

Correspondence. Surnames, 'Hayward' to 'Howie'

Contributors

The Wellcome Trust Centre for the History of Medicine at UCL

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Fax: +44 (0) 20 7679 8193

19th March 2004

Dear Dr Hayward

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

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

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

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

Continued/... Page 2

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

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

To: john.hayward@newhampct.nhs.uk
Cc: Daphne; Chalmers, Sir Iain
Subject: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth



CORTIhaywardinvitDRAFTcorticoFLYERWHATIS--april2004r
r.doc 190404.doc evdc.DOC

Dear Dr Hayward, Please find attached an invitation to the above meeting. A previous invitation was sent on 19th March to the wrong address. A hard copy letter and attachments will be sent to you in the post today. Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
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21 April 2004

Dear Dr Hayward

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality
associated with preterm birth
Tuesday 30th March 2004 2.00 pm – 6pm

We wrote to you on 19th March, inviting you to attend the above meeting. As we have not had a reply, but have been experiencing difficulties with our post, our original letter, or your reply, may therefore have gone astray. We enclose a copy of that letter and look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

To: gerry.ross@newhampct.nhs.uk
Subject: Prenatal corticosteroid Witness Seminar: 15 June 2004 - flyer & website



DRAFTcorticoFLYER
190404.doc

Please find attached a flyer and details of the website where the flyer is posted. I have also put a further copy in the post for your information. The website address is: www.ucl.ac.uk/histmed
Wendy Kutner

Mrs Wendy Kutner
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27 April 2004

Dear Dr Hayward

**The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality
associated with preterm birth
Tuesday 15th June 2004 2.00 pm – 6pm**

We wrote to you on 21st April, enclosing our original invitation letter to the above meeting, but the date of the meeting on the reminder letter was incorrect. Please note that the date of the meeting is Tuesday 15th June 2004.

Yours sincerely

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey

Wendy Kutner

To: john.hayward@newhampct.nhs.uk
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal Corticosteroids - 15 June 2004



DRAFTcorticoFLYERCORTICOHaywardlt
190404.doc r.doc

Dear Dr Hayward, Further to my conversation with your Secretary Gerry Ross this morning, I attach a copy letter together with a publicity flyer and programme for your information, and very much look forward to seeing you at the meeting tomorrow at the Wellcome Building, 183 Euston Road, London NW1 in Franks II, Mezzanine Floor. We are delighted that you are able to attend the whole meeting, but note that you will need to leave at 5.45pm. You will see that I have copied this e-mail to Sir Iain Chalmers and Dr Hey, so that they are aware of your departure time. Yours sincerely, Wendy Kutner

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29 April 2004

Dr Hayward

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

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

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

Continued/... Page 2

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

From: Hayward John Dr - Director of Public Health [john.hayward@newhampct.nhs.uk]
Sent: 29 April 2004 17:12
To: 'w.kutner'
Cc: Ross Gerry - PA to John Hayward
Subject: RE: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Okay no problem will do my best board members permitting!!

Gerry can you schedule this in after the board on 15 June please with venue details etc
thanks

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

From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 29 April 2004 17:10
To: Hayward John Dr - Director of Public Health
Cc: Daphne; Chalmers, Sir Iain
Subject: RE: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Dear Dr Hayward, I telephoned Sir Iain when I received your reply and read him your e-mail. He is very keen for you to come. You are scheduled to speak at the end of the meeting in the draft programme and your late arrival would be borne in mind if you feel you are able to arrive at the time you mention. Wendy

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

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

From: Hayward John Dr - Director of Public Health [mailto:john.hayward@newhampct.nhs.uk]
Sent: 29 April 2004 16:43
To: 'w.kutner'
Subject: RE: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Could you just check with Iain though whether my arrival so late in the day would really be of value - I did lead a specific project to implement the evidence on steroids in preterm labour and could talk briefly to it if necessary even though it was in 1997!!

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

From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 29 April 2004 16:38
To: Hayward John Dr - Director of Public Health
Cc: Daphne; Chalmers, Sir Iain
Subject: RE: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Dear Dr Hayward, Thank you so much for your swift reply. If you can possibly make it, we would really appreciate your attendance. Wendy Kutner

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From: Hayward John Dr - Director of Public Health
[mailto:john.hayward@newhampct.nhs.uk]
Sent: 29 April 2004 16:19
To: 'w.kutner'
Subject: RE: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Thank you for the invitation.
Unfortunately I have a PCT Board meeting in the afternoon from 2-4.30pm I could try and come along after it but would not get to you till about 5.30 I reckon

So can you let me know if that would serve any useful value to your meeting??

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

From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 29 April 2004 15:58
To: john.hayward
Cc: Daphne; Chalmers, Sir Iain
Subject: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

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Web Site :

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16 June 2004

Dear Dr Hayward

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

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

recd 4/11/05
ack "

Newham **NHS**
Primary Care Trust

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Fax: 020 8271 1349
www.newhampct.nhs.uk

22nd December 2004

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey
215 Euston Road, London,
NW1 2BE,

Dear Dr Christie

Witness Seminar

Thank you for sending me the transcript. I have made a few alterations in the test – see marker.

I enclose a very brief biography and a signed copyright form.

Please do not include me in marketing mailings.

With best wishes,

Yours sincerely



JH Dr John Hayward
Director of Public Health

Corrected 8/6/05 copy of corrected pages sent 8/6/05

Dr John Hayward was a GP for 16 years before re-training in Public Health. In 1994-6 he led the "effective Care Project" in maternity services for Camden and Islington Health Authority. He is currently the Director of Public Health in Newham

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

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

EDITED BY D A CHRISTIE AND E M TANSEY

Participants

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

Dr John Hayward
Dr Edmund Hey (Chair)
Dr Ian Jones
Professor Richard Lilford
Professor Miranda Mugford
Mrs Brenda Mullinger
Professor Ann Oakley
Dr Sam Richmond
Dr Roger Verrier Jones
Professor Dafydd Walters
Mr John Williams

*Died 2004

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, ^{EXTERNAL CEPHALIC VERSION} ~~or L.T. tie~~ 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 *women* ~~people get filtered in~~ actually get given steroids and when. What had never been done before is that they had not done a *prospective* ~~perspective~~ audit, and they had not shared it with the MSLC, and they undertook to do that. So that eventually a *prospective* ~~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 *VICRYL* ~~vitrol~~ for the nurses to use, midwives to use, for repairing the perineum, whereas otherwise only the doctors were given the expensive *VICRYL* ~~vitrol~~, 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, *were* the main barriers for these interventions. Steroids there weren't really

"VICRYL"

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} eruptions, 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 ^{who} had tried to introduce it and told in no uncertain circumstances, they were not to use it because it was dangerous. We had ^{had been} ~~these~~ ^{the following} sorts of discussion. The clinicians would say it's a dangerous procedure, there's no evidence to support its effectiveness, except ~~the~~ ^{we answered that there were trials from} trials that have been published in South Africa. ~~Answer well and~~ Zimbabwe and California, ~~and~~ ^{we would} Denmark, and Holland, and here's the evidence, plonk it on the table, "Oh it doesn't apply to us, ^{they said, our} 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 ^{was the barrier to} ~~was~~ ^{implementation}. I think, apart from power, vested interests, empire building and struggles and political competition between trusts, this ^{was} ~~is~~ the time of ~~the~~ 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} ~~resist~~ ^{resist} on being told to

do something that they don't think ^{was safe} ~~is safe~~ 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 ^{this sort of study} 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 ^{them} ~~it~~ and that means clear inclusion and exclusion
 criteria. Another important agent for change ^{are} ~~are~~ users, and if you have
 women asking these questions, after a while ^{up} 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 ~~at~~ not
 afraid of consultants, ^{so that we could} ~~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

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

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Signed John Hayward Date 21 December 2004

To evaluate the work of the Effective Care Sub-Group of Camden and Islington Maternity Services Liaison Committee (MSLC)

Dr John Hayward

20 February 2001

ReFeR summary

Aim/Principal research question

The Camden & Islington Effective Care Project involved work by a subgroup of the district Maternity Services Liaison Committee (MSLC), investigating the use of four clinical interventions in three maternity units within the district. These interventions were:

The use of steroids prior to likely preterm delivery, Prophylactic antibiotics for caesarean section, Management of perineal repair, External cephalic version for breech presentation at term. The project was externally evaluated over a fifteen month period, the evaluators working alongside the project team from the beginning. The evaluation estimated the performance of the project against its agreed objectives, examined its acceptability to the participants and assessed its external applicability.

Methodology

Evaluation, Interview(s), Observation, Qualitative study over 15 months period, involving non-participant observation and semi-structured interviews with all participants on two occasions. The evaluation explored the different perceptions of members of the MSLC compared with the health professionals in the maternity units regarding the project's objectives, the desirability of similar clinical practices in different units, and the robustness of evidence used to underpin policy. The views of the staff in the maternity units was sought about the research evidence used in the project, and about the relation between the evidence and clinical policy.

