and Cosby W M: Antenatal glucocorticoid therapy for the prevention of respiratory distress syndrome in the premature infant. Obstetrics and Gynecology 50: 186, 1977.

4. Morrison J C, Shybrew W D, Bucovaz E T and Schneider J M. Injection of corticosteroids into mother to prevent neonatal respiratory distress syndrome. American Journal of Obstetrics and Gyecology 131:358 1978.

5. Papageorgiou A N, Desgranges M F, Masson M, Colle E, Shatz R and Geltand M M. The antenatal use of betamethasone in the prevention of respiratory distress syndrome. A controlled double blind study, Pediatrics 63: 73, 1979.

6. Taeusch H W, Frigoletto F, Kitzmiller J, Avery E M, Hehre A, Fromm B, Lawson E and Neff R K. Risk of respiratory distress syndrome after prenatal dexamethasone treatement. Pediatrics 63:64, 1979.

7. Doran T A, Swyer P, MacMurray B, Mahon W, Enhorning G, Beinstein A, Falk M, Wood M M Results of a double blind controlled study on the use of Betamethasone in the prevention of respiratory distress syndrome. American Journal of Obstetrics and Gynecology 136: No 3 313-320.

8. Ballie P, Malan A F, Saunders M C, Davey D A. Active management to pre-term labour and its effect on fetal outcome. Australian and New Zealand Journal of Obstetrics and Gynaecology 16: 94, 1976.

9. Whitt Gerald G, Buster John E, Killam Allan P, Scragg William H. A comparison of two flucocorticoid regimes for acceleration of fetal lung maturity in premature labour. American Journal of Obstetrics and Gynecology 124: No 5 479-452

The consensus seems to be that Dexamethasone is useful in preventing RDS for between 24 hours and seven days after administration when the gestational age is between 28 and 34 weeks.

In summary, unless you can convince yourself that the two groups are comparable then you probably should resist the temptation to seek publication. Having said that about these data, let me remind you that I'm still panting to see your case-control follow-up of 'jittery' babies. Have you submitted it for publication?

Love to Katey; have a happy Christmas.

Yours aye,



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16 June 2004

Dear Iain

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 myself, how grateful we are to you for your many contributions to yesterday's meeting? It was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers. We are very grateful to you for your considerable help in arranging it so successfully.

As you know, the taped proceedings of the meeting will now be sent for transcription, and we hope to have a draft manuscript to send to all our contributors in about three months time. 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. I'm sure you will agree that it will make an important contribution to the historical record.

Once again, thank you so much for your help.

With best wishes

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.

Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 18 June 2004 08:09
To: Graham Liggins (E-mail); Ross Howie (E-mail)
Cc: Jane Harding (E-mail); Daphne Christie (E-mail); Tilli Tansey (E-mail); Wendy Kutner (E-mail)
Subject: Witness seminar

Dear Mont and Ross

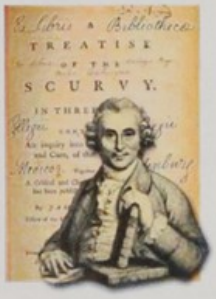
Thank you for the very important contributions you made in advance of Tuesday's Witness Seminar on Prenatal Corticosteroids. Jane did a superb job on the day, and it doesn't bear thinking about just how different it would have been without her representation of the Auckland team.

The transcript of the seminar should be available in a couple of months and sent to both of you as well as to Jane. That way, you'll have the opportunity to correct any misapprehensions and add anything that you feel would clarify this record of an important part of medical history, from which hundreds of thousands of babies and their parents continue to benefit today.

With best wishes, Iain

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13/12/04

Dear Daphne,
Thanks for your letter of 7 December. Annotated transcript returned herewith. Best wishes, Iain.

CHALMERS
UCL 20/12
ACK 20/12

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

Reid Dec 04 corrected 1-2/6/05

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

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

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

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

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

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

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

I think that we should start by asking Mel who has come all the way from Boston, although I think she's been 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 that you meeting somebody who spends some days in the lab and some days on the farm or in the animal laboratory, but you can tell us the story, because years ago, much of what we understand now about the lung came from the combination of those interests, didn't it?

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

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

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

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

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

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

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

Mont then described how he worked on this idea, that the onset of labour was controlled by the fetus not the mother, and how he spent a sabbatical period at the Vet school at the University of California at Davis, 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 ..... 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

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, 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.

Hey: Still the biggest trial.

Harding: Still the biggest trial. The original publication that everybody cites from 1972 was only the first 418, I think. 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, 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 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.

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 have made to the history of perinatal care. ~~and~~ If you haven't planned to do ~~that~~ so already, ~~during the contact with them,~~ could you think about letting them know ~~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

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 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 in an undergraduate lecture in 1974 and it obviously made an immense impact on me because a few weeks after hearing about antenatal steroids the first baby I ever delivered as an undergraduate died, a neonatal death, from respiratory distress syndrome despite weighing 7

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

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

the results. That preterm study group contained 14 papers about total tocolysis and two papers about fetal lung maturation, and that indicates what the thinking was in British obstetrics at that time. The focus was on trying to stop labour and not on trying to improve the outcome for the baby, for the premature baby, by accelerating lung maturation. And there were papers on ethanol, nifedipine, many papers on all the different beta-mimetics, and most of these tocolytic drugs had pharmaceutical backgrounds and emphasis and every meeting that one went to in those days had some kind of drug representation promoting tocolytic drugs, whereas no pharmaceutical companies were promoting antenatal steroids. In 1980 at Hammersmith Hospital Dan Corkham (?) had recently started a new journal, the *Journal of Obstetrics and Gynaecology* and he received a paper from a British obstetrician working in the USA, a review of the adverse effects of antenatal steroids and the lack of evidence to support their efficacy. He handed me this manuscript and said have a look around and see if you can find evidence to write an opposing view to this. And that led to me producing this paper, written in 1980, published in 1981, and I chose the title 'Corticosteroids in Pregnancy', but then I changed it to 'The Benefits Outweigh the Costs', because the boyfriend at the time was a economist who was interested in cost–benefit analysis, so that's where the title came from. I was either lucky or lazy, I decided not to bother with all the observational levels, and nobody had told me that the randomized control trial was the best form of evidence, but instinctively I hit on it and I found four randomized control trials of antenatal steroids and I put all the results together in two tables and there it was, the result. This paper was published in 1981, by which time I had started a 9-

month attachment at the National Perinatal Epidemiology Unit, which was one of the best nine months of my life, apart from the nine months *in utero*, I suppose. Anne Anderson and Iain Chalmers read the paper and invited me to supply a chapter on antenatal steroids for a book that they were planning on *Effective Care in ~~Labour~~ Elective Delivery*. This was a planned book which was a follow-on from Effectiveness in ~~....section in antenatal care~~ and Satisfaction in Antenatal Care. I was going to write a chapter on fetal lung maturation and antenatal corticosteroids and any other intervention. There was another drug knocking around at that time called ambroxol, and I was going to look at the evidence in favour of these agents to accelerate lung maturation. That book never actually was written, because Anne Anderson died, things moved on, and the main focus of interest at the time was the Oxford database of perinatal trials, where all the randomized control trials available in the world literature in perinatal medicine, brought together and collected in a library of perinatal trials.

I left Oxford in 1981 and returned to Dublin to train as an obstetrician and over the next three years I maintained my contact with the National Perinatal Epidemiology Unit and every so often my former colleagues there would draw my attention to a new trial that would have been uncovered by the people who were hand-searching the literature to find randomized trials, and over the next three years all of that data appeared on the Auckland studies and in 1981 the results of the US NIH collaborative study on antenatal steroids was published. Now with hindsight we could ask whether the US collaborative 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 worked,

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 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.

In 1994 the National Institute of Health consensus on antenatal steroids took place and at that contributed an updated version of the dramatic review in antenatal steroids to that three-day meeting. The rest of the three days were taken up with many observational studies, and ….. papers on antenatal steroids and following the three-day meeting a very strong recommendation was released urging obstetricians in the USA to use antenatal steroids.

In 1996 the Royal College of Obstetricians updated a Guideline they had issued in 1992, about the use of antenatal steroids, much stronger than …. in 1992, and further …….antenatal steroid use which began to cover more than 70 per cent of preterm babies. Within a year of this, a very short gap between urging people to use a single-dose of antenatal steroids, within a year or two, we had people using multiple doses of antenatal steroids without any evidence to support it, and without any guideline telling them to use repeated doses of steroid, and it was just a blink of an eye between obstetricians not using them at all, to widespread use of repeated doses of antenatal steroids, and now round the world there are randomized trials going on where people are endeavouring to address the question of the benefits and hazards of single versus repeated doses of antenatal steroids. This is, of course, a question that should have been addressed perhaps in the 1980s after the large world randomized trials, collaborative trials of antenatal steroids, that should have followed the Auckland trial, suffer in the seventies, there should have been a world collaborative trial on antenatal steroids, and following the publication, have backed the question of repeat doses, it should have been addressed in the 1980s. So we are still about 20 years behind where we should be.

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

Avery: It was frustrating.

Hey: Well I mean 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 long-term follow up. I spent hours with Ross Howie, urging him to please keep track because the Swiss were talking about inhibiting lungs seriously, 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. All animal. It was done by the group in Berne, by Voyers (?) and I think it is Bury is the fellow who is still publishing on beware, beware, and I cannot counter that, I'm glad he's looking at it, and I just think we have to be vigilant and those of us who spend more time with babies than I am, have to keep track of the babies. Hard as it is to control, because so

many interterm events take place over 30 years, but I hope we learn some more at this meeting.

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

Avery: I think we have to think in terms of 1970s versus the 1990s and over 2000, because up until the seventies the control trials were very supportive of efficacy of prenatal glucocorticoids, but that was an era when we didn't have lots of babies under 800 g. Now the story's different. We have babies of 600 g and 700 g and 800 g, who are getting glucococorticoids, and we assumed that they wouldn't have any serious toxicity. But along came Pepra Hoopie from Geneva who worked with us at Harvard and who had developed a great experience with imagining studies of the brains of these babies and there is no

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 LS ratios and amniotic fluid

before and after steroid treatment and points out that they don't change consistently, so that amniotic testing on the 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 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 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' 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 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 Unit 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

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 school uptake levels and it did seem to us that in the seventies there had been some increase in uptake and there was a supported 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 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

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.

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. 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 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 were one of the major concerns, sub-analysis in the collaborative study. 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 be 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 of time, and that's clearly incorrect. But why did anyone think to look in the first place?

Avery: Thank you. First there is definitely a difference between male and female and white and non-white. The Asian population is more ..... and 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, but it's a very interesting issue, I think about taking into consideration the chance that you might have all girls and look at the output in terms of scoring. Now whatever you are measuring .

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, I think there is a difference. Maybe somebody else has a reference.

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 physio~~pathological 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.

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.

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

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

Hey: I will just interject that the Ross conference report that you mentioned in 1976, there are five papers from the USA saying that they tried to do a trial and it was too difficult. We moan now about trials being difficult. You go back, they have always been saying that they were difficult. I think they are more difficult, but it's always been so. Yet sometimes it goes very well.

Gyte: I am moving away or back to a theme that was around before. As a consumer representative, I have always been very interested in the implementation of research findings, and my experience around this area came when I was a consumer representative on the Oracle trial, which was a trial looking at antibiotics in preterm labour. And in the development of the protocol, the researchers were wanting to do a second randomization of steroids within the main trial, and it was actually not our organization, the National Childbirth Trust, but another consumer organization, the Association for the Improvement in Maternity Services, who very much 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*. The relevance is that one of the uncertainties that remains about steroid use is whether it is a wise thing to do for a mother's sake, when there is premature rupture of membranes, because you may, in doing something good for the baby, increase the risk of the mother developing a generalised septicaemia. So the people couldn't see that there was an unanswered question there presumably.

Gyte: I went to *Effective ~~Campaigns in~~ Childbirth* and read Patricia's chapter to give an NCT perspective actually, 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 are now approaching antenatal steroids, how we have heard that it was very difficult to get antenatal steroids uptake, particularly in the

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.

Hey: Because people are still asking the question, 'Does it work in twins?' or 'Should you give it in ~~t~~hypertension?'.

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

the issues about clinicians using multiple courses of steroids, that their threshold for starting antenatal steroids is lower because if they are wrong, and the woman doesn't deliver soon, they can always give a second course. If you restrict people to giving a single course of steroids they may delay starting until there are stronger evidence, if you like, of impending preterm birth. So the groups of women selected into these trials is interestingly quite different I think in the current steroid group than the single steroid group, and that will make the interpretation of the results interesting.

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

Chalmers: ~~Very briefly.~~ The MRC has ~~got~~ a working paper under the chairmanship of Peter Dukes, ~~that~~ is ~~in fact~~ creating circumstances, ~~group pilots,~~ through which it would be possible for anyone receiving an MRC grant to archive their data. So ~~at least~~ biomedicine is catching up with the social scientists.

Dr Gino Giussani: I wanted to draw together some 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, accumulating evidence, that antenatal steroid therapy in doses, in those 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 the adult. We have not talked about other 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 controlling blood pressure are being laid down are being programmed to control blood pressure for long life, such as baroreceptors. We have evidence that antenatal glucocorticoid therapy reset the baroreceptors to run or to maintain blood pressure at a greater level. And of course we don't know whether that would lead

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

TEA BREAK

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

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

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

Sir Iain Chalmers: It's good that Patricia Crowley has already described some of the history that I might have covered. Given that I am going to be talking about the Cochrane logo, I might as well start with Archie Cochrane. Cochrane's famous book - Effectiveness and efficiency: random reflections on health services – was published in 1972 [1] and I read it in 1973. It changed my life! [2] In spite of the fact that I had been 'licensed to kill' six years earlier, after studying at the Middlesex Hospital Medical School 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 an American social scientist, Gene Glass.[3]

The first opportunity that I took to do a systematic review using meta-analysis related to different ways of monitoring babies during labour.[4] 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

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[1] Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: Nuffield Provincial Hospitals Trust, 1972.
[2] Chalmers I. Foreword to the new edition. In: Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: Royal Society of Medicine Press and Nuffield Trust, 1999:xiii-xvi.
3 Glass GV. Primary, secondary and meta-analysis of research. Educational Researcher 1976;10:3-8.
4 Chalmers I. Randomized controlled trials of fetal monitoring, 1973-1977. In: Thalhammer O, Baumgarten K, Pollak A, eds. Perinatal Medicine. Stuttgart: Georg Thieme, 1979:260-265.

Metaanalysis text added 1/6/05.

if the heart rate trace had raised concerns. It was being suggested by some people that these more intensive methods of intrapartum fetal monitoring should replace intermittent auscultation using fetal stethoscopes. I set about analysing three published reports of RCTs comparing different methods of intrapartum fetal monitoring, and the findings from one unpublished RCT, which were kindly made available to me by the investigators. About 2000 babies had been born to the women who had been entered into these four trials. Thirteen 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. 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.[5] 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 cancer and cardiovascular disease.[6 7 8]

As has already been noted by Patricia Crowley, during the following decade hundreds of people volunteered to collaborate in helping to prepare systematic reviews of RCTs assessing the effects of interventions in during pregnancy, childbirth and early infancy. For example, to identify relevant studies for a register of RCTs,[9]

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[5] MacDonald D, Grant A, Sheridan-Pereira M, Boylan P, Chalmers I. The Dublin randomized controlled trial of intrapartum fetal heart rate monitoring. American Journal of Obstetrics and Gynecology 1985;152:524-539.

6 Stjernsward J, Muenz LR, von Essen CF (1976). Postoperative radiotherapy and breast cancer. Lancet 1:749.

7 Chalmers TC, Matta RJ, Smith H, Kunzler A-M. (1977). Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. N Eng J Med 297,1091-96.

8 Lancet (1980). Aspirin after myocardial infarction. Lancet 1:1172-3.

[9] National Perinatal Epidemiology Unit. A classified bibliography of controlled trials in perinatal medicine 1940-1984. Oxford: Oxford University Press (for the World Health Organization), 1985.

some of these people helped to hand-search over 70 obstetric and paediatric journals back to their 1950 issues,[10] while others developed an agreed methodology for analysing the data from these studies.[11] 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 [12 13 14] as well as electronically, so that the analyses could be kept up to date.[15] It was very important that an institutional base for this work existed - the National Perinatal Epidemiology Unit. The Unit was funded by the Department of Health, which recognised 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.[16] 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 longer than a few years, I accepted this challenge, and the (UK) Cochrane Centre was opened in 1992.[17]

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[10] Chalmers I, Hetherington J, Newdick M, Mutch L, Grant A, Enkin M, Enkin E, Dickersin K. The Oxford Database of Perinatal Trials: developing a register of published reports of controlled trials. Controlled Clinical Trials 1986;7:306-324.

[11] Chalmers I, Hetherington J, Elbourne D, Keirse MJNC, Enkin M. Materials and methods used in synthesizing evidence to evaluate the effects of care during pregnancy and childbirth. In: Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford: Oxford University Press, 1989:39-65.

[12] Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford: Oxford University Press, 1989.

[13] Enkin M, Keirse MJNC, Chalmers I. A Guide to Effective Care in Pregnancy and Childbirth. Oxford: Oxford University Press, 1989.

[14] Sinclair JC, Bracken M. Effective care of the newborn infant. Oxford: Oxford University Press, 1992.

[15] Chalmers I. The Oxford Database of Perinatal Trials. Oxford: Oxford University Press, 1989-1992 (contents subsequently transferred to and maintained in The Cochrane Database of Systematic Reviews).

[16] Peckham M. Research and development for the National Health Service. Lancet 1991;338:367-371.

17 Chalmers I. The pre-history of the first Cochrane Centre. In: Bosch X, ed. Archie Cochrane: Back to the front. Barcelona, 2003:242-253.

The Centre used as part of its logo the results of the first seven trials of prenatal corticosteroids (I overlooked, inadvertently, an eighth trial which 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, 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 organisation.[18] [19]

I want to end with a statement that may sound rather carping, but I am keen that it should be on the record, given that this seminar is supported by the Wellcome Trust. Although the Trust supports clinical trials in some other parts of the world, it has always discouraged applications for support of clinical trials in the UK. In addition, I have it on good authority that some of the governors of the Trust have not only been unsupportive, but actually dismissive of the 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.[20] Given that those assessing payback from research [21] and others

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[18] Chalmers I. The Cochrane Collaboration: preparing, maintaining and disseminating systematic reviews of the effects of health care. In: Warren KS, Mosteller F, eds. Doing more good than harm: the evaluation of health care interventions. Annals of the New York Academy of Science 1993;703:156-163.

[19] Chalmers I, Sackett D, Silagy C. The Cochrane Collaboration. In: Maynard A, Chalmers I, eds. Non-random reflections on health services research: on the 25th anniversary of Archie Cochrane's 'Effectiveness and Efficiency'. London: BMJ Books, 1997:231-249.

[20] http://www.wellcome.ac.uk/doc%5Fwtx022708.html (accessed 6 December 2004)

recognise 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. 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. [22]

[21] Hanney s, Mugford M, Grant J, Buxton M. 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 2004 **[Volume and page numbers needed]**

[22] Chalmers I. Evaluating "payback" on biomedical research: biomedical funding decisions should be audited. BMJ 2000;321:566.

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monitoring had been introduced in obstetrics not long previously, sometimes accompanied by fetal ~~with~~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 fetal monitoring ~~, and people were suggesting it~~ should replace intermittent auscultation~~(?)~~ using fetal~~(?)~~ stethoscopes. I set about analysing ~~, and there have~~three published reports of RCTs comparing different methods of intrapartum fetal monitoring, ~~trials~~and the findings from one unpublished RCT~~report to which the authors very~~, which were kindly made available to me by the investigators. ~~allowed me access.~~ About 2000 babies had been born to the women who had been entered into these four trials. Thirteen of their babies had had neonatal convulsions. W~~And with~~ the help of a medical statistician - Klim McPherson - ~~experiments of comparing different fetal monitoring methods~~ I analysed~~looked at~~ the distribution ~~pattern~~of these babies among the~~se different~~ comparison groups~~,~~ in the RCTs. This revealed that the pattern was very unlikely to have occurred by chance (~~,~~less than 1 in a 100): the analysis suggested~~in fact~~ that continuous electronic fetal heart rate~~tract~~ monitoring with scalp sampling might reduce the risk of neonatal convulsions.

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~~TAPE TWO: SIDE TWO:~~

~~13000 women and their babies and in fact~~ The results of the Dublin trial of fetal monitoring confirmed the hypothesis generated by~~that had arisen from that 1978~~ my systematic review and meta-analysis. That ~~So that~~ seemed to me to provide~~actually quite~~ encouraging evidence that systematic reviews and meta-analyses could be useful for generating and testing~~deriving good~~ hypotheses about the effects of healthcare interventions. ~~and the testing of good hypotheses as well. We have been hearing just now from Jane.~~ Furthermore, it was becoming clear that this approach was regarded as promising in other fields, particularly cancer and cardiovascular disease.[6 7 8]

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[5] MacDonald D, Grant A, Sheridan-Pereira M, Boylan P, Chalmers I. The Dublin randomized controlled trial of intrapartum fetal heart rate monitoring. American Journal of Obstetrics and Gynecology 1985;152:524-539.

6 Stjernsward J, Muenz LR, von Essen CF (1976). Postoperative radiotherapy and breast cancer. Lancet 1:749.

7 Chalmers TC, Matta RJ, Smith H, Kunzler A-M. (1977). Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. N Eng J Med 297,1091-96.