Sample groups

Consultants, midwives, audit staff in provider units, members of the Effective Care Sub-Group

Outcome measures

processes and activities; time and resources used; perceptions and attitudes of personnel involved; changes occurring

Findings

Policy became explicit for all 4 interventions in the three units. Of 12 policies, seven were consistent with research evidence and 5 were not. In all cases where unit policy did not reflect the evidence, unit staff felt the differences were justified. In several cases there were substantive differences of view between staff in different units, but no differences were expressed between staff in the same unit. There were three different types of concern about the research evidence:

- 1) concerns about the adequacy or completeness of the evidence;
- 2) concerns about the local applicability of the evidence;
- 3) concerns about local capacity to act on the evidence.

During the evaluation one minor but no major policy changes took place. However, two major changes occurred within nine months following the completion of the external evaluation.

This is an important lesson. Policy changes as a result of this sort of initiative may take longer than anticipated. Although it is likely that these changes took place directly because of the project, (and policies were indeed reviewed because of it) it was not possible to show this conclusively because the evaluation was over.

Other findings included the agreement of a series of clinical audit projects in relation to the four interventions concerned. In one of these it was found that a universal policy (to use antibiotics for caesarean section) was not being reflected in universal practice.

The project had large opportunity costs for all parties.

Conclusions

MSLCs can be appropriate forums for the discussion of clinical policies across several providers, so that differences and the basis for them can become explicit. MSLC terms of reference should capture the issue of clinical effectiveness. This has been reflected in national guidance (1996).

Clinical policy changes can probably be stimulated by such a review process although there is an opportunity cost. (Four interventions in a year is probably over-ambitious).

Clinical audit can be initiated by MSLCs if there is evidence to suggest the topics are a priority for the local maternity service. Brief audits of universal policy should be encouraged as part of routine performance review.

Citation

Hayward J (2001). To evaluate the work of the Effective Care Sub-Group of Camden and Islington Maternity Services Liaison Committee (MSLC). *The Research Findings Register*. Summary number 474. Retrieved 8 June 2005, from <http://www.ReFeR.nhs.uk/ViewRecord.asp?ID=474>

About this summary

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Research programme	NHSE(LRO) - research implementation
Contact (principal investigator)	Dr John Hayward Brent & Harrow HA Grace House Harrovia Business Village, Bessborough Road, Harrow, Middx. HA1 3EX
Document created	20 February 2001
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Mrs Lois Reynolds
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of Medicine at University College London
210 Euston Road
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NW1 2BE

23rd June 2005

Dear Mrs Reynolds,

Witness Seminar: Prenatal Corticosteroids, 15 June 2004

Thank you for sending me the latest version of the transcript of the meeting in June last year. I have gone through it in detail and written any alterations I have made by hand. If you have any difficulty reading my writing please do not hesitate to phone me. I shall next be in the office in Newham on Wednesday 29th June.

Amongst the alterations you will see that I have suggested that most of one paragraph is deleted on page 63. It feels very uncomfortable reading this at a distance and I am sure it should not be there! Otherwise the only alterations I have made are to make the text a little clearer.

I have also given you the full reference of the paper in Quality in Healthcare which was published in 1997, and which related to the Effective Care Project which I described in my witness statement.

Please do not hesitate to contact me if you need any further information or assistance in getting the final version out.

Best wishes,

Yours sincerely,

Dr John Hayward
Consultant in Public Health Medicine

NOTE: Please note that although I am no longer Director of Public Health in Newham, I was until very recently and so my title on the witness documents should remain as it is.

corrected 19/8/05 ✓
Rec'd + ack: 24/6/05

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

Participants

Dr Mary Ellen (Mel) Avery
Sir Christopher Booth
Dr Peter Brocklehurst
Sir Iain Chalmers
Professor Patricia Crowley
Professor John Gabbay
Professor Harold Gamsu¹
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, Ms 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 Robertson, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

¹Died 31 August 2004

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*.³⁴ 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~~ ^{this is} [?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. While speaking to other people in this room today who knew me 40 years ago, one person spoke [??to me??] as a medical student, another as my fellow applicant, who got a job that he hadn't applied for, and I got the job that he applied for. It was bizarre. It's nice to see Sir Christopher Booth here, although I never did work for him. Interestingly, I also worked with Cliff Robertson when he was paediatrician at Hillingdon Hospital, London, and was having difficulty in getting a job.

What strikes me is that during my own career as GP – getting interested in systematic reviews, training in public health, and then returning to public health, a weird career ~~that does a lot of the i's~~ – the same issues keep cropping up. There is always a concern whether we have looked at the subjects right? What will the long-term detrimental effects be? Everybody is actually influenced by some horror that they have come across. And that's perhaps not so much the case for steroids, but it's certainly true if you look at ~~the extent of the~~ ^{the} [?] breech presentation for example. My statement later will be

external cephalic version of

³⁴ 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: e373–7.

Best
remove
completely
please

about how we looked at getting research ^{evidence into practice.} ~~and practice and values to it.~~ 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, 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 now alive 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 reading for students of health economics was published in 1972.³⁵ 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 NPEU, as

³⁵ Cooper M H, Culyer A J. (1973) *Health Economics: Selected readings*. Harmondsworth: Penguin.

stroke after you have given streptokinase,⁵⁸ 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.⁵⁹ The staff at St David's had taken up steroids to a greater extent than the University Hospital of Wales based the Liggins and Howie trial.

Hayward: I wonder whether it might be useful to briefly describe ^{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.⁶⁰ I am Director of Public Health in Newham, but I am here because I was then [in 19xx] a public health specialist in training ~~for~~ ^{at} Camden and Islington Health Authority, ~~and~~ I have also ~~been~~ 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 one of the local pubs that it would be interesting to look

⁵⁸ For a discussion of the streptokinase trials, see Reynolds and Tansey (2005), Appendix 3.

⁵⁹ Jones R V. (xxxx) XXXX

⁶⁰ Suggested reference??

~ Mhau Gifford should have this

at four of those interventions,⁶¹ and to take them around three units, using the MSLC. What ~~would make~~ ^{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 1997.⁶² and 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 is 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~~ ^{is} ~~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 automatically ~~can~~ ^{can} compare ~~other~~ ^{your} information.

What we did was to visit each of the units, asking them to share with us their policies ~~[on these four interventions]~~ ^{section}, giving them an advance of what was ~~then~~ ^{later} going to be ~~called what was~~ the Cochrane library, but in those days ~~the~~ ^{it} was the ~~Cochrane Centre~~ ^{and} had been established ~~and~~ we still referred to ECPC - Effective Care in Pregnancy and Childbirth.⁶³ 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.~~

We took the evidence that was in ~~the actual trials~~ ^{and} ~~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~~ ^{varieties} of those

⁶¹ The four interventions were: the use of steroids prior to likely preterm delivery; prophylactic antibiotics for caesarean section; management of perineal repair; and external cephalic version for breech presentation at term.

⁶² Hayward J. (2001). To evaluate the work of the Effective Care Sub-Group of Camden and Islington Maternity Services Liaison Committee (MSLC). *The Research Findings Register*. Summary number 474. Retrieved 8 June 2005, from <http://www.ReFeR.nhs.uk/ViewRecord.asp?ID=474>.

⁶³ See note 22.

No!
✓

~~Also~~ fully described in this paper:...

Bennett D, Humphrey C, Hayward J. Understanding the relationship between research and clinical policy: a study of clinicians' views. *Quality in Health Care* 1997; 6: 181-6

blobograms from Patricia Crowley's original work.⁶⁴ 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 ~~for~~
~~with~~ [?resolve?] difficult complex issues about ~~the~~ odds ratios[??] or whatever, but we never needed a statistician. 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.

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

⁶⁴ Could we have a copy of the bloobograms?

We ran into less trouble with steroids than we did with the others and I want to say that we did persuade one hospital to introduce vicryl⁶⁵ for the ~~nurses and~~ *widwives* to use to repair the perineum, whereas otherwise only the doctors were given ~~these~~ *these* expensive sutures, never mind the outcomes. That was a dramatic change. One hospital that used antibiotics for caesarean section ~~had~~ *but when* realized, of course, that it's the anaesthetist who tended to give it, ~~and~~ the anaesthetist ~~had~~ audited it, ~~it~~ actually only 60 or 70 per cent of women who should have been getting antibiotics actually did. That was changed. And, the most difficult thing was ECV (external cephalic version), where the baby is presented by the ~~bottom~~ *aw* [breech?], there's an opportunity to turn the baby round *in utero* before labour, provided it is done close to ~~labour~~ *term*, and ~~in~~ *in* a(n operating) theatre ~~is~~ available with consent for an emergency section obtained. You can, if necessary, bail out by doing an emergency section if anything goes wrong.