8 Lancet (1980). Aspirin after myocardial infarction. Lancet 1:1172-3.

As has already been noted by ~~That led to a number of exercises and I won't go over them in detail.~~ Patricia Crowley, during the following decade ~~has been over them, but it certainly involved~~ hundreds of people~~mostly~~ volunteer~~ed~~ing to collaborate in helping to prepare systematic reviews of RCTs assessing the effects of interventions in during pregnancy, childbirth and early infancy. For example, to identify relevant studies for a register of RCTs,[9] some of these people helped to ~~-~~hand-search~~:~~ over~~About~~ 70 obstetric and paediatric~~and obstetric~~ journals back to their 1950 issues, ~~to identify relevant studies for this register of control trials~~[10] while o~~It involved getting~~ others~~, or sometimes the same to~~ developed an agreed~~to use a~~ methodologi~~cally set out approach~~ for analysing these data from these studies.[11] ~~, and to producing the~~Some of the resulting systematic reviews~~se,~~ 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 [12] [13] [14] as well as~~both the~~ electronically,~~publications,~~ so that the analyses could be kept up to date~~, and book publications as well.~~[15] ~~That happened during the late 1980s and very early 1990s in the case of the Effective Care of New Born Infants, which was Jack Sinclair's and Michael Bracken's contribution, but again based on this register, which was very important. That, in essence, was the data set, which then got analysed by all of these volunteers. And I~~it was very ~~, very~~ important that ~~to have~~an institutional bas~~cis~~ for this~~at~~ work existed - the National Perinatal Epidemiology Unit. The Unit was funded by ~~it was very nice that~~the Department of Health, which recognised that systematic reviews of existing evidence were a relevant way of identifying priorities for ~~i~~new research. ~~and that we got encouragement from people like David Paintin, Frank Hytten and Sheila Duncan in the British Journal of Obstetrics and Gynaecology, who accepted some of our reports as journal articles.~~

So what about the~~is~~ logo of the Cochrane Collaboration? ~~And how do I explain this thing. Well t~~These publications that had come~~, if you like,~~ from this 'pilot study' in the perinatal field~~,~~ were quite widely well received. Importantly, an oncologist~~s~~, Michael Peckham, who had been appointed in 1991 to establish a new NHS research and development programme, ~~an~~commented favourably on our work in a Lancet article

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[9] National Perinatal Epidemiology Unit. A classified bibliography of controlled trials in perinatal medicine 1940-1984. Oxford: Oxford University Press (for the World Health Organization), 1985.
[10] Chalmers I, Hetherington J, Newdick M, Mutch L, Grant A, Enkin M, Enkin E, Dickersin K. The Oxford Database of Perinatal Trials: developing a register of published reports of controlled trials. Controlled Clinical Trials 1986;7:306-324.
[11] Chalmers I, Hetherington J, Elbourne D, Keirse MJNC, Enkin M. Materials and methods used in synthesizing evidence to evaluate the effects of care during pregnancy and childbirth. In: Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford: Oxford University Press, 1989:39-65.
[12] Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford: Oxford University Press, 1989.
[13] Enkin M, Keirse MJNC, Chalmers I. A Guide to Effective Care in Pregnancy and Childbirth. Oxford: Oxford University Press, 1989.
[14] Sinclair JC, Bracken M. Effective care of the newborn infant. Oxford: Oxford University Press, 1992.
[15] Chalmers I. The Oxford Database of Perinatal Trials. Oxford: Oxford University Press, 1989-1992 (contents subsequently transferred to and maintained in The Cochrane Database of Systematic Reviews).

about his plans for the new programme.[16] He also responded encouragingly in that year when I ~~a~~suggested that a centre~~should~~ 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~~while~~ giving ~~it~~the proposal three years to see whether we~~they~~ could make anything of it. As I have never had a contract for longer than a few years, ~~certainly nothing approaching tenure, and~~ I accepted this challenge, and~~in 1992~~ the (UK) Cochrane Centre was opened in 1992.[17]

The Centre used as part of its logo the results of the first seven trials of prenatal corticosteroids (I~~, as I admit in the handouts w~~ overlooked, inadvertently, an eighth trial which had been published during this time period. It happened to have exactly the same confidence interval as one of the others, and~~so~~ I had thought that we might have been double counting). The reason that we used the steroid trials~~that~~ was that we wanted to show that, within ten years of the Liggins and Howie trial, there had been crystal clear evidence that this was a very important way~~treatment in terms~~ of reducing neonatal deaths. In launching the Cochrane Centre, w~~W~~e 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. ~~, when we launched the centre in 1992, and indeed i~~In the brochures we produced and the talks we gave to introduce the objectives of the Centre to others, we made ~~that is~~the point~~that,~~ that tens of thousands of babies had suffered and died unnecessarily (and~~as it happens~~ cost ~~the h~~Health s~~S~~ervices 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~~was being ignored. We went around the place beating this drum, and as Patricia has already said, it was the first systematic review of metaanalysis. It was entered into the software that we developed for all of this., this particular example~~ In 1993, a year after the Cochrane Centre had opened for business, we convened the meeting at which t~~T~~he international Cochrane Ceollaboration was founded~~a year~~, and the Centre's logo was adopted by the new organisation.[18] [19]~~It had to be internationalised, there was no way that this was something that a single country could take on.~~

I want to end with a statement that may sound rather~~a bit~~ carping, but I am keen that it should be on the record, given that this seminar is supported by the Wellcome Trust. Although the Trust supports clinical trials in some other parts of the world, it has always discouraged applications for support of clinical trials in the UK. In addition,~~, and I know this because one of the Governors of the Trust is a good friend, and~~ I have it on~~really~~

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[16] Peckham M. Research and development for the National Health Service. Lancet 1991;338:367-371.
17 Chalmers I. The pre-history of the first Cochrane Centre. In: Bosch X, ed. Archie Cochrane: Back to the front. Barcelona, 2003:242-253.
[18] Chalmers I. The Cochrane Collaboration: preparing, maintaining and disseminating systematic reviews of the effects of health care. In: Warren KS, Mosteller F, eds. Doing more good than harm: the evaluation of health care interventions. Annals of the New York Academy of Science 1993;703:156-163.
[19] Chalmers I, Sackett D, Silagy C. The Cochrane Collaboration. In: Maynard A, Chalmers I, eds. Non-random reflections on health services research: on the 25th anniversary of Archie Cochrane's 'Effectiveness and Efficiency'. London: BMJ Books, 1997:231-249.

good authority that some of the governors of the Trust, ~~it~~ haves 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.[20] ~~: There's been really no support until very recently from the Wellcome Trust for any of this work.~~ Given that those assessing payback from research [21] and others recognise 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. 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. [22]

[20] http://www.wellcome.ac.uk/doc%5Fwtx022708.html (accessed 6 December 2004)
[21] Hanney s, Mugford M, Grant J, Buxton M. 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 2004 **[Volume and page numbers needed]**
[22] Chalmers I. Evaluating "payback" on biomedical research: biomedical funding decisions should be audited. BMJ 2000;321:566.

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's just ridiculous that anyone should just not look at this. Economists, it's not very fashionable to look at areas where in fact there is a win–win situation. The exciting academic work all goes on at the fringes of where benefits perhaps might not be worth the costs.

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

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

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

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

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

Replacement text already supplied

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

Hey: Getting research into practice. We have already started down the path haven't we?

Lilford: Thank you very much, it's a great honour to be here today to say a few words about moving knowledge into clinical practice. I was plucked from obscurity in 1991 I think it was by the then President of the Royal College of Physicians, a gynaecologist, Stan Simmons, who called me into his office and said he wanted me to take over the audit committee. I thought for a moment, and I thought well I certainly could do this as he had asked me. I went down to the first meeting as their Chair, I had never been on it before, and it was a very boring meeting, it didn't seem to go anywhere, I cannot remember what its contents were, but I do remember I was very unimpressed with the meeting as a whole, and my application of my chairmanship of it. So on the train I went back I thought I had better do something a bit better than that with this position, and so the idea came into my head, I suppose because the guidelines were just coming into existence in people's consciousness then. The idea came into my head that what I should do with the committee was actually ….[?] guidelines. So I told the council how I was going to do this, and they must have had something else in their mind that day, because they sort of bundled it through, and went on to the next thing. So I don't think they quite worked out what they had signed themselves up to, but you know a mandate to go into these guidelines, which would then be disseminated. The next thing was what to do the guidelines on. Now Iain Chalmers had recently published with his colleagues his book, I think it was *Effective Care in Pregnancy and Childbirth*, and so

I thought well okay that's what we will do, we will go through all these trials, and we will come out with lots of guidelines. So I called a small group together, Marc Keirse, who was an obstetrician, I think he now works in Australia, but he was then an associate of Iain's, and a chap called Jim Thornton who was my clinical partner, and we sat down and we went through this whole data… in a day, came up early in the morning, whipped round [From the floor: 'In a day!']. Yes in a day, a long day I can tell you, but it was a day. I remember it went on into the evening and Iain came round to our house for supper after, and we went through the whole thing in a day, and I thought we would have say 100 guidelines, and the book was very thick, but when we went through it, we cut off at 21, only 21. That really surprised me, I had no idea it would be as little as that. How many trials were there in those days, there would have been about 20 000 trials [From the floor: Three and a half thousand]. From these 3500 trials, so what do you get? Twenty-one guidelines, which you can say, this is what people should do. Even some of those were quite close to the edge. The one that worried me most, was the Ventouse, but I think subsequent events have vindicated us from that, or just, or not, as the case may be. We'll leave that one open shall we. But the Ventouse was on the extreme right of the distribution, you know just got in. But one of the ones that made it through, very comfortably, I think second only to antibiotics, …….caesarean section or something like that, was the one that we have been hearing about today, which is giving steroids antenatally. Anyway this was our yield, 21, and we went and showed it to a bemused council who made a few derogatory, not derogatory, but a few non-committal remarks, and off it went. So it was then distributed with the President's signature, to all the people

practising obstetrics and gynaecology in the country. Of course, as so often happens in life, in our modern complex society, and I wasn't alone, Edmund Hey wrote me a letter, and told me all the other things that were going on at the time, there was a publication, a commentary by Liam Donaldson, who was then just a regional director of public health, in the *British Medical Journal* which .....had touched on the issue in passing, and I will say is a problem with the methodology of his study. I am not criticising the chief medical officer you understand, that wouldn't do me any good at all. I am just saying that there was a problem with the methodology for that. Then there was a publication from the *BAPM*, *British Association of Perinatal Medicine*, and there were letters in the *Lancet* in 1993. An NHS Management Executive letter, EL93 1115 in 1993. There was NIH consensus development conference. So there was quite a lot of buzz going on, and I didn't realize that my idea was so unoriginal, but there again that's life. So anyway we did, and I rested myself content, and in fact we went on and did some other guidelines about communication in maternity services and organizational standards that were studiously ignored. I then applied with Lesley Page, a Professor of Midwifery....., for a prize from BUPA. They gave a prize for he or she who communicated best that year, and we didn't get it. The reason we didn't get it, again it was quite proper, all we had done was propagate these guidelines, and we hadn't investigated what effect they had. So I then discerned that we should apply for a grant so that Jenny Hewison, the same Jim Thornton, a GP called Ian Watt and many other people I cannot remember all their names. We applied for a grant and got it to do a study of the uptake of guidance. Now Ed also sent me a paper by a very nice man called John Sinclair, and in it

he says and I quote from it, 'Despite the evidence of efficacy, effectiveness I guess, in reducing as well as RDS and death rates, the use by obstetricians of antenatal corticosteroids has remained low by many accounts. For example, in the Canadian multicentre trial' and it goes on to explain. I look at the reference and it's also early 1990s. So the question really was had something suddenly changed between before the systematic review, the guidelines that followed the systematic review. Has something changed following that, because a lot of these publications that people complained about, preceded first of all the collection of evidence and what's now the Cochrane database, the systematic review as Pritchard (?) did and the emanating of guidelines to give them some sort of societal authority. Or a lot of the complaints about ….. [?] were before all that endorsement took place. After all, if it wasn't necessary to have systematic reviews, if it wasn't necessary to put them into databases, and if it wasn't necessary to show that they had societal endorsement, why then would we have needed all that thing? So the question seems to me, the interesting question isn't that people didn't take them up before, what would you have expected? The interesting question would be, 'Well, then what happened after that?'. That was what our study was designed to find out. So we took four guidelines which were the Ventouse, the stitching up of the perineum by different materials, it having been discovered that whatever you do you should not use cat gut to do this, antenatal steroids, antibiotics in preterm labour. Then we added one on the hoof, because during the course of the study, ……. ……. [Lily Duley] and her colleagues published a spectacular trial, it must be *the* trial of the 1990s I think, which was about magnesium for the treatment of a horrible condition of labour called eclampsia, when

magnesium was better for the woman treated than the treatment such as currently being promulgated on this side of the Atlantic. So we quickly took the opportunity of seeing what effect that had. Anyway the results were published and I did try to circulate a copy of the paper, and so you can see the results there. There is one thing to say about these results with particular reference to corticosteroids and that is this. We have said right from the start that simply looking at who had given preterm birth, and seeing whether or not they had had corticosteroids, was not going to tell you the right information. It would be like be like the ecological fallacy experiment. Because what you really need to know is when there was a woman who through the eyes of the person caring for her, should have prompted the use of antenatal steroids, didn't or did get it. That's what you really want to find out, not that she had it. In fact the same situation arises in audit of the treatment of people with a heart attack. Some audits have been done on treatment of heart attacks, you know that's one of the tenets of good care for if you are having a heart is a clot busting drug ought to be given to you, and some people have done studies which have shown only 50 per cent of people who had a heart attack had had the clot busting drug and that gives you a huge underestimate, because when you arrive in casualty, the clot busting drug can only be given for a short period of time after you have started the onset of pain, a day or so. If you come into casualty and they don't think you have had a heart attack, you haven't got raised ST segments on your ECG and that is what it comes down to, if you haven't got that, then they quite properly don't give you the clot busting drug, because it can have some nasty side-effects, and cause a brain haemorrhage itself. When you go to leave hospital many of those people will have been

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

Just since I have titivated you all, I will just mention magnesium as well. Within a year of ~~Lily~~ Lelia Duley published her study, she and her colleagues, within a year of that 80 per cent, from zero, 80 per cent of women in this country with eclampsia were getting magnesium. So

that was without any guidelines and analysis. But that was a particularly powerful study and very useful.

I have got one last thought to leave you with and the thought is this. You know that the whole notion of diffusion of information into a community of experts is one that has been studied for a long time, and I understand that it started with a man called Rogers, who was looking at the uptake of effective agriculture practice, in farmers back in the 1930s. And he wrote, described the original diffusion curve, you know people are very avant guarde and take it right away, going through to the middle ground, and then a few laggards, who were very slow to take it up. That all comes from Rogers. Now you can think of that in two ways. The way it's always thought of is of a particular technology, so are the farmers using the latest and best fertiliser? Are the obstetricians using the latest treatment of a particular thing, shall we say of antenatal steroids? That's one way to look at it. The diffusion of that technology. But of course underneath all that lies an epistemological issue about what is perceived by the society of experts, the society of farmers, or the society of obstetricians, what is it that they perceive as being authoritative knowledge in a period of time? What I believe and we can discuss whether later if you wish, what I believe is this, that not only have obstetricians and indeed other people, it's exactly the same with a group of cardiologists for example, where similar studies have been done, not only have specialists taken on the idea of particular treatments like clot-busting drugs in cardiology or antenatal steroids in obstetrics, but they have taken on the idea that you should change your practice quite expeditiously in line with the evidence. So the notion of evidence-based practice has also been solved. I believed that

through my professional career there has been a sea change in that respect, and so I don't think we need to be quite so pessimistic in the future as we have been in the past about the uptake of new practice. That is the first part of my last point.

The second part of this is that not only has there been a change in the hearts and minds of practitioners, but there has also been a change in response to that about in a societal sense how we organize ourselves to receive new evidence. So for example, in the case of all those trials that were done on antenatal steroids, back in the 1970s and 1980s and so on, the trials were done, so the idea of doing trials had been solved, with an original idea that came from people like Brian Bateman, Austin Bradford Hill. Those ideas were coming into quite widespread use in the 1970s, that's why all these trials have been done. What we didn't have was a method, a societal method to receive the results of the trial. So the trial would be done and that would be that. And then no one knew what to do with it. How do you react to these trials? When is the trial evidence sufficient for a guideline to be developed? Now what I did in a way, I suppose, back in the college in those early days of 1992, was to start to provide some kind of societal mechanism to pick up the results of research and it's not surprising it took us a while to learn how to do this, and of course that's now been formalised much more, some would say too much, with organizations such as NICE and its equivalents in other parts of the world. Thank you very much.

Williams: For practising clinicians another anything new and accelerated factor which is a thing called the clinical negligence

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

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

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

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

on Confidential Enquiries into Maternal Deaths.

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

Just to clarify his experience Hospital in Cardiff,

Vernier Jones The

stuff at St David's steroids the

because John Gabbay misunderstood what had happened.

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

Basically, what happened was that a number of things happened to coincide, as is usually the way when you start an initiative, and in fact somebody who had actually seen the draft of those clinical audit suggestions was on the maternity services liaisons committee for Camden and Islington, which covered three maternity units, that's the Whittington, the Royal Free and UCLH, just round the corner here. And we hatched an idea over a beer in one of the local pubs that it would be interesting to look at four of those interventions, and take them around three units, using the MSLC. And the thing that would make it uniquely different was that there would be women, users of services, involved in the work 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, and my guess is that nobody would have read it, and it certainly isn't on Richards 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 maternity service liaison committees nationally, but my guess that a very few of them have been able to do what we did, because we had a particularly unusual committed bunch of users who were really passionate to get into it, we also had three units to deal with. Most MLCs are only dealing with one. It's much easier to deal with three, because you automatically try to collate all your information. So basically what we did was that we took these four interventions around each of the units, by visiting them, asking them to share with us their policies, giving them an advance of what was then going to be called what was the Cochrane library, but in those days the Cochrane centre had been established and we still referred to ECPC, Effective Care in Pregnancy and Childbirth, and all our users

had already got the users copies I may say. The Cochrane Pregnancy and Childbirth Database I think was what it was actually called at the time. So we took the evidence that was in those, the actual trials, abstracts, 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 varies of those blobograms from Patricia Crowley's original work. I remember ringing you up in Dublin once, right at the beginning of this, to ask you something about it, and you were extremely helpful, I cannot remember what it was now, but you were, and we reserved the right that we might ask a statistician to help us get into difficult complex issues about PT odds ratio or whatever. In fact, 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 about the precision of the results, they understood that instantly. We never needed a statistician. So we went round with four interventions. One was steroids, the other was suture materials, the third one was antibiotics for caesarean section, …….. antibiotics, and the fourth one was one you didn't mention Richard, was the difficult one which was ECV, st…..tic (?) version for breech presentation near term. We did steroids first, because we knew that they were all supposed to be using them, and we did ECV last, because we knew they certainly weren't and the other two were sort of in between. So we went round through the processes. 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. The thing that was not transparent was eligibility and exclusion

criteria which is of course the crunch to determining how many people get filtered in actually get given steroids and when. What had never been done before is that they had not done a perspective audit, and they had not shared it with the MSLC, and they undertook to do that. So that eventually a perspective 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, and women asked laser-like questions, like why aren't your figures as good as 'St Elsewheres', not very easy, but really important issues. We ran into less trouble with steroids than we did with the others and I won't labour it, except to say that we did persuade one hospital to introduce ~~vittol~~ ?Vicryl for the nurses to use, midwives to use, for repairing the perineum, whereas otherwise only the doctors were given the ~~vittol~~ Vicryl expensive, never mind the outcomes. So that was a dramatic change. One hospital that was using antibiotics for caesarean section had realized, of course, that it's the anaesthetist who tended to give it, and the anaesthetist had audited it, so actually only 60 or 70 per cent of women who should have been getting antibiotics actually were. So that was changed. And the most difficult thing was ECV (external cephalic version). This is basically if the baby is not presented by the head, but presented by the bottom, and there's an opportunity to turn the baby round in utero, before labour, provided it is done near to labour, and provided a theatre is available, consent for an emergency section has been obtained, and you can if necessary bail out by doing an emergency section if anything goes wrong. What we discovered, the main barriers for these interventions. Steroids there weren't really

major barriers, just bits of detail. Suture was a misunderstanding about cost and appropriateness. Antibiotics were about not getting the audit done by the right people. But ECV was different. The main barrier here was fear of death of baby or mother. There used to be a time, I remember when I was a medical student, seeing ECV done in the antenatal clinic and every so often you would get 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. One was using it intermittently and the third one, rather further away, somewhere near Hampstead, was not using it at all, except a few junior doctors had tried to introduce it and told in no uncertain circumstances, they were not to use it because it was dangerous. We had these sorts of discussion. 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. Answer well and Zimbabwe and California, and Denmark, and Holland, and here's the evidence, plonk it on the table. Oh it doesn't apply to us, and anyway that 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. We had those sorts of discussions. But what emerged after this hostility, was actually they had all experienced a death or near miss, and that

I think, apart from power, vested interests, empire building and struggles and political competition between trusts, this is the time of purchaser provider split and market competition was a really important issue around 1995–96. The main barrier was fear of something going horrendously wrong. People would then distort their perception of the evidence and vigorously resisting, on being told to

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 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 on the trial. I know that Brenda Mullinger and Clive Dash had a lot of difficulty keeping the momentum up, trying to recruit babies, to recruit women, even though ..... [?] were reaching the volunteers. As you possibly remember from the paper, 60 per cent of the cases came from patients who were recruited from three hospitals, the rest of them just put it away.

Hanney: We have been looking at the benefits from health research for about ten years now, and this particular stream of work seems to us to have been one of the most interesting, and I have worked on it with Miranda and Martin Buxton and Jonathan Grant, and I apologise for I will check on my notes from time to time, because I am trying to pick up on what various people have said today on what I think is an interesting session. For instance, John, we at least read your work. There is a paper that set out most of the list of the detail in press and is going to be published in *Social Science and Medicine*. So I will just highlight all the key points for now. Apologies, perhaps

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 .....team, thirdly better informing policies of why the policies are widely interpreted, fourthly, health gain and 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 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 the gains 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 were lots of weaknesses in it, but for an analysis 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 really electric analysis undertaken in this

field undertaken by the Foster 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 the figures in the 1980s, somewhat unclear, but it was definitely higher in Australia and New Zealand. By the 1990s there seemed to be this consensus that the pickup rate was between perhaps 10 and 20 per cent, and a somewhat 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. 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 due to the reduced incidence of RDS, and also there were the cost savings, even if these were cost savings....

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 1989–90s, we have heard, and perhaps particular attention was focused on this systematic review for several reasons. The ..... of the logo Cochrane Collaboration, the fact that ..... 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 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 ~~dis~~consensus 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 the terrible courses that babies would go through before death, and ~~perhaps~~

indeed before surviving, and the accompanying anxiety ~~that goes with that~~, those things haven't been made explicit ~~and I suspect that if,~~ we had hoped that there would be a woman here who had received prenatal corticosteroids, ~~now I don't know what her history was at all, but~~ I was ~~certainly quite~~ impressed by Barbara Stocking, ~~who is~~ now chief executive of OXFAM, saying that in her first pregnancy she had delivered prematurely and her son went through a really rough time. After she read Patricia's systematic review ~~and in~~ 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. ~~, and~~ I have come across more than one mother, maybe Gill Gyte can enlighten us here, who has ~~they have~~ lobbied to have this, ~~because they~~ obviously as parents, they ~~actually~~ think this is important, ~~obviously~~ because they are worried about their children, possibly also but so that they ~~can perhaps~~ have less to worry about themselves.

Gyte: I don't have any personal experience of antenatal classes, but I know that the ~~NCT~~ National Childbirth Trust do ~~not~~ ~~NTT~~ does lobby very much to implement evidence, generally in terms to implement evidence-based care.