What we discovered were the main barriers for these interventions. Steroids had few major barriers, just bits of detail. Suture was a misunderstanding about cost and appropriateness. Antibiotics were *[?restricted by lack of an]* audit done by the right people. But ECV was different. The main barrier here was fear of death of baby or mother. I remember as a medical student having seen an ECV done in the antenatal clinic and every so often there would be cord entanglements, or placenta abruptions, haemorrhages and disasters. When we got into the ~~project~~ meetings, one unit was using ECV regularly and felt that everybody should do so. One used it intermittently and the third, rather further away somewhere near Hampstead, was not using it at all, except a few junior doctors who ~~had~~ *had* tried to introduce it and had been told that they were not

⁶⁵ A polyglactic-acid suture. Christine Kettle, a midwife at North Staffordshire NHS Trust, Stoke-on-Trent, conducted a randomised trial comparing suture materials by following up the treatment of 1500 women over 12 months. The trial results showed that *Vicryl Rapide*, a fast-absorbing synthetic thread, was the most effective. Kettle C, Hills R K, Jones P, Darby L, Gray R, Johanson R B. (2002) Continuous versus interrupted perineal repair with standard or rapidly absorbed sutures after spontaneous vaginal birth: a randomized controlled trial. *Lancet* 359: 2217-23. See also Kettle C, Johanson R B. (2000) Absorbable synthetic versus catgut suture material for perineal repair. *Cochrane Database Systematic Review* (2): CD000006.

to use it because it was dangerous. We had the following sorts of discussions: the clinicians would say, 'It's a dangerous procedure, there's no evidence to support its effectiveness, except the trials that have been published in South Africa'. We answered that there were trials from Zimbabwe and California, Denmark, and Holland, and plonk the evidence on the table.⁶⁶ 'Oh, it doesn't apply to us', they said, 'and anyway our women's pelvises are different, ECV is easier in South Africa and doesn't apply to our case mix.' Excuse me, we are in London. But what emerged after this hostility, was actually that they had all experienced a death or near miss, and that was the barrier to implementation.

Apart from power, I think that vested interests, empire building and struggles and political competition between trusts ~~were~~ ^{was} barriers – this ~~is~~ ^{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 ~~they~~ ^{yes} [~~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, and I think it was a painful and difficult process for ~~them~~ [✓] [~~everyone?~~].

May I just mention the main conclusions from this particular piece of work? Don't expect this sort of study to get it into the *British Medical Journal*. It won't ~~happen~~ [✓] [~~be accepted?~~]. Secondly, advocates are really important when it comes to getting guidelines ~~happening~~ [✓] [~~to be 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

⁶⁶ For example???

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 some body – 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 ~~can~~ ^{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: 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

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

Dr Edmund Hey

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

Professor Ross Howie

Dr Ian Jones

Professor Richard Lilford

Professor Sir William Liley

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

Professor Sir Graham (Mont) Liggins

FRCOG FRCS (Edin) PhD (b. 19xx) graduated in medicine at University of Otago in 1949. He was appointed to a personal chair at the Postgraduate School of Obstetrics and Gynaecology, University of Auckland, in 19xx, specializing in Endocrinology and Fetal Physiology. His most important discovery was that the time of birth was controlled by the fetus, not the mother.

Hayward

Thank you

A few minor alterations have
been added

JH

26/8/01



please see pages 58-59, 79-84
and biographical note on pages 114-15

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

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

Edited by L A Reynolds and E M Tansey

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PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

Participants

Dr Mary Ellen (Mel) Avery	Dr John Hayward
Sir Christopher Booth	Dr Edmund Hey (Chair)
Dr Peter Brocklehurst	Dr Ian Jones
Sir Iain Chalmers	Professor Richard Lilford
Dr Patricia Crowley	Professor Miranda Mugford
Professor John Gabbay	Mrs Brenda Mullinger
Professor Harold Gamsu [†]	Professor Ann Oakley
Dr Dino Giussani	Dr Sam Richmond
Mrs Gill Gyte	Dr Roger Vernier Jones
Dr Stephen Hanney	Professor Dafydd Walters
Professor Jane Harding	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 Robertson, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

[†]Died 31 August 2004

Chalmers: The MRC has a working party under the chairmanship of Peter Dukes, which is creating circumstances through which it would be possible for anyone receiving an MRC grant to archive their data.⁹⁰ So biomedicine is catching up with the social scientists.

Dr Dino Giussani: I wanted to draw together some of many comments, in particular one made by Iain Chalmers as to how do we translate evidence that we find in animal studies to the human situation. We haven't talked about many of the more subtle effects of antenatal glucocorticoid therapy that may prove detrimental in the long term to the adult. In the animal, there is overwhelming evidence now accumulated that antenatal steroid therapy, in the doses and dose intervals, used in human clinical practice today, have detrimental effects on the development of the adrenal gland. For example, fetuses that have been treated by steroids have an overreactive adrenal function, which may lead to long-term consequences in adult life. We have not talked about maturational effects on other systems, such as the cardiovascular system. We know that glucocorticoids in fetal life increase blood pressure in a sustained manner, at a time that mechanisms that are going to control the blood pressure of the individual in adult life are being programmed, such as baroreceptors. We have evidence that antenatal glucocorticoid therapy reset the arterial baroreceptors to run or to maintain blood pressure at a greater level. And of course we don't know whether that would lead eventually to detrimental effects. We all agree that glucocorticoids are life-savers, but we have to begin to think as to whether some of these more fine-tuned side-effects may become detrimental in later life.

I was also wondering whether we will talk later about refining some of the dosing of the regimens of glucocorticoid therapy today, in an effort to

the Joint Information Systems Committee (JISC) of the Higher Education Funding Councils and the University of Essex.

⁹⁰ Iain, any update on this?

maintain the beneficial effects, but to 'weed out' the unwanted, adverse side-effects.

Harding: If I can make a very brief comment about that? This is another example of a new question for which the old data already had the answers. The blood pressure of the six-year-old children was recorded, but never analysed and published, and it will be published very shortly in *Paediatrics*.⁹¹ We found the archives in the roof of the hospital, dragged them down, and said, 'Would you mind if we analysed these and published them?' There is no difference in blood pressure at six years or, incidentally, at 30 years, but I think the issue for this conference again is one of new questions to which old data actually has the answer.

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

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

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

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).

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

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 is that ~~X~~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

¹⁴² The four interventions were: use of steroids prior to likely preterm delivery; prophylactic antibiotics for caesarean section; management of perineal repair; and external cephalic version for breech presentation at term.

¹⁴³ Berrow *et al.* (1997).

¹⁴⁴ See note 43.

¹⁴⁵ See Figure 4, page xx.

odds ratios or whatever, but we never needed one. The women understood it instinctively, because blobograms graphically are so striking. You immediately see the effect size, and the size of the wings on the aircraft, as it were, give you an idea of the confidence level, about the precision of the results. They understood that instantly. [See Figure 5]

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

We ran into less trouble with steroids than we did with the others and I want to say that we did persuade one hospital to introduce vicryl for the midwives to repair the perineum, whereas otherwise only the doctors were [??had been??] given these expensive sutures, never mind the outcomes.¹⁴⁶ That was a

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dramatic change. One hospital that used antibiotics for caesarean section had realized, of course, that it's the anaesthetist who tended to give it, but when the anaesthetists had audited it, actually only 60 or 70 per cent of women who should have been getting antibiotics actually did. That was changed. And, the most difficult thing was ECV, where the baby is presented ^{by the} breech, and there's an opportunity to turn the baby round *in utero* before labour, provided it is done close to term, with an operating theatre available and consent for an emergency section obtained. You can, if necessary, bail out by doing an emergency section if anything goes wrong.

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

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

May I just mention the main conclusions from this particular piece of work? Don't expect this sort of study to get it into the *British Medical Journal*. It won't be accepted. Secondly, advocates are really important when it comes to getting guidelines adopted and I think opinion leaders are really important within institutions, but the important thing is that the guidelines have got to be written in such a way to be usable, understandable and accessible to those who are going to implement them. That means clear inclusion and exclusion criteria. Another important agent for change are the users, and if you have women asking these sorts of questions, after a while people do get a bit embarrassed coming up with the same answers that clearly won't be supported by evidence or by colleagues. I would like to see women users being far more involved in ways in which we can encourage the implementation of best practice. I am not surprised that there was no sign of managers actually implementing any change in Richard's study. It's a scary business. There was blood all over the carpet when we were dealing with the ECV meetings, and it required somebody – like the users who were tough, or somebody like me who's a public health specialist and who has been a GP and is not afraid of consultants – to hold the line if necessary. Managers cannot do that, and I don't think we should expect them to. I think it's exceedingly difficult. The

most important barrier, the most important influence to achieve change, is the personal experience of the person making the clinical decision. When new interventions are being rolled out we must encourage people to be at the centre of it, so they get feedback of the positive results. Then it is much easier to get change implemented.

Hey: That rings true for a lot of us, I think. You went over time, but I think you said something very important. We are beginning to get very tight for time and so I am going to ask Stephen Hanney to speak next. But Harold [Gamsu], while you were out of the room we did hear that quite a lot of units said that they couldn't join your trial, because they were already using it so widely and that occurred at the time when in actual fact we know that less than 6 per cent were really using steroids nationally. Did being involved in the trials themselves influence the centres? Did the centres that had been involved in the research take up the outcome of that research more than those who only read about it?