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

projects that I worked on in 1974 involved an observational study of an antenatal clinic at a hospital in London which has of course got to be nameless, and I hung around this clinic for about a year observing what the doctors were doing, and I was absolutely astonished in my second week, I think there was a changeover the most junior doctors, and two of them came to me and they asked me what consultant X would recommend in a particular case, because they didn't know what they were supposed to be doing because they hadn't met their consultant yet. I didn't realize that the eight different consultants who ran this clinic all had different policies. I mean what I was doing was learning what those policies were, but then I was passing on this information to the junior members of their team, so that they could also practice non-evidence-based medicine. That was a long time ago, but I think it is still the case that many people believe that doctors and other experts know what they are doing. So another issue in all of this is about the epidemiological shift in people in general in society understanding that experts including those in other fields, and I spend a lot of my time at the moment with professors of education who don't believe in systematic reviews of the evidence. But it is about the role of the expert, and the relationship between research, evidence and the evidence and form of policy across a whole lot of different sectors.

Crowley: In 1985 as an obstetric senior registrar, I inherited a woman who was having an anti..... haemorrhage at 37 weeks as we thought, and we thought she was 37 weeks because the registrar who did her first antenatal visit had made a mistake about her dates. She was in fact 33 weeks and I delivered the baby in consultation with the

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

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

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

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

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

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

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

survived the six years. I think, and I was discussing this with Jane during the break this afternoon. She thinks that in Australia and New Zealand, well they have got some evidence down in Australia and New Zealand, that the amount of steroid use is going down. I think it is going down in the UK slightly 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, but clearly the messages that are coming out are not that steroids are bad, but that we need to be more sophisticated in how we use them and how that is interpreted appears to be immediate response to stop using them. So the issues for the future I think in terms of our current gaps, the biggest one I think is that we cannot identify women who are to deliver preterm very effectively. We can agree we are going to deliver them preterm electively, but for the vast majority of women who deliver spontaneously, we are not very good at recognizing them. And things like people fibronectin, cervical length of screening may help us identify a group of women who are at a much higher risk of preterm delivery, and we can target our intervention more effectively and I am sure we will see much more of that in the future. At what age to use, what formulation, what dose, and what route of administration I think are questions that we will have to tackle in the future. What gestational age to give this. Nobody has mentioned yet the trial that has only been published in abstract that Peter Stutchfield did in Wales where they recruited women who going for elective caesarean section at greater than 37 weeks. They randomized nearly 1000 women to receive steroids or not and showed a significant decreased admission to the neonatal unit with respiratory symptoms in the

group given steroids. So even beyond 37 weeks at term, if you deliver electively by caesarean section, steroids seem to work. So 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 as I said is still wide open although we will see more evidence of that over the coming years, and it may hopefully answer some of the questions, although I suspect little. A big lesson which has come out of the steroids trial not only antenatal steroids, but postnatal steroids, is that we 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. I was reading in *Time* magazine recently 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 perfectly reasonable justification for raising the age at which you can vote. 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 we think we can just look at RDS and ignore the potential long-term effects. I think we are beginning to realize now that we cannot do that, that intervention that shows short-term benefits like neonatal dexamethasone, may then be counteracted by long-term harm. Not that there's no benefit in the long term, but that the long-term effects may be in the opposite direction. That very sophistication means that long-term follow ups (?) and cohorts become essential and yet the current situation in the UK I would suggest, in terms of being able to follow-up people, is making it more and more difficult and more and more expensive.

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 blood steroid levels and that reassured him that that was an appropriate placebo. To come back to Peter Brocklehurst's point about how come they chose the best dose and the best drug. I don't think we know that they did. Nobody's looked and almost all of the issues that Peter rose, the repeat steroids, which dose, which drug, how often, at what gestation, to which pregnancy,

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 the quotation for the original papers, and said cos 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 be~~en Director of the UK Cochrane Centre (1992–2002), ~~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).

Editor, James Lind Library (2003–).

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,

Corrections
Iain Chalmers
UCL 7 Dec'04

Sir Iain Chalmers: It's good that Patricia Crowley has already described some of the history that I might have covered. Given that I am going to be talking about the Cochrane logo, I might as well start with Archie Cochrane. Cochrane's famous book - Effectiveness and efficiency: random reflections on health services – was published in 1972 [1] and I read it in 1973. It changed my life! [2] In spite of the fact that I had been 'licensed to kill' six years earlier, after studying at the Middlesex Hospital Medical School 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 an American social scientist, Gene Glass.[3]

The first opportunity that I took to do a systematic review using meta-analysis related to different ways of monitoring babies during labour.[4] 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

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[1] Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: Nuffield Provincial Hospitals Trust, 1972.
[2] Chalmers I. Foreword to the new edition. In: Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: Royal Society of Medicine Press and Nuffield Trust, 1999:xiii-xvi.
3 Glass GV. Primary, secondary and meta-analysis of research. Educational Researcher 1976;10:3-8.
4 Chalmers I. Randomized controlled trials of fetal monitoring, 1973-1977. In: Thalhammer O, Baumgarten K, Pollak A, eds. Perinatal Medicine. Stuttgart: Georg Thieme, 1979:260-265.

if the heart rate trace had raised concerns. It was being suggested by some people that these more intensive methods of intrapartum fetal monitoring should replace intermittent auscultation using fetal stethoscopes. I set about analysing three published reports of RCTs comparing different methods of intrapartum fetal monitoring, and the findings from one unpublished RCT, which were kindly made available to me by the investigators. About 2000 babies had been born to the women who had been entered into these four trials. Thirteen 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. 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.[5] 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 cancer and cardiovascular disease.[6 7 8]

As has already been noted by Patricia Crowley, during the following decade hundreds of people volunteered to collaborate in helping to prepare systematic reviews of RCTs assessing the effects of interventions in during pregnancy, childbirth and early infancy. For example, to identify relevant studies for a register of RCTs,[9]

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[5] MacDonald D, Grant A, Sheridan-Pereira M, Boylan P, Chalmers I. The Dublin randomized controlled trial of intrapartum fetal heart rate monitoring. American Journal of Obstetrics and Gynecology 1985;152:524-539.

6 Stjernsward J, Muenz LR, von Essen CF (1976). Postoperative radiotherapy and breast cancer. Lancet 1:749.

7 Chalmers TC, Matta RJ, Smith H, Kunzler A-M. (1977). Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. N Eng J Med 297,1091-96.

8 Lancet (1980). Aspirin after myocardial infarction. Lancet 1:1172-3.

[9] National Perinatal Epidemiology Unit. A classified bibliography of controlled trials in perinatal medicine 1940-1984. Oxford: Oxford University Press (for the World Health Organization), 1985.

some of these people helped to hand-search over 70 obstetric and paediatric journals back to their 1950 issues,[10] while others developed an agreed methodology for analysing the data from these studies.[11] 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 [12 13 14] as well as electronically, so that the analyses could be kept up to date.[15] It was very important that an institutional base for this work existed - the National Perinatal Epidemiology Unit. The Unit was funded by the Department of Health, which recognised 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.[16] 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 longer than a few years, I accepted this challenge, and the (UK) Cochrane Centre was opened in 1992.[17]

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[10] Chalmers I, Hetherington J, Newdick M, Mutch L, Grant A, Enkin M, Enkin E, Dickersin K. The Oxford Database of Perinatal Trials: developing a register of published reports of controlled trials. Controlled Clinical Trials 1986;7:306-324.
[11] Chalmers I, Hetherington J, Elbourne D, Keirse MJNC, Enkin M. Materials and methods used in synthesizing evidence to evaluate the effects of care during pregnancy and childbirth. In: Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford: Oxford University Press, 1989:39-65.
[12] Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford: Oxford University Press, 1989.
[13] Enkin M, Keirse MJNC, Chalmers I. A Guide to Effective Care in Pregnancy and Childbirth. Oxford: Oxford University Press, 1989.
[14] Sinclair JC, Bracken M. Effective care of the newborn infant. Oxford: Oxford University Press, 1992.
[15] Chalmers I. The Oxford Database of Perinatal Trials. Oxford: Oxford University Press, 1989-1992 (contents subsequently transferred to and maintained in The Cochrane Database of Systematic Reviews).
[16] Peckham M. Research and development for the National Health Service. Lancet 1991;338:367-371.
17 Chalmers I. The pre-history of the first Cochrane Centre. In: Bosch X, ed. Archie Cochrane: Back to the front. Barcelona, 2003:242-253.

The Centre used as part of its logo the results of the first seven trials of prenatal corticosteroids (I overlooked, inadvertently, an eighth trial which 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, 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 organisation.[18] [19]

I want to end with a statement that may sound rather carping, but I am keen that it should be on the record, given that this seminar is supported by the Wellcome Trust. Although the Trust supports clinical trials in some other parts of the world, it has always discouraged applications for support of clinical trials in the UK. In addition, I have it on good authority that some of the governors of the Trust have not only been unsupportive, but actually dismissive of the 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.[20] Given that those assessing payback from research [21] and others

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[18] Chalmers I. The Cochrane Collaboration: preparing, maintaining and disseminating systematic reviews of the effects of health care. In: Warren KS, Mosteller F, eds. Doing more good than harm: the evaluation of health care interventions. Annals of the New York Academy of Science 1993;703:156-163.

[19] Chalmers I, Sackett D, Silagy C. The Cochrane Collaboration. In: Maynard A, Chalmers I, eds. Non-random reflections on health services research: on the 25th anniversary of Archie Cochrane's 'Effectiveness and Efficiency'. London: BMJ Books, 1997:231-249.

[20] http://www.wellcome.ac.uk/doc%5Fwtx022708.html (accessed 6 December 2004)

recognise 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. 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. [22]

[21] Hanney s, Mugford M, Grant J, Buxton M. 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 2004 **[Volume and page numbers needed]**

[22] Chalmers I. Evaluating "payback" on biomedical research: biomedical funding decisions should be audited. BMJ 2000;321:566.

Copy.

Sir Iain Chalmers,
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The James Lind Initiative, Summertown Pavilion,
Middle Way,
OXFORD, OX2 7LG

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

10 August 2005

Dear Sir Iain,

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

We would like to ask your permission to reproduce the letter from Professor Sir Graham Liggins to you dated 6 April 2004, as an appendix in Reynolds L A, Tansey E M. (eds) (2005). Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth, *Wellcome Witnesses to Twentieth Century Medicine*. Vol. 25. London: The Wellcome Trust Centre for the History of Medicine at UCL. This transcript is scheduled for publication as a freely available pdf on our website, www.ucl.ac.uk/histmed and as a hard copy available from www.amazon.co.uk or www.amazon.com in November 2005.

I would be most grateful if you could sign the attached form and return it to me.

A second copy is provided for your files.

Yours sincerely

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey

enc. Draft appendix to Volume 25.

witedit/contribpermissltr.doc

Rec'd + ack 15/8/05
Please sign + return

To: The History of Twentieth Century Medicine Group

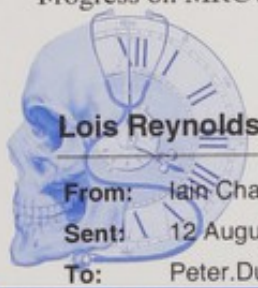
I agree to the above request to reproduce the letter from Professor Sir Graham Liggins to me dated 6 April 2004, as an appendix, to be described as:

Liggins to Chalmers, 6 April 2004.

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

Signed Iain Chalmers Dated 12/8/05

Sir Iain Chalmers,
Editor, James Lind Library,
The James Lind Initiative, Summertown Pavilion,
Middle Way,
OXFORD, OX2 7LG



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Lois Reynolds

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 12 August 2005 09:41
To: Peter.Dukes@headoffice.mrc.ac.uk
Cc: l.reynolds@ucl.ac.uk
Subject: Progress on MRC's data archiving initiative

Dear Peter

As I explained on the phone just now, Lois Reynolds is editing the transcript of the Wellcome Trust Centre for the History of Medicine's Witness seminar on the development and use of antenatal corticosteroids for lung maturation.

Following a discussion of the way that data collected in a trial done 30 years ago has been used successfully to test new hypotheses, Richard Lilford drew attention to the UK Data Archive at the University of Essex. Commenting on this, I said "The MRC has a working party under the chairmanship of Peter Dukes, which is creating circumstances thorough which it would be possible for anyone receiving an MRC grant to archive their data." Lois has asked me whether any update on that statement could be added in a footnote.

Please would you provide Lois (to whom I am copying this message) with some words for a footnote, informing readers of this document about progress in pursuing the objectives of your working party.

With best wishes, Iain

SIR >IAIN CHALMERS

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Lois Reynolds

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 12 August 2005 11:51
To: ucgarey@ucl.ac.uk
Subject: RE: Progress on MRC's data archiving initiative[Scanned]

Dear Lois, I've re-read everything, annotated the transcript, signed the permission, etc and put everything in the post to you just now. Have a good holiday. Best wishes, Iain

---

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 12 August 2005 10:44
To: Iain Chalmers
Subject: RE: Progress on MRC's data archiving initiative[Scanned]

Many thanks, Iain. The post is much more efficient than we suspected. Hope you have had a good summer. I look forward to your comments on my return from leave on 31 August. Best wishes from Lois

-----Original Message-----
From: Iain Chalmers [mailto:IChalmers@jameslindlibrary.org]
Sent: 12 August 2005 09:41
To: Peter.Dukes@headoffice.mrc.ac.uk
Cc: l.reynolds@ucl.ac.uk
Subject: Progress on MRC's data archiving initiative

chased 29/9/05

Dear Peter

As I explained on the phone just now, Lois Reynolds is editing the transcript of the Wellcome Trust Centre for the History of Medicine's Witness seminar on the development and use of antenatal corticosteroids for lung maturation.

Following a discussion of the way that data collected in a trial done 30 years ago has been used successfully to test new hypotheses, Richard Lilford drew attention to the UK Data Archive at the University of Essex. Commenting on this, I said "The MRC has a working party under the chairmanship of Peter Dukes, which is creating circumstances thorough which it would be possible for anyone receiving an MRC grant to archive their data." Lois has asked me whether any update on that statement could be added in a footnote.

Please would you provide Lois (to whom I am copying this message) with some words for a footnote, informing readers of this document about progress in pursuing the objectives of your working party.

With best wishes, Iain

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'Promoting better controlled trials for better health care'

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12 August 2005

Lois Reynolds
Wellcome Trust Centre
for the History of Medicine at UCL
210 Euston Road
London
NW1 2BE

Dear Lois

Prenatal Corticosteroids for reducing morbidity and mortality after preterm birth

Thank you for your two letters dated 10 August, and for inviting me to look over the 'pre-final' proofs of the Witness Seminar. You, Daphne and Tilli have done a great job! I'm very grateful to you and I'm sure others will be too.

The 'Liggins to Chalmers' Appendix: I have signed the permission request attached to your letter, which I am returning herewith. However, I hope that you will add the images from the other two slides that Mont sent to me. As I mentioned in my email message to you, I handed over all three slides at the meeting, so the other two will presumably be wherever the first was located. Also, please align and close up the passages taken from the last page of Mont's letter to me.

The transcript: I have reread the whole transcript, responded to the two specific queries mentioned in your letter, provided some information you have requested of others, and marked some places where corrections are needed (for example, in the legend for Figure 4). I am returning the annotated draft herewith. I have made copies of the annotated pages, so don't hesitate to let me know if any of my hieroglyphs are enigmatic.

With best wishes

Yours sincerely

Iain

Sir Iain Chalmers

Encl.

Recd 15/5/05 UK alt 15/8/05

Sent to : Chalmers, Howie, Liggins,

Appendix 1:

April 6, 2004

Sir Iain Chalmers
James Lind Library
Summertown Pavilion
Middle Way
Oxford OX2 7LG, UK

Dear Iain,

As you say, it would be nice to be fit enough to do this face-to-face.I will do my best to answer your queries. There is no video-recording of an appropriate interview. Nor can I provide pages from a lab book. Lacking your sense of history, All my records were consigned to the scrap heap when I retired. The best I can do is enclose a slide of a photo taken of those very first lungs showing partial inflation after fetal infusion with cortisol at 118 days of gestation The lamb had delivered during the night.To my great surprise, I found it still alive in the morning, gasping but surviving. I was fully occupied with studies of parturitional physiology and was not inclined to pursue it further at that time. However, I did tell Mel Avery who was visiting NZ soon afterwards. She got on the phone and called one of her Fellows in her lab and told him to give cortisol to some fetal sheep. Our observation was published in 1969 was soon followed by DeLemos and Avery in 1970 which confirmed the finding as well as providing direct evidence of accelerated appearance of surfactant as we had postulated.
When I returned to a position as Senior Lecturer in O & G at National Women's Hospital in 1959 after 6 years of clinical work and no research in the UK, I realised that my academic appointment required me to do some research. I asked my friend, Bill Liley, of fetal transfusion fame how to choose a topic. He said to look for a major problem which was potentially soluble. The major problem was easy. Prematurity stood out above everything else. I naively thought that all I had to do was solve the ancient question of what controlled the onset of labour at term and the reason for premature onset would become apparent. I thought it might be a fetal activity although at the time it was generally believed maternal activity via release of oxytocin from her pituitary. But I had some



Slide from Mont (June 2005) IC asked if this is the same as those sent by Mont in 2004. [4.8.05] Three slides are mentioned in the text of the letter.

See my email dated 4 Aug.

Sent to : Chalmers, Howie, Liggins,

circumstantial evidence to support my idea.The second slide enclosed shows two sheep brousing on veratrum californicum or skunk cabbage in the mountains. They don't like it bit will eat it in times of drought. Binns et al in 1960 described how the lambs were cyclopian and had prolonged pregnancies.At autopsy they found defective pituitaries. With this titbit I set out to hypopyhsectomise fetal sheep.Having no money and no animal lab I called on friends at Ruakura Animal Research Station 80 miles south of Auckland. They generously provided everything I needed. So over the next sheep season I worked out how to do fetal hypophysectomies and adrenalectomies. The following year I had a sabbatical and went off to the Vet School at Davis, California and put the techniques to the test. The results were dramatically successful.Pregnancies continued on and on after hypophysectomy.

← add slide

Back in Auckland I needed a lab and money. The Hospital gave me an abandoned shed [see slide 3] and the Wellcome Trust courtesy of that wonderful man, Peter Williams, gave me money. My first experiments were to test the idea that the effects of the pituitary were mediated by the fetal adrenal. Infusion of cortisol or ACTH caused premature delivery at any gestational age.With that lengthy background we have arrived at the subject of the seminar although there is plenty more to the parturition story.

Add slide.

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

close up and align

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

Judging by the number of trials that soon followed there was a lot of interest amongst obstetricians particularly in US. I got the impression on visits to the UK that paediatricians there were luke warm perhaps because there was a perception that their territory was being encroached on. Judging by the 20 years that it took the RCOG to come out in favour despite your constant nagging there was a problem with British obstetricians too though I don't understand it.

Iain, please regard this as a trial run, to be amended as you wish.

Best wishes, Mont

Mont.

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

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

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

Ross N Howie
Auckland, New Zealand
2 June 2004

Firstly my warmest greetings to Mel Avery, who was in at the very beginning of the whole surfactant story. My only regret for her is that she is not yet in at the end of it, at least as a major public health problem. If anyone had asked me at the time Mont Liggins and I first published in 1972 [1] how I thought the New Zealand work would be viewed in the year 2004, I would have replied that by then advances in our understanding and management of preterm delivery and its associations would surely have made it irrelevant. Which only goes to show how naïve it can be to try to divine the future.

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

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

A word on the setting. Possibly few single centres in the world could have carried out such a trial at that time. It needed one with a large number of births that was also academically well enough developed. Overseas, academic units tended to have relatively few births, and the large obstetric services tended not to have close academic ties. In Auckland the National Women's Hospital (NWH) then had about 5000 deliveries a year, among which were concentrated mothers and babies of the highest risk from about 15 000 in the region. The hospital had within it the Postgraduate School of Obstetrics and Gynaecology, which had a background of research starting with Bill Liley and his rhesus work, which Mont Liggins rejoined shortly after.

Nor, in other places, did it seem common for obstetricians and paediatricians to talk much with each other. The two disciplines had differences of outlook and values that were not always easy to bridge, but a good collaboration had been established at NWH. This was thanks very largely to successive heads of the Postgraduate School, Harvey Carey and Dennis Bonham, to the then senior paediatrician, Jack Matthews, and to Bill Liley. Drs Liley and Matthews had set up a Rhesus Committee about 1960, which brought together the obstetric, paediatric and other staff likely to be involved with the rhesus deliveries. From his coming in 1964, Dennis Bonham (fresh from his monumental work with Neville Butler in the British Perinatal Mortality Survey) reinforced this approach. In my medical school years (1952-6) I never heard the word 'perinatal' [2], and the outlook the word implied was in many places some time in the future.

At the time Mont was doing his relevant basic research in the late 1960s, the death rate of babies in the newborn period was at least five times the present. Far the leading cause of death then was respiratory failure in babies born early. I was the only person in Auckland (and for that matter in the whole of the country) who could ventilate babies. I did not do it very well: techniques were crude, equipment limited, and nursing staff and other support short. This was to my oft- and forcibly-expressed regret, strongly supported by my two paediatric colleagues, Jack Matthews and Leo Phillips. The facilities of modern newborn care are now taken for granted, but it was a long and hard fight to get them. In those days I felt I spent altogether too much time up at nights looking after babies, and was very ready to welcome any development that might reduce that need – never to mention, of course, benefit to the babies in keeping them away from the tender mercies of intensive care.

The development came in a way that, if not familiar to members of your seminar, will presumably be explained by Mont himself. I still remember the excitement I felt at my first evidence of it, when he handed me the lungs of twin lambs for pressure-volume studies. The lambs had been delivered very early (?127 days): one had been infused with glucocorticoids and the other not. Lungs of the infused lamb were perfectly stable after inflation: pink, fluffy and floated in water. In total contrast, the lungs of the other remained solid and liver-like and sank. After Mont had confirmed the effect in further animal studies, he looked to set up the first human trials and called me in. He looked after the maternal side and I that of the babies.

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

If the therapy worked at all, it seemed *a priori* that it would work under some conditions and not others, and under yet others might be hazardous. In the words of Claude Bernard (?), what is true in general is likely to be false in particular. I was also

conscious of the history of so many 'advances' in medicine, which have come in phases: one of initial and uncritical enthusiasm, followed by one of debunking, and finally – if the development is worth while – one of a more sober balance. We were keen to see the project through all these phases and find out as much as possible of the limitations of the therapy before others did. I set myself up at the outset as a chief sceptic, and have remained so.

We felt that only a very large study could hope to give results of any reliability. As a result the trial may have been kept going for longer than would meet with the approval of an ethics committee today, but the results may be on a firmer footing as a result.