Gamsu: I don't know the answer to that I am afraid. We didn't follow that point up, but as far as I know Brenda Mullinger might know something about it. All I can say is that there were local reasons that indicated against the use of steroids. There was quite a lot of gossip about this and we have heard some examples of this today. The risk of infection especially in ruptured membranes, and the unexplained deaths in hypertensive women from Liggins's original report which turned out to be spurious.

The other thing that I found was influencing obstetricians was the increased risk of pulmonary oedema which people widely accepted as a complication of steroid therapy. In fact it was a complication of tocolytic agents that were used, especially when those agents were given in large volumes of fluid. As far as I know, steroids given alone were not tocolytic agents and did not result in pulmonary oedema. So I think we had quite a lot of persuading to do even in

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 Development at 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.

2005 He was Director of Public Health in Newham, London, from 2002 until 200x. See Hayward (2001).

Dr Edmund Hey

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

Professor Ross Howie

Mr Ian Jones

(b. 1945) has been Publisher at the Wellcome Trust since 19xx.

Dr William ('Bill') Henry Kitchen

AM, MD BS FRACP FRACOG (b.1926) trained at the University of Melbourne Medical School who joined the Children's Hospital in 1953 as a Junior Resident and the following year was Research Registrar for a year under Drs Howard Williams and Charlo Anderson. Until 1965 he combined work as an Outpatient Physician at the Hospital with a private paediatric practice. In 1965 he was appointed to a

full-time position as First Assistant (equivalent to Associate Professor) in both the University of Melbourne Department of Paediatrics and the Department of Obstetrics and Gynaecology, continuing in this post until 1991. See www.cshs.unimelb.edu.au/programs/jnmhu/witness/references1.html (visited 2 August 2005).

Professor Sir William Liley

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

Professor Sir Graham (Mont) Liggins

FRCOG FRCS (Edin) PhD (b. 19xx) graduated in medicine at University of Otago in 1949. He was appointed to a personal chair at the Postgraduate School of Obstetrics and Gynaecology,

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

Professor Richard Lilford

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

Professor Miranda Mugford

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

incorporated into economic evaluation techniques. See Macfarlane and Mugford (1984).

Mrs Brenda Mullinger

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

Professor Colin Normand

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

Professor Ann Oakley

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

Lois Reynolds

From: Hayward John Dr - Consultant in Public Health Medicine
[john.hayward@newhampct.nhs.uk]
Sent: 21 October 2005 11:26
To: 'ucgarey@ucl.ac.uk'
Subject: RE: Witness Seminar: Corticosteroids: Last query

It was rejected by BMJ (submitted as a short report) and not submitted to the Lancet. It was accepted in a longer version by Quality in Health Care and you have the citation I think

Dr John Hayward
Consultant in Public Health Medicine
Francis House
760-2 Barking Rd, Plaistow
London E13 9PJ

020 8271 1376
mobile: 07930 395795
john.hayward@newhampct.nhs.uk

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

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 20 October 2005 16:30
To: Hayward John Dr - Consultant in Public Health Medicine
Subject: Witness Seminar: Corticosteroids: Last query

Dear Dr Hayward,

We would be glad if you could say whether your research study was submitted to the BMJ or the Lancet, and if it was then rejected -- in one or two sentences for a footnote.

Best wishes from Lois

0-0-0-0

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

0-0-0-0

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

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Dr Joe Herbert
Cambridge University
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Downing Street
Cambridge CB2 3DY

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Fax: +44 (0) 20 7679 8193

24 March 2004

Dear Dr Herbert

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

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

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

We have drawn up a list of possible participants, including clinicians and representatives from relevant organisations, and would like to include physiologists/endocrinologists from the 1960s and early 70s. Sir Graham Liggins is unable to attend but we hope to have Marc Keirse to introduce his work. I am therefore writing to ask if you might be able to help with names of scientists, particularly those who were involved in the work on sheep during the 1960s.

I do hope you will be able to help.

I look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

Dr Edmund Hey
51 Alwinton Terrace
Newcastle-upon-Tyne NE3 1UD

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

18 February 2004

Dear Dr Hey

History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality
associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is beginning to organise a Witness Seminar on Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth, to take place on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Sir Iain Chalmers is assisting us in the organisation. We would like to invite you to chair this meeting.

As you know, these seminars address issues of medical-historical interest in the latter half of the twentieth century, focusing on British contributions. We invite witnesses of particular events or developments to reminisce, discuss and debate between themselves, in a chairman-led meeting and with an audience of historians, scientists, clinicians and others, most of whom also contribute with questions, comments and their own reminiscences. The proceedings are recorded, transcribed and prepared for possible publication. Throughout we address questions such as "What was it like at the time?", "Why did things happen the way they did?" This is a particularly fruitful way of generating interest in, and providing material sources for, the study of significant events in recent medical history.

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey



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

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20 February 2004

Dear Dr Hey

History of Twentieth Century Medicine Group

Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Tuesday 15th June 2004

2.00 pm – 6pm

The Wellcome Trust Centre's History of Twentieth Century Medicine Group is beginning to organise a Witness Seminar on Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth, to take place on Tuesday 15th June 2004, from 2.00pm – 6.00pm, in The Wellcome Building, 183 Euston Road, London NW1. Sir Iain Chalmers is assisting us in the organisation. We would like to invite you to chair this meeting.

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

recd 24.2.04

reply ✓ 25/2/04
copy + send to ✓
Saini Chalmers.
25/2/04

51 Alwinton Terrace,
Newcastle upon Tyne,
NE3 1UD

22nd February 2004

Dear Dr Christie,

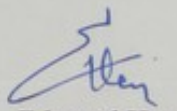
Thank you for your letter of February 20th asking me to chair the proposed witness seminar on June 15. I find it a somewhat daunting prospect but, with Sir Iain to keep me on the rails, I trust I will acquit myself of this task without making a complete fool of myself. I do vividly recall the ferment of activity and interest there was at the time over how the mammalian lung developed *in utero*, what damaged, controlled, or facilitated surfactant production, and what other hormonal influences prepared the lung to work without a hitch from the moment of delivery.

Quite a lot of the animal work was done 'down under' (where sheep seemed to be two a penny) or in America (where research budgets were deeper than those available to research scientists in the UK) but I do recall the work the late Leonard Strang and his team did on this at UCH, especially on the way the lung cleared itself of pulmonary fluid within minutes of birth.

However on this occasion I guess the main aim will be to show just how fruitful the liaison between the clinician and the research scientist was during that uniquely fruitful decade, and to trace all the struggles that ensued before clinicians finally came to accept that this was, for once, a real clinical break-through. There is a lot for today's clinicians to learn by hearing this story retold

I was not part of any of this, but I did have a ring-side seat as the story unfolded, and will enjoy facilitating its re-telling.

Your sincerely,


Edmund Hey

Dr Daphne Christie

From: Dr Daphne Christie [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

✓
25/2/04

Dr Daphne Christie
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25 February 2004

Dear Dr Hey

History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality
associated with preterm birth
Tuesday 15 June 2004, 2.00–6.00pm

I am delighted that you are able to accept our invitation to chair the above Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' to be held at 2.00 pm on Tuesday 15 June. I have sent a copy of your reply to Sir Iain.

I will keep you regularly informed of our progress and will be in touch to formulate a programme in due course. Please let me know of names of possible main witnesses you feel should be invited.

I look forward to working with you on this project. I am sure it will make an excellent witness seminar.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 10 March 2004 09:23
To: w.kutner
Subject: FW: Witness seminar on prenatal corticosteroids

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

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

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 Robertson was based in Cambridge, not Cardiff, and has now retired to the Isle of Skye. Jonathan Wigglesworth worked at the 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 meagerly funded trial looking at the effect of giving betamethasone antenatally to mothers having 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. Better check with Peter 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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Virus scanned by edNET.

Wendy Kutner

To: Edmund Hey
Cc: Daphne Christie
Subject: Witness Seminar - Prenatal corticosteroids - 15 June 2004



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hk.doc

Dear Dr Hey, Plans for the meeting are proceeding well.

I attach a draft attendance list for the above meeting with replies received to date.

Our list includes clinicians and representatives from relevant organisations. We would like to include endocrinologists and physiologists from the 1960s and early 70s, particularly those who were involved in the work of sheep during that period. We would be grateful if you could suggest some scientists we could approach.

I also attach a revised draft flyer for your information. We would be happy to incorporate any changes you might like to make. We will be in touch again soon.
Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
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Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 09:43
To: Edmund Hey
Cc: Wendy
Subject: RE: Wellcome meeting on June 15

Dear Dr Hey

Thank you for your suggestion. We will send an invitation to Peter Stutchfield and let you know his reply. Best wishes, Daphne.