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

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

We asked them instead, and they very kindly agreed, to fund us to carry out long-term followup studies. ('Long-term' to us then meant to 6 years. The 30-year followup would at the time have seemed an impossible dream.) In this we were singularly well placed by having a happy association with Barton MacArthur, an educational psychologist in the University. He was (and still is) New Zealand's leading authority on tests of cognitive function in young children, and brought to his work a meticulousness and rigour unmatched among psychologists in my experience.

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

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

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

I well remember January 1975 – just after the trials finished – as a watershed in the development of our own services. In 1974 I was away from the unit for two weeks in Geneva discussing our proposed followup studies with WHO, and found on my return to Auckland that during my absence two relatively large babies had died from uncomplicated RDS. Both, I was sure, would have survived if treated very simply with George Gregory's technique of continuous positive airway pressure (CPAP). I hit the roof and sent in my resignation. For some reason the powers that were felt it necessary to talk me out of it, but we did achieve more staff. Our first full-time clinical specialist (Sue Sayers) took up her post in 1975, and only then did 'neonatal intensive care' become a sustainable reality in our hospital.

In all developed countries to my knowledge, perinatal survival improved strikingly in the second half of the 20th century. In New Zealand it improved possibly more than most due to a remarkable nation-wide effort very ably led by the successive heads of the Postgraduate School of O&G, Harvey Carey and Dennis Bonham. In the 40 years after the hospital was established, the national perinatal mortality rate (by the WHO definition of the time [3]) fell by nearly 80%, from 34.6 per 1000 births in 1950 to 7.4 in 1990. Steroid therapy was a welcome advance during this time, but it would be hard to attribute to it more than a small fraction of the improvement.

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

If some of what I have written seems provocative, I can at least claim that is in a good early National Women's Hospital tradition. It is one that various pressures have caused to be sadly less in evidence during the past 20 years. If there was any greatness in that hospital in its early days (as I believe there was), much of it was due to an environment of questioning conventional wisdom and challenging authority (and doing so constructively and with rigour). It was one especially fostered by the second head of the Postgraduate School (Harvey Carey, ?1955-62). Examples: Bill Liley and fetal transfusion (everyone knew that blood could not be absorbed intact from the peritoneal cavity), and Mont Liggins with the work that was the basis of the advance related in this account (everyone thought that it was the mother that determined the onset of parturition). I felt privileged indeed to be part of the hospital in those times.

Acknowledgments

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

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

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

Notes and references

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

2. On the history of the word 'perinatal', I wonder whether anyone in the Wellcome Trust Centre can enlighten us. The coining of the word was a landmark that surely deserves recognition. A quick check of the US NLM website PubMed for occurrences of the words 'perinatal' and 'perinatale' in titles of journal articles showed none earlier than 1952, when there were 3. I tentatively concluded that the first use of the word may have been in Europe in a language not English, French or German, but possibly Dutch, Scandinavian or Eastern European. At this point I found myself out of my depth and in need of more expert help.

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

Chalmers

please see pages:
8, 21-22, 30, 32, 44, 48, 57, 60
63-70, 71, 78-79, 89-90 and
biographical note on page 113.

See also note 74, pg 47.

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY AFTER ~~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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PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY ~~IN~~ AFTER 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 Verrier 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

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

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]

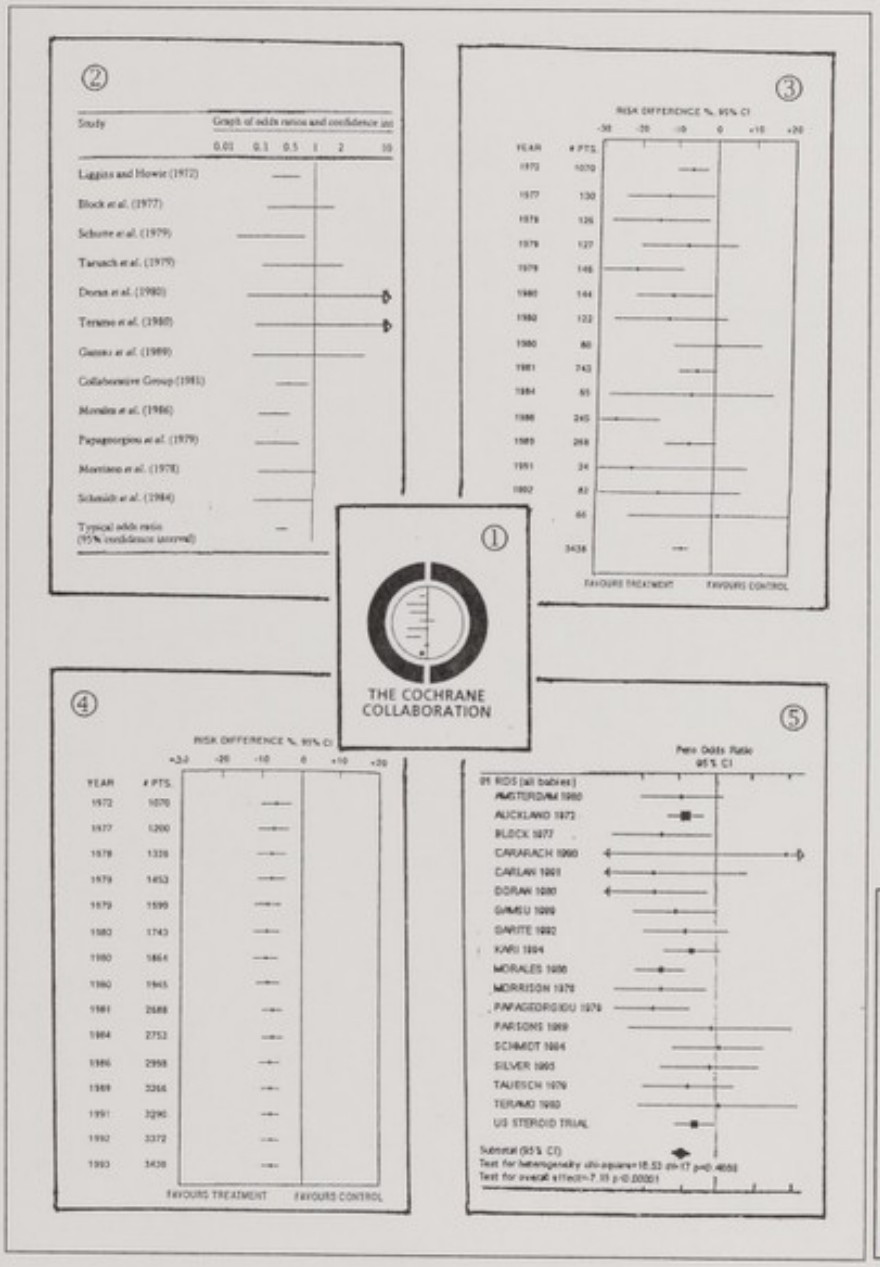


Figure 4: Patricia Crowley' meta-analyses, 1992–2004.

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

Cumulative meta-analysis of first 15 trials

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

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 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 Iain 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 asked to comment

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

Mont + Ross contacted by email for comments 9/8/06

Suggest deleting

[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.

consumers

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

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[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~~ were 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]

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.

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 regiments 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? See email 12/8/05 to Peter Dukes, copied to you

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).

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

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

Mugford: We can say that over the last 20 years the resources devoted to neonatal intensive care, you had a different seminar on this subject[96] – I haven't looked at the living witness results on [??transcript of??] that seminar – but [?what has expanded?]having incredibly expanded and there are very many more nurses, doctors, ventilators and techniques for the care of preterm babies than there were 20 years ago.[97]

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

Chalmers: It's good that Patricia Crowley has already described some of the history. Given that I am going to be talking about the Cochrane logo, I might as well start with Archie Cochrane, whose famous book – *Effectiveness and Efficiency: Random reflections on health services* – was published in 1972.[98] I read

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[96] See the Witness Seminar, 'Origins of Neonatal Intensive Care in the UK', Christie and Tansey (eds) (2001), also freely available online at www.ucl.ac.uk/histmed following the link to Publications.

[97] Macfarlane A, Johnson A, Mugford M. (1999) Epidemiology, in Roberton N R C, Rennies J. (eds) *Text book of Neonatology*, 3rd edn. Edinburgh: Churchill Livingstone, 3–33.

[98] Cochrane (1972).

it in 1973 and it changed my life![99] In spite of the fact that I had been 'licensed to kill' six years earlier after studying at the Middlesex Hospital Medical School, London, to qualify as a doctor, I had not previously been aware of the term 'randomized controlled trial (RCT)'. Cochrane showed me how I might adjudicate among incompatible clinical opinions about treatments, a common situation faced by me and other junior doctors, and it was after reading Cochrane's book that I started to collect reports of RCTs. A librarian in Cardiff, Steve Pritchard, designed a Medline search to identify these studies for me, and I started noting those in my special area of interest (perinatal care) during my reading of journals and books.

In 1976, because it was clear that this was an insufficiently systematic method of finding reports of RCTs, I outlined a plan for using a more systematic approach both for finding published reports, and for identifying unpublished studies (because biased under-reporting of RCTs means that unpublished studies tend to have less dramatic results than those that get into print). This plan, which was set out in a letter to Martin Richards, a psychologist in Cambridge, also stated an intention to use statistical synthesis of the results of similar by separate studies (meta-analysis) to reduce Type 2 errors (false negatives) in estimating treatment effects. My letter to Martin Richards happened to be sent to him during the same year as the term 'meta-analysis' was introduced by the American social scientist Gene Glass.[100]

The first opportunity that I took to do a systematic review using meta-analysis related to different ways of monitoring babies during labour.[101] Electronic fetal heart rate monitoring had been introduced in obstetrics not long previously, sometimes accompanied by fetal scalp blood sampling to assess fetal acid-base status, particularly if the heart rate trace had raised concerns. It was being suggested by some people that these more intensive methods of intrapartum

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[99] Chalmers (1999).

[100] Glass (1976).

[101] Chalmers (1979).

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).

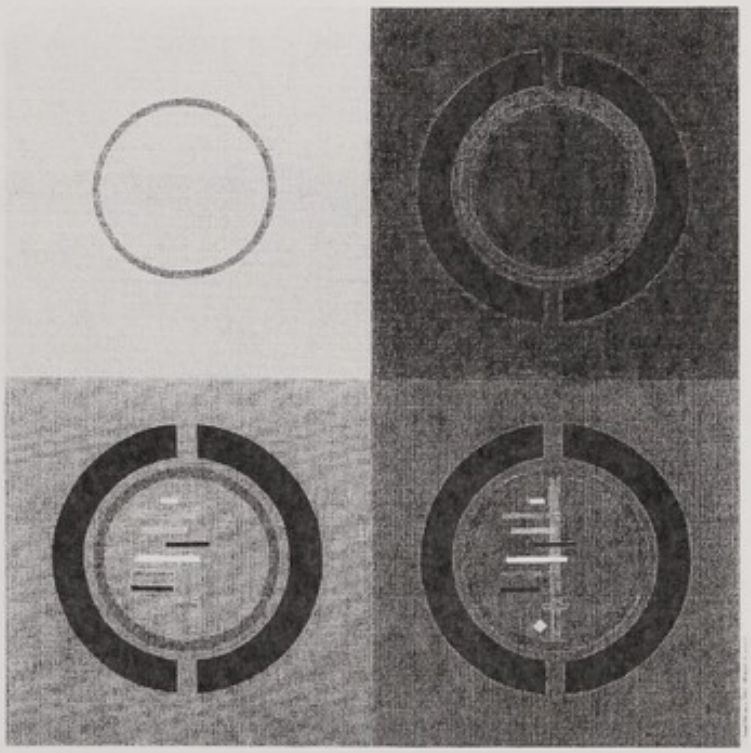
[109] Chalmers (1989–92). The contents subsequently transferred to and maintained in The Cochrane Database of Systematic Reviews, accessible through the Cochrane Library at http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME (visited 2 June 2005).