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 11 April 2004 13:58
To: d.christie
Cc: Iain Chalmers
Subject: Wellcome meeting on June 15

Iain Chalmers is suggesting that I should be passing comments regarding the organisation of this meeting direct to you rather than through him. Can I reinforce his suggestion therefore that Peter Stutchfield from Glan Clwyd Hospital in Rhyl should be invited to the meeting to bring the story up to date. It is still widely believed that antenatal steroids only work for certain babies (and it is often held that they only work for babies of 24-34 weeks gestation). Peter can more usefully than anyone else speak to this misconception. Given that, unlike many of the other potential witnesses currently being discussed, he only lives 150 miles from London, I am sure you can afford to issue him an invitation.

E Hey

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

From: Iain Chalmers
To: Edmund Hey
Cc: Patricia Crowley (E-mail) ; James P Neilson (E-mail) ; Peter Brocklehurst (E-mail) ; John Sinclair ; Daphne Christie (E-mail)
Sent: 11 April 2004 12:01
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 latest issue 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 tapering of that dose over a further 21 days.

E

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Virus scanned by edNET.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 09:44
To: Wendy
Subject: FW: Wellcome meeting, 15 June
Follow Up Flag: Follow up
Flag Status: Flagged

I don't think I have 'Iain's latest comment'? do you? thanks, Daphne

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 14 April 2004 09:43
To: Iain Chalmers; Stuart Dalziel
Cc: Daphne Christie (E-mail)
Subject: Re: Wellcome meeting, 15 June

Stuart,

I can only second Iain's latest comment. It would make all the difference to the planned Wellcome Witness Seminar to have at least one of you over from New Zealand to speak to these latest developments in the flesh and also act as a spokesperson and witness on Mont's behalf.

I might even be able to find at least half of one return air fare if that made it possible for someone to be actually present in London on June 15th do speak to the origins of this study, stress how it had a paediatric as well an obstetric content from the outset, and say just a little about these latest impressive follow up findings - not just what you found but how you managed to do it - irrespective of what you found.

It is critically important not to let this valuable and illuminating story get lost in the sands of unrecorded history as so much is nowadays.

Edmund

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 09:59
To: Wendy
Subject: FW: Wellcome Meeting

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 15 April 2004 08:12
To: Jane Harding
Subject: Re: Wellcome Meeting

Jane,

I will get Daphne Christie, who runs the Witness Seminar meetings for the Wellcome Trust Centre for the History of Medicine in London, to contact you just as soon as she is back from her Easter break. These informal meetings provide a vehicle for capturing and securing for posterity some of the oral history surrounding seminal medical advances in the 20th century. Iain Chalmers suggested to them that the seminal trial by Liggins and Howie was one such event that needed to be captured and they took up the suggestion enthusiastically. Mont feels he is now too frail to travel, but it would make all the difference to have someone present who can speak from first hand knowledge about the work of these two pioneers and an even greater bonus for one of you to be able to update everyone on the latest chapter of that story.

Edmund

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 10:21
To: Edmund Hey
Cc: Wendy
Subject: RE: Wellcome Meeting

Dear Dr Hey

We sent an invitation to Peter Stutchfield on 31 March and as far as I am aware we haven't received a reply. However, I have been away on leave until this morning so will check through my correspondence and e-mails and let you know as soon as I have any news.

I will contact both Jane Harding and Stuart Dalziel, as you suggest. We can offer accommodation for the night of the meeting and and some help towards one return air fare might just do the trick. Are you able to give me a figure on how much this might be?

Best wishes,
Daphne Christie

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 15 April 2004 08:03
To: Daphne Christie (E-mail)
Subject: Fw: Wellcome Meeting

Daphnie,

This is an EXTREMELY important development. To have Jane Harding and/or one of the other members of the team who are working on the long term follow up of the patients from the seminal Liggins and Howies trial that was the trigger for Iain's suggestion that you should have a witness seminar on this subject actually come to the meeting would mean that we now have the potential to capture a huge trench of oral history that is otherwise likely to be soon lost for ever.

Please contact both Jane Harding and Stuart Dalziel as soon as you get back to the Office, explain what the Witness Seminar is all about, and extend a three line whip for at least one person to come across from New Zealand. I might even find some money towards one return air fare if we can secure the attendance of at least one person from this group at the meeting on June 15th.

I hope you also got my message about the importance of getting Peter Stutchfield from Wales along too and that you will fire this invitation off too just as soon as you get back if you have not already done so.

Edmund

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

From: Jane Harding
To: 'shey@easynet.co.uk'; 'ichalmers@jameslindlibrary.org'
Cc: 'd.christie@ucl.ac.uk'; Stuart Dalziel
Sent: 14 April 2004 23:13
Subject: Wellcome Meeting

Dear Iain and Ed,

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

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

be tempted by the opportunity to 'represent' in some way how the original study happened and all the subsequent ramifications, but you will understand that travel from NZ to UK is tedious and expensive and we will need to think further about it once we have some more information. Even a small financial contribution is also likely to help!

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

Best wishes

Jane

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

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 10:26
To: Wendy
Subject: FW: Wellcome Meeting

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 15 April 2004 08:03
To: Daphne Christie (E-mail)
Subject: Fw: Wellcome Meeting

Daphnie,

This is an EXTREMELY important development. To have Jane Harding and/or one of the other members of the team who are working on the long term follow up of the patients from the seminal Liggins and Howies trial that was the trigger for Iain's suggestion that you should have a witness seminar on this subject actually come to the meeting would mean that we now have the potential to capture a huge trench of oral history that is otherwise likely to be soon lost for ever.

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I shall look forward to hearing more about the seminar. I do hope we will be able to

make some arrangements for a 'down under' contingent to be present.

Best wishes

Jane

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

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 16 April 2004 12:29
To: Wendy
Subject: FW: Wellcome meeting on June 15

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 11 April 2004 13:58
To: d.christie
Cc: Iain Chalmers
Subject: Wellcome meeting on June 15

Iain Chalmers is suggesting that I should be passing comments regarding the organisation of this meeting direct to you rather than through him. Can I reinforce the suggestion therefore that Peter Stutchfield from Glan Clwyd Hospital in Rhyl should be invited to the meeting to bring the story up to date. It is still widely believed that antenatal steroids only work for certain babies (and it is often help that they only work for babies of 24-34 weeks gestation. Peter can more usefully than anyone else speak to this misconception. Given that, unlike many of the other potential witnesses currently being discussed, he only lives 150 miles from London, I am sure you can afford to issue him an invitation.

E Hey

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

From: Iain Chalmers
To: Edmund Hey
Cc: Patricia Crowley (E-mail) ; James P Neilson (E-mail) ; Peter Brocklehurst (E-mail) ; John Sinclair ; Daphne Christie (E-mail)
Sent: 11 April 2004 12:01
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 latest issue 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 tapering of that dose over a further 21 days.

E

--
Virus scanned by edNET.

Cc: Daphne Christie (E-mail)
Subject: Re: Mont Liggins JY Simpson Lecture
Importance: High

Dear Tilly and/or Daphne

I am sure it would be good to have a short extract of Mont speaking in person at the Witness Seminar meeting in June. I do hope you can arrange this. Who is going to be asked to select the most appropriate extract?

I am even more exercised, however, about making sure we get a representative over from New Zealand who can speak in person on Mont's behalf and also update everyone as to the latest spin-offs and follow up findings from this pivotal study. I shall hope to hear that you have managed to get in contact with both Jane Harding and Stuart Dalziel and that at least one of them can be persuaded to come over for the seminar. It would enhance the whole occasion considerably.

On a related point I gather that although we originally invited Mont nobody ever thought to invite his Paediatric co-author Dr RN Howie. The study was a very real partnership between the two of them and the paediatric element has often been underplayed. I do hope we can make it clear that when Dr Harding and/or Dr Dalziel come over we will be hoping that they can bring with them some of the thoughts and reminiscences of *both* these two illustrious pioneers.

You sent me a brief list of those who had and had not yet responded to the invitations you sent out several weeks ago now. Do you think you could send me an update of that list so I can see how things now stand?

I have just spoken to Dr Sam Richmond and found that he has not yet responded. Now he knows rather more about what it is all about, he is very pleased to accept the invitation and will be replying to you in the next couple of days. I am equally keen to know whether Peter Stutchfield feels able to come. If you have not yet had a reply from him it might be sensible for me to contact him myself.

Edmund Hey

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 20 April 2004 08:45
To: Wendy
Subject: FW: Mont Liggins JY Simpson Lecture
Importance: High

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 19 April 2004 18:29
To: ucgatlt; Iain Chalmers
Cc: Daphne Christie (E-mail)
Subject: Re: Mont Liggins JY Simpson Lecture
Importance: High

Dear Tilly and/or Daphne

I am sure it would be good to have a short extract of Mont speaking in person at the Witness Seminar meeting in June. I do hope you can arrange this. Who is going to be asked to select the most appropriate extract?

I am even more exercised, however, about making sure we get a representative over from New Zealand who can speak in person on Mont's behalf and also update everyone as to the latest spin-offs and follow up findings from this pivotal study. I shall hope to hear that you have managed to get in contact with both Jane Harding and Stuart Dalziel and that at least one of them can be persuaded to come over for the seminar. It would enhance the whole occasion considerably.

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Edmund Hey

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 20 April 2004 11:59
To: Wendy
Subject: FW: Mont Liggins JY Simpson Lecture
Importance: High

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

From: Dr Tilli Tansey [mailto:ucgatlt@ucl.ac.uk]
Sent: 20 April 2004 11:54
To: Edmund Hey; Iain Chalmers
Cc: Daphne Christie (E-mail)
Subject: RE: Mont Liggins JY Simpson Lecture

Dear Dr Hey,

My colleague Daphne Christie is in charge of the arrangements for this meeting, and I hope she is consulting with you about progress so far - obviously with Easter holidays there have been some delays, and Daphne herself is only just back from vacation, but she will be in touch. I need to listen to the tapes to assess their quality, and speak with the AV technicians about reproducing a segment - I will then ask Daphne to consult with you and Iain about what, if any, sections to reproduce. Experience has taught us that presenting large chunks of material from absent participants is not particularly effective, so we must consider the tape, and its use, carefully when we have all heard it.

As far as a NZ representative is concerned, I'm not desperately worried that this will be too serious a lacuna, considering the rest of the cast assembled - we are not aiming to provide THE history of the work, its developments and impact, but a variety of historical voices and perspectives that will contribute to such a history. Sometimes it actually works well if the major figure in a field is absent - e.g. we did 'Endogenous Opiates' without Hans Kosterlitz. Each meeting generates its own dynamic, and I am confident that this meeting can make a useful contribution to the historical literature at the very least.

I'm afraid that as far as I know, this is the first time someone has suggested that Dr Howie be invited! We ask everyone associated with the meeting and all the invitees to suggest further contributors, but I don't think anyone has mentioned his name yet. I therefore assumed he was dead. Do you have contact details for him? If so, perhaps you could pass them to Daphne and she can follow up the suggestion.

I'm looking forward to meeting you again at the seminar, or probably beforehand to discuss the proceedings.

best wishes, tilli tansey

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: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 19 April 2004 18:29
To: ucgatlt; Iain Chalmers

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 21 April 2004 09:47
To: Edmund Hey
Cc: Wendy
Subject: RE: Mont Liggins JY Simpson Lecture

Dear Dr Hey

I asked Wendy to send you an up-to-date list of those who had and had not yet responded to the invitations we sent out several weeks ago now. Today we intend to send follow up letters to those people who have not replied and to send a publicity flyer to everyone on the list. We have room capacity for up to 55 people.

We have sent letters to Jane Harding and Stuart Dalziel and will let you know as soon as we have a response.

We will also work on the programme and send you a draft copy for comments.

With best wishes

Daphne Christie

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 20 April 2004 15:48
To: ucgatlt; Iain Chalmers
Cc: Daphne Christie (E-mail)
Subject: Re: Mont Liggins JY Simpson Lecture

Dear Tilly,

I will await Daphne's response once she has got through the other things waiting in her in-tray. For the record

[1] I was not suggesting that it would be appropriate to have more than a minute or so of Mont's recorded lecture.

[2] I am not even sure myself whether Dr Howie is still alive - my concern is merely not to commit the *faux pas* of addressing our only invitation to Mont and just assuming that Dr Howie is dead. I am sure Jane Harding will be able to clear this all up very quickly for us.

Edmund

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 21 April 2004 12:53
To: Edmund Hey
Cc: Wendy
Subject: RE: Meeting on June 15

Dear Dr Hey

Thank you for your e-mail. Indeed it would be great if Jane Harding and/or Stuart Dalziel attend. They should have both received the invitation by fax (we also sent a copy by post). I will let you know as soon as we get a response.

We will send an invitation asap to Howie when we have a contact address. Thank you for finding out the information and apologies for not having him on our list in the first place.

It would be good to find someone who might speak about Peter Stutchfield's work. I'll wait to hear from you and in the meantime may do a little research myself.

With best wishes

Daphne Christie

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 21 April 2004 12:06
To: Daphne Christie (E-mail)
Subject: Meeting on June 15

Thank you for the latest message. I did get the updated invitation/attendance list late yesterday. I was also in contact with Jane Harding overnight. She had not, at that time, seen the fax your people were said to have sent but she implied that she (and/or Stuart Dalziel) would very much like to attend. If we can secure their attendance it will add immeasurably to the value of the whole meeting.

More importantly a little fishing on my part elicited the information that Ross Howie is still alive (although rather frail). It was something of a faux pas on the part of Iain and myself that although we originally invited Mont Liggins we never sent Ross an invitation. I am told that he would almost certainly turn it down if asked (especially if he could be assured that Jane Harding will be attending and will be in a position to relay on his reminiscences of what happened thirty years ago now) but I am told any such invitation would give him great pleasure. I am sure, in the circumstances, it would be extremely remiss of us not to extend him an invitation. I will extract an address for you that could be used to send out something in the next 48 hours.

On a related matter I note that Peter Stutchfield (from Wales) says he will not be able to attend. I was also in contact with him overnight to say that (although it was not for me to say who could and could not come to the June meeting) I did just wonder if there was not some collaborator who could speak up in his absence and tell everyone something about the trial he has just completed and how it came to get done against, I suspect, quite formidable odds. I hope that is OK by you.

Edmund Hey

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

From: Dr Daphne Christie
To: Edmund Hey
Cc: Wendy
Sent: 21 April 2004 09:46
Subject: RE: Mont Liggins JY Simpson Lecture

Dear Dr Hey

I asked Wendy to send you an up-to-date list of those who had and had not yet responded to the invitations we sent out several weeks ago now. Today we intend to send follow up letters to those people who have not replied and to send a publicity flyer to everyone on the list. We have room

capacity for up to 55 people.

We have sent letters to Jane Harding and Stuart Dalziel and will let you know as soon as we have a response.

We will also work on the programme and send you a draft copy for comments.

With best wishes

Daphne Christie

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

From: Edmund Hey [mailto:shey@easynet.co.uk]

Sent: 20 April 2004 15:48

To: ucgatlt; Iain Chalmers

Cc: Daphne Christie (E-mail)

Subject: Re: Mont Liggins JY Simpson Lecture

Dear Tilly,

I will await Daphne's response once she has got through the other things waiting in her in-tray. For the record

[1] I was not suggesting that it would be appropriate to have more than a minute or so of Mont's recorded lecture.

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Edmund

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 22 April 2004 09:00
To: Edmund Hey
Cc: Wendy
Subject: RE: June 15th
Importance: High

Dear Edmund

Thank you for this. The letter to Howie will go out this morning.

I'm sorry that the fax hasn't reached Jane Harding. We will resend this morning.

Best wishes

Daphne

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 22 April 2004 08:48
To: Daphne Christie (E-mail)
Cc: Iain Chalmers
Subject: Fw: June 15th

Daphne

Here is Ross Howie's address as promised. I also have independent confirmation from Iain (who spoke to Mont) that this is where Ross has recently moved. I leave you to draft an appropriate letter indicating how good it would be to have him present but accepting that he may well prefer to ask Jane to speak for him given the short notice and the distances involved..

Please note also that the Fax you sent on Tuesday does not seem to have found Jane Harding yet.

Edmund

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

From: Jane Harding
To: 'Edmund Hey'
Sent: 21 April 2004 22:20
Subject: RE: June 15th

Dear Ed,

Ross Howie's address is:
2 Matata St
Blockhouse Bay
Auckland
Ph 828 5543
E-Mail h.r.howie@xtra.co.nz

I'm afraid I don't have a fax number for him. Nor has a fax about the meeting has reached me at the number below (best) or any other I frequent, so I shall await the 'snail mail' unless you have opportunity to get it resent.

Best wishes

Jane

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



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

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www.ucl.ac.uk/histmed • +44 (0) 20 7679 8100



Dr Edmund Hey
51 Alwinton Terrace
Newcastle-upon-Tyne
NE3 1UD

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

26 April 2004

Dear Dr Hey

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

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

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

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

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

Yours sincerely

pp Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

Wendy Kutner

To: Edmund Hey
Cc: Tilli; Daphne; Chalmers, Sir Iain
Subject: Witness Seminar: Prenatal corticosteroids - 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.

I would be grateful if you could please send me a contact address for Dr Howie, so we can send him an invitation.

Thank you

Wendy

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

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

Wendy Kutner

To: Edmund Hey

Subject: RE: Witness Seminar: 15th June 2004 - Prenatal corticosteroids

Dear Dr Hey, Thank you for your e-mail. We do not show slides or overheads at the meetings, as we wish to encourage informal interchange and conversation. If however, participants would like any material to be available to the audience, we could photocopy a diagram or article, and leave a copy on every chair. 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: Edmund Hey [mailto:shey@easynet.co.uk]

Sent: 28 April 2004 10:20

To: w.kutner

Cc: Iain Chalmers; Daphne

Subject: Re: Witness Seminar: 15th June 2004 - Prenatal corticosteroids

Thank you for sending me the updated list. We certainly have the key quorum needed for a valuable session now as long as we get Stuart and/or Jane from New Zealand, but I will continue to cast around to see if we can get a few more people along. I am, in particular, still keen to get someone to speak about the outcome of the recently completed Astecs trial.