[110] Peckham (1991).

longer than a few years, I accepted this challenge, and the (UK) Cochrane Centre was opened in 1992.[111]

[Figure 5 here]

[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

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

[116] Chalmers (2000).

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 immenent as to negate any possible benefit; and (c) to whom there were no contra-indications.

The same situation arises in the audit of treatment of people with a heart attack.[128] We know that one of the tenets of good care if you are having a heart attack is that you should be given aspirin and a clot busting drug like streptokinase. Some studies have shown that only 50 per cent of people who had a heart attack received the clot busting drug. But this gives a considerable underestimate of proper care, because the clot busting drug can only be given for a short period of time after the onset of pain (a day or so). Furthermore some people do not have clear evidence of heart 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

[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.

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 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 ess 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 particular 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

[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

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

corticosteroids.[157] 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

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[158] More about patient???

No, because I hope Barbara Stocking will write a Foreword for you!

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?

Enkin M, Keirse MJNC, Chalmers I. A guide to effective care during pregnancy and childbirth. Oxford: Oxford University Press, 1989.

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 Ross 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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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.



www.lindalliance.org

PATRICIA ATKINSON
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Email: patkinson@lindaliance.org

3 November 2005

Mrs Lois Reynolds
Research Assistant
The Wellcome Trust
210 Euston Road
London NW1 2BE

Dear Mrs Reynolds,

Re: ***Transcript of Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth***

Thank you for your letter dated 2 November, I am writing to you on behalf of Sir Iain Chalmers. Iain is overseas at present and will respond to you as soon as he can after his return on the 7 November.

I notice that the date for return of any corrections or comments is TUESDAY 8 NOVEMBER. If this date can be extended for Sir Iain to submit his comments please let me know as soon as possible. I have also left a message for you on your answer machine.

With best wishes

Yours sincerely

P. Atkinson

Patricia Atkinson
Administrator
James Lind Alliance Secretariat

Iooke 3/11/05

OK
whenever he can.

Lois Reynolds

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 06 November 2005 20:18
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: prenatal corticosteroids: Many thanks

I look forward to seeing the report, Lois. Interesting that the Trust continues to be unwilling to defend its views on systematic reviews in public, Lois. I will draw attention to this in a chapter I am preparing for a book to be published by the Lancet next year. Best wishes, Iain

✓ 7/11/05

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 31 October 2005 16:15
To: Iain Chalmers
Subject: Witness Seminar: prenatal corticosteroids: Many thanks

Many thanks, Iain, for all your help. The Trust has decided not to reply in
a footnote to your comment about their funding of RCT, but will reply privately. The text and prelims go to the designer tomorrow, so our flexibility has been curtailed.

Hope all is well with you.
Best wishes from Lois

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine
at UCL
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email: l.reynolds@ucl.ac.uk
Fax: 020 7679 8192
www.ucl.ac.uk/histmed

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charity, no. 210183.

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need ack: 7 NOV 05 correction suggested to EMT, 7/11/05

Lois Reynolds

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 07 November 2005 19:30
To: ucgarey@ucl.ac.uk
Cc: patc@indigo.ie; j.harding@auckland.ac.nz; jneilson@liv.ac.uk; sonjah@liverpool.ac.uk
Subject: RE: Witness Seminar: Prenatal Corticosteroids : updated Cochrane Review

Dear Lois

I think this footnote is important, but I suggest adding an anticipated date of publication for the updated Cochrane Review. I'm copying these messages to the people who should be able to provide this information.

Best wishes, Iain

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 18 October 2005 17:06
To: Iain Chalmers
Subject: RE: Witness Seminar: Prenatal Corticosteroids : Verrier Jones

Thanks, Iain. Dr Verrier Jones has been in touch. Tilli would like your opinion on the footnote on the new Cochrane Review mentioned as the follows. Best wishes from Lois

0-0-0-0

Harding: Yes, there has. 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.(FN 1)

FN1. See, for example: Carlan *et al.* (1991); Garite *et al.* (1992); Kari *et al.* (1994); Botet *et al.* (1994); Lewis *et al.* (1996); Silver *et al.* (1996); Amorim *et al.* (1999); Pattinson *et al.* (1999); Qublan *et al.* (2001) Fekih *et al.* (2002). The new Cochrane Review was not available by December 2005 [will be available in 2006?].

0-0-0-0

>
> Harding: Yes, there has. There have been at least four trials in the
> 1990s and I am sure Dr Crowley will talk about this. But the new
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> Review, which is in the process of being produced, will show clearly
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> and in the four randomized placebo control trials done in the
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> et al. (1994); Botet et al. (1994); Lewis et al. (1996); Silver et al.
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> (2001) Fekih et al. (2002). The new Cochrane Review was not available
by
> December 2005 [will be available in 2006?].
>
> 0-0-0-0

Jim Neilson
Professor of Obstetrics and Gynaecology
Head of School of Reproductive & Developmental Medicine
University of Liverpool
Liverpool Women's Hospital
Crown Street
Liverpool L8 7SS, UK.
Tel: (44) 151 702 4100

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Lois Reynolds

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 07 November 2005 19:51
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: copyright assignment

Chalmers alternative - permission to reproduce

Dear Lois

I never assign exclusive copyright in my work, but I am happy to authorize the Wellcome Trust to publish my contributions to the Witness Seminar, and to report or reproduce them in any form or media including offprints, providing that it is understood that the Trust's right to do so is non-exclusive.

With best wishes

Iain

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 27 October 2005 14:23
To: Iain Chalmers
Subject: Witness Seminar: copyright assignment

Dear Iain,

We would be grateful if you could sign and return the attached copyright assignment form for our files.

I assume that you are away from the office at present, but that you will wish to reply to the Wellcome Trust's defence of their grant system, which I hope to send you on 31 October. The volume goes to be set the following day, and after that very little change in the layout can be made, particularly the footnotes.

Publication is scheduled before Christmas (simultaneously appearing on our website and available for order from Amazon), with complimentary volumes distributed in January. It should be 'live' on Amazon by the third week in December, if anyone has last minute presents.

Many thanks for your help.

Best wishes from Lois

Mrs Lois Reynolds
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Lois Reynolds

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 07 November 2005 20:09
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal steroids

rec'd 8/11/05
acK 8/11/05

Dear Lois

I have looked over the material you sent with your letter of 2 November. It looks very good to me, although - conscious of your deadlines - I must admit that I haven't used a fine-toothed comb.

To respond to your specific queries:

We do use italics when referring to The James Lind Library when we remember to do so, so I would be grateful if you would too. ✓ only in titles, as italics ✓

I would be grateful if you would use the summary of my letter responding to Roger Verrier Jones sent to you in a separate email.

On the page listing Participants, I was uncertain about some of the entries in the subsection entitled 'Among those attending the meeting'. I am fairly certain that neither Richard Beard nor (Sir) Muir Gray attended. ✓

On the last line of text of that page there are two commas before 'Dr Peter Williams'. ✓

Finally, in the title of Appendix I on page 128, it looks as if a space may be needed between 'THE and 'MANAGEMENT'. ✓

I very much look forward to seeing the finished product. Thanks for doing such a good job.

Iain C

-----Original Message-----
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Sent: 07 November 2005 19:51
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Iain

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Lois Reynolds

From: Iain Chalmers [IChalmers@jameslindlibrary.org]
Sent: 05 January 2006 19:40
To: ucgarey@ucl.ac.uk
Cc: c.mitchell@wellcome.ac.uk; t.tansey@ucl.ac.uk
Subject: RE: Wit 25: prenatal corticosteroids

Happy New Year, and well done, Lois. I'm fairly confident I could make use of 50 flyers.

And thank you for your kind words. I enjoyed working with you and your colleagues on this.

It's kind of you to have suggested in the report that I suggested the topic. However, I have a feeling that the initial suggestion was made by Mark Walport. Could you either reassure me that you have the history correct, or explain the oversight to Mark!! He and I may disagree on quite a lot, but the man deserves credit where credit is due!!

With best wishes for 2006.

Iain

-----Original Message-----
From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 05 January 2006 18:24
To: Iain Chalmers
Subject: Wit 25: prenatal corticosteroids

Dear Iain,

We are delighted that corticosteroids went 'live' on the website and on Amazon on 20 December 2005. I have just returned to my desk and hope to send you a copy tomorrow with a quantity of flyers to distribute to those who might not know of its publication. The usual quantity is 20, but more can be added if you wish.

The website address is: www.ucl.ac.uk/histmed following the links to Publications/Wellcome Witnesses.

If you have a list of those who might be particularly interested I would be happy to add them to our flyer distribution list, which will probably be sent out sometime next week.

The New Zealand group have also been warned of publication. It has been a pleasure, and an honour, to work with Liggins and Howie. You have very good ideas.

We are very grateful for your assistance with the volume, many times beyond the call of duty. We hope you had a wonderful Christmas and Happy 2006.

Best wishes from Lois

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Lois Reynolds

From: Dr Tilli Tansey [t.tansey@ucl.ac.uk]
Sent: 06 January 2006 13:11
To: Iain Chalmers; ucgarey
Cc: c.mitchell
Subject: RE: Wit 25: prenatal corticosteroids

dear Iain,

Thank you for your message. We think the volume looks splendid, and hope you think so too. I will bring you a copy, and the flyers, on Tuesday, as I understand we are both dining with Chris and Joyce that evening.

You raise the question about who suggested prenatal corticosteroids as a suitable subject. The suggestion did come from you, when we were talking during the tea break at the 'Short term chemotherapy for TB' Witness Seminar. I believe you had been talking to Mark Walport earlier that day, and so you may be absolutely correct in saying that he had made the suggestion to you, but as far as I am aware, the proposal to us came from you, hence the acknowledgement. If you or Mark feels that this needs correction or amendment, please let me know, as we can probably change the on-line version, and if necessary stick an erratum slip in the hard copy.

If you have any further suggestions re publicity, please do tell us. The on-line version has already had almost 450 hits, which is not bad considering it went on the web on the 22nd December, and there has, as yet, been no publicity for it. Six of our volumes feature in our Centre's top ten (much to the chagrin of most of my colleagues, who dislike this approach), and 'Platelets' has achieved 22,300 hits since the beginning of August - quite astonishing!

Best wishes for 2006,

Yours,

Tilli

Dr Tilli Tansey
Historian of Modern Medical Sciences/Convenor of the History of Twentieth Century Medicine Group
Wellcome Trust Centre for the History of Medicine,
UCL, 210 Euston Rd, LONDON NW1 2BE
tel 020 7679 8124 (sec 8106); fax 020 7679 8193
http://www.ucl.ac.uk/histmed

-----Original Message-----
From: Iain Chalmers [mailto:IChalmers@jameslindlibrary.org]
Sent: 5 January 2006 19:40

To: ucgarey
Cc: c.mitchell; t.tansey
Subject: RE: Wit 25: prenatal corticosteroids

Happy New Year, and well done, Lois. I'm fairly confident I could make use of 50 flyers.

And thank you for your kind words. I enjoyed working with you and your colleagues on this.

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Iain

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