Can you please tell me what people should do if they want to make a short illustrated point during this meeting. Do they come with a reprint, a paper hand out, a 2 x 2 slide, or powerpoint or what? Please enlighten me.

E

Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 29 April 2004 14:44
To: 'w.kutner@ucl.ac.uk'
Cc: Daphne; Edmund Hey
Subject: RE: Witness Seminar: 15th June 2004 - Prenatal corticosteroids

Dear Wendy

Here are contact details for the three people who may not have received your initial invitation.

Best wishes, Iain

Dr Nicholas Hicks
Director of Public Health
Milton Keynes, Primary Care Trust
Hospital Campus, Standing Way
Eaglestone
Milton Keynes
MK6 5NG

nicholas.hicks@mkpct.nhs.uk
sue.gardiner@mkpct.nhs.uk

Dr John Hayward
Director of Public Health
Newham Primary Care Trust
Directorate of Public Health
3rd Floor Francis House
760 - 762 Barking Road
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Tel. 020 8271 1376
Fax. 020 8271 1349
john.hayward@newhampct.nhs.uk

Dr Alison Hill
Director, Public Health Resource Unit
Institute of Health Sciences,
Old Road,
Headington,
Oxford
OX3 7LF
Tel. 227096
Fax. 226959
alison.hill@phru.nhs.uk

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

From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: 27 April 2004 13:01
To: Edmund Hey; Chalmers, Sir Iain
Cc: Daphne
Subject: Witness Seminar: 15th June 2004 - Prenatal corticosteroids

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
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

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Virus scanned by edNET.

Wendy Kutner

From: Edmund Hey [shey@easynet.co.uk]
Sent: 05 May 2004 15:46
To: d.christie; Iain Chalmers
Cc: Wendy
Subject: Re: prenatal corticosteroids witness seminar 15 june 2004

I agree with Iain. Your suggested programme is fine, but it would be much improved if we could find enough room to let Jane Harding speak first. We would want her presentation, however brief, to include a clear description of how the work by Liggins and Howie came to be done as well as a brief description of the 30 year follow up study that she is herself now mounting. If she could come armed with a brief recorded message from one or both of the people whose work forms the core reason for our meeting that would be an even more welcome bonus.

It is obviously going to be important for Jane and Mel to confer before the meeting, if Jane does finally agree to come; so that they cover all the key events between them while trying not to go over the same ground twice.

E

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 05 May 2004 16:26
To: Edmund Hey
Cc: Wendy
Subject: RE: prenatal corticosteroids witness seminar 15 june 2004

Thanks. I'll follow this up as you suggest and let you know as soon as I have news. Daphne

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

From: Edmund Hey [mailto:shay@easynet.co.uk]
Sent: 05 May 2004 15:46
To: d.christie; Iain Chalmers
Cc: Wendy
Subject: Re: prenatal corticosteroids witness seminar 15 june 2004

I agree with Iain. Your suggested programme is fine, but it would be much improved if we could find enough room to let Jane Harding speak first. We would want her presentation, however brief, to include a clear description of how the work by Liggins and Howie came to be done as well as a brief description of the 30 year follow up study that she is herself now mounting. If she could come armed with a brief recorded message from one or both of the people whose work forms the core reason for our meeting that would be an even more welcome bonus.

It is obviously going to be important for Jane and Mel to confer before the meeting, if Jane does finally agree to come, so that they cover all the key events between them while trying not to go over the same ground twice.

E

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 18 May 2004 08:50
To: Tilli Tansey
Cc: Wendy
Subject: FW: Wellcome Meeting

shall we offer lunch before the meeting? thanks, daphne

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 14 May 2004 23:12
To: d.christie
Cc: Iain Chalmers
Subject: Re: Wellcome Meeting

Thank you for the e-mail news that you have been able to offer Professor Jane Harding something towards accomodation and the air fare. It will make a huge difference to have her at the Seminar.

Thank you also for the letter inviting me to supper at a local restaurant after the meeting is over. Sadly I really will have to decline this. I had had a holiday booked in the south of France with close family friends for some time before any thought of this Witness Seminar ever came up, and I have had to arrange to fly back into Heathrow early that morning and back out again at 8 pm the same evening in order to attend since I did not want to cancel the holiday altogether just to make the meeting.

However I *do* think it is very important that we should do something to show our gratitude to Jane Harding and to Mary Ellen Avery for travelling half way round the world merely to make this half day meeting, and I had wondered if it would not be possible for you and Iain Chalmers to set up something for both of them. If it were possible to hold this before the meeting I would even be able to attend myself since the only available flight from Lyon airport gets me into Heathrow quite early in the morning.

Edmund Hey

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 19 May 2004 14:52
To: Edmund Hey
Cc: Wendy
Subject: RE: Meeting on June 15

Dear Dr Hey

Thank you for your e-mail. Regarding your query on copyright clearance, copyright clearance is not necessary for a small portion of original work (up to 10 per cent) for academic purposes. We introduced this paragraph in our draft programme in an attempt to emphasize the historical nature of our meetings. It worked for the last one we held!

Best wishes

Daphne Christie

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 15 May 2004 08:04
To: Daphne Christie (E-mail)
Cc: Jane Harding; Iain Chalmers
Subject: Meeting on June 15

I am interested that you put a quote from the radio talk that Peter Medawar gave back in 1963 at the top of your latest circular outlining the theme for the meeting on June 15th, because this was exactly the approach I used (and the phrase I quoted) when I first contacted Jane Harding telling her what the meeting was about and urging her to come over for the meeting, both so she could tell us what she is herself currently doing but also to act as a repeteur for the story of the early days we are hoping to capture indirectly from the lips of Mont Liggins and Ross Howie.

Is this a phrase you have used to describe the purpose of *other* meetings or did you think it particularly apt for this one? I had not thought there was really any reason for me to say anything at the start of the meeting, although you will probably tell me that I have not done my allotted job properly if I do not. I had wondered about reading out what was, in effect, the last but one paragraph of that talk, because it sets the scene perfectly. Would you need copyright clearance to include it in the small book you eventually see as coming out of this meeting? I guess it is possible that copyright for this originally unscripted talk rests with the BBC.

Edmund

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 21 May 2004 11:39
To: Edmund Hey
Cc: Wendy
Subject: RE: Wellcome Meeting

Dear Edmund

I am sorry that you will not be able to attend the supper after the meeting and note that you do not require a taxi to take you to Heathrow.

I hope you enjoy your holiday and look forward to seeing you on the 15th.

With best wishes

Daphne Christie

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 20 May 2004 11:25
To: Daphne Christie (E-mail)
Subject: Fw: Wellcome Meeting

Thank you for that response. I am glad to hear that you are not only finding accommodation for the overseas speakers, but also inviting them to a meal afterwards. It would have been something of a discourtesy not to have done something like that.

However I only discovered this for the first time on speaking to Iain about a totally unrelated matter earlier today. Had you said any of this to me last week I might have been able to change the plans for my return flight and come along. However I fear it is too late to do that now (it would also cost too much to change the tickets that I have bought). Please give my apologies to those who will be there.

Please don't think of paying for me to get a taxi to Heathrow - I will go by underground as I usually do. You might instead put the money that this would have cost into covering a little more of the personal cost that Jane Harding has been put to in order to come to this meeting at very short notice.

Edmund

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

From: Dr Daphne Christie
To: Edmund Hey
Cc: Wendy
Sent: 19 May 2004 11:05
Subject: RE: Wellcome Meeting

Dear Dr Hey

Thank you for your e-mail. We are very grateful that you have made special arrangements to be with us on 15 June and are sorry that you will not be able to attend the supper after the meeting. Professor Harding and Dr Avery have both been invited to supper and have also been offered accommodation (Professor Harding has also been offered £100 towards her fare). Unfortunately, it will be difficult to arrange something before the meeting.

Please let me know if you would like us to organize a taxi for your return journey to Heathrow.

With best wishes,

Daphne

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Sent: 14 May 2004 23:12
To: d.christie
Cc: Iain Chalmers
Subject: Re: Wellcome Meeting

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Edmund Hey

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Sent: 21 May 2004 11:39
To: Wendy
Subject: FW: Wellcome Meeting

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Subject: Fw: Wellcome Meeting

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Cc: Wendy
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Daphne

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Edmund Hey

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 02 June 2004 09:42
To: Edmund Hey
Cc: Wendy
Subject: RE: Witness seminar meeting - June 15

Dear Dr Hey

Thank you for your email. These are the contact details for Dr Mary Ellen Avery: tel: 617 335 8330; fax: 617 730 0486; mary.avery@tch.harvard.edu

Best wishes

Daphne Christie

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

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: 31 May 2004 23:03
To: Daphne Christie (E-mail)
Subject: Witness seminar meeting - June 15

Dr Christie,

I am in now contact with most of the key speakers for the meeting on June 15. I am trying to ensure that, while all the key issues get covered during the afternoon, we avoid any unnecessary repetition. However I do not have a contact address or, more importantly an e-mail address, for Dr Mary Ellen Avery. Could you give me one please as a matter of some urgency?

There is a real risk that she and Dr Jane Harding will arrive expecting to cover almost the same ground unless I speak to both of them in the next 48 hours. I see Dr Harding is down to speak first, but I rather suspect that it might be more appropriate to have Dr Avery speak first. I think we should take their views into account over this.

E Hey

Wendy Kutner

From: Wendy Kutner [w.kutner@ucl.ac.uk]
Sent: 08 June 2004 11:48
To: Edmund Hey; Chalmers, Sir Iain
Cc: Daphne
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004



CORTIattendances
t.doc

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

Wendy Kutner

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



CORTIntg150604A
ATTENDANCE LIST...

Please find attached attendance list for tomorrow. Please note this is subject to change. Tomorrow's list will be available for you at the meeting, together with a named programme and various papers. Wendy

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
Euston House
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Dr Edmund Hey
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Newcastle-upon-Tyne NE3 1UD

Dr Daphne Christie
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Tel: +44 (0) 20 7679 8106
Fax: +44 (0) 20 7679 8193

16 June 2004

Dear Dr Hey

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

May I say on behalf of the History of Twentieth Century Medicine Group and myself, how grateful we are to you for your contributions to yesterday's meeting? It really was a splendid occasion, and we hope that you enjoyed it as much as those of us who were observers. We are very grateful to you for your considerable help in arranging it and for chairing 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. Thank you for your offer of help during the editorial process. 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.

We are very grateful to you for interrupting your holiday in France and travelling overnight to chair the meeting.

With best wishes

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

THE WELLCOME TRUST

WITNESS SEMINARS

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1. NAME Dr Edmund Hey

2. ADDRESS

51 Alwinton Terrace,
Newcastle-upon-Tyne NE3 1UD

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

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

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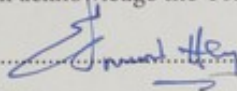
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Signed.....

Date.....10.12.04.....



Vice - 14/12
all 15/12

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

24 Eversholt Street • London • NW1 1AD
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Fax: +44 (0) 20 7679 8193

7 December 2004

Dear Dr Hey

Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality

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

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

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

- Please check your biographical piece on page 109 and confirm that it is correct.
- Please sign and return the standard form assigning copyright to the Wellcome Trust.
- Please let us know if you do not want your name included in our twice-yearly marketing mailings.
- We would like to include illustrations of early work in the volume. If you have any suitable images or figures, please include these with the pages. They will be carefully scanned and returned in protective packaging.
- A final proof version, incorporating the changes made by all the participants, added footnotes, and any queries will be sent to you in **September 2005** for return within a week. **At this stage only minor corrections, such as those of a typographical nature, will be possible.**

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

I look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

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

please note:

Jain Chalmers has
overlaid his contribution
on page 66-71 and
necessary changes will
be incorporated in the
next draft.

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

Popper's ideas on scientific method, your answer was 'Yes it is a fraud — a fraud in the sense that it systematically conceals or distorts the way in which the ideas were thought out or developed' Have any of your scientific papers been in this sense fraudulent?" And Peter Medawar replies:

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 ~~ferrifying~~ on the third programme, ~~yes~~ it was called the third programme, back in 1963, and since we are in reminiscing mood, I had just started my first job as a MRC physiologist/clinician/animal worker, working with Kenneth Cross. I heard his talk on the day and it had an absolutely profound effect on me. I thought I might read a bit of it, but then I ~~decided~~ I found another talk in which he was actually interviewed just three years later, defending this, and I think we will come back to this at the end of the day. The issue is what he meant about research being fraudulent. I will just read a couple of sentences. The interviewer says; "arising out of your paper 'Is the scientific paper of fraud?' which was written under the influence of Karl ~~philosophy, you said it is a~~ fraud. So how many of your scientific papers have been a fraud. And he said,

a good many
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~~ by the vacuous collection of facts which then tumbled somehow into place. I think I have adopted a compromise.

should

*amazing, I
Yes*

7

Let me

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

to get
of something
in

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 ^{much of the} ~~the vast part of~~ today wondering why we perspired quite as heavily as we ^{have} ~~had~~ over this particular inspiration, and why it is that some of us are still mopping our brow and realising that we still haven't got things sorted.

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

back
on to

it is not fairly clear how Mont Liggins came to make the discovery he did. The paper he wrote ~~on this~~ describes the process very succinctly. If we can agree about this

about
this

than they are often are nowadays. Certainly in the UK. It's very uncommon ^{for} ^{to} ~~that~~ you ^{meeting} ~~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

after I said that lambs were perfectly normal by 147 days[very quiet] anything we were looking for and Mont said, 'Well, what if I told you we can identify accelerated maturation in the lambs at 115 days? 147 days in Boston, 115 days with acceleration? That's too big to be an error. New Zealand lambs were different from the lambs in the USA, I didn't believe that, neither did he. It appeared that in fact hydrocortisone could accelerate maturation of lambs, the ones with this vegetative surfactant production that had come along at the same time. Thiswas a very rewarding one. There are others which I shall show you in a few minutes.

The story of the glucocorticoids moved ahead by light years when Liggins and Howie proposed a randomized control trial,I think 100 days before the birth of the lamb, and it was obvious that thereproducible effect, and the Ross Conferences, some of you were there at those meetings. This was followed by more controlled trials than you can ever imagine. Every paediatric meeting was, posters and the like were varying at things a little bit. You had all these materials testing at another time. You could try other interventions. And the ones that mattered the most I think were directly from the central ideas of[Boris?]. I would also like to pay tribute to Sue Buckingham, a fellow at the Presbyterian medical school, probably well known to you. She presented at a federation meeting to Nashville. Sue Buckingham wrote an abstractthe effects on the mice she was studying, mice and babies coming together in her mind, the lung, the gut arteriologically, and remained at the same time of the appearance of markers [sense?]. In 1969 she made that point, and I thought it was frivolous. Then we had a series of observations not well put together at that time but confirmed over

and over, that glucocorticoids.....maturation, not only of the intestine, but also of the lung. I, by then, had finished my Marcol Fellowship and Sue, alas, died shortly after that meeting, which was a great tragedy, but her contribution was valuable. This is the story in which I had first-hand involvement, but I never got over wanting to know what would be the long-term output of anything that's invasive, I was scared. Sidney Gallus, the paediatrician from in the USA, was saying never should a baby be allowed to die without a course of glucocorticoids. Gosh, that really sent a chill down my spine, because we were 'throwing them around'. You don't know what to do, give them cortisone. A sad commentary in a way but the doses used and so on didn't seem to make much difference one way or another, except in the context of accelerating maturation of the fetal lung and intestine. There are still those who are worried about long-term outcomes and I think we will hear more about that from some of the participants here. I too have been concerned that there has been a temptation to if a little bit is good, more is better, give more than one shot, just let's try it, postnatally, maybe we don't need to give it prenatally, we will give it postnatally and we will give bigger doses, because you might get a bigger effect. The literature is cluttered and I use that word wisely, with I think very inappropriate studies pertaining to this. I am delighted therefore to look into this and hope to learn from all of you and see you in Boston someday.

[check tape]

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.

works

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

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

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

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

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

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

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

organs, helped I must say by my secretary. And I remember one morning, there was a lamb lying in a cage with its mother. A lamb that had been infused as a fetus with cortisol. And to my surprise this lamb was still breathing, not very healthy breathing, but it was alive and breathing. It had no right to be, it was so premature that its lungs should have been just like liver, and quite uninflatable. And this struck me as surprising. When we came to do the autopsy the lungs were partly inflated and this was absolutely surprising. So rather than decide by that the cortisol had accelerated the maturation of enzymes in the lung that caused accelerated maturation. Now at that timefacilities 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

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

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

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

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

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

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

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

never

they
must be

that, if

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

lasting, so that it didn't have to be given too frequently to pregnant women and decided that something that would last for 24 hours and therefore two doses would give you about a 48-hour effect would be adequate, based on the animal studies. He therefore set about looking for a drug that would be clinically easy to manage, long-lasting, and which had an identically appearing placebo. This is not easy, because all the long-lasting preparations, 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 sights 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?

fresh ?
Did ?

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

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

HYPOPHYSECTOMY

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

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

as before

labour

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

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

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

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

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

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

follow up happened, and he himself therefore was never right through I think into the early 1980s recommending that anybody else should act on the basis of their trial alone, and was very encouraging of other trials. I was asked about the follow up and the NIX 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

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.~~

steroid
who
were getting treated

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 ⁱⁿ 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 ^{are} ~~were~~ difficult. I think they are ~~more~~ difficult, but it's always been ^{getting} so. Yet sometimes it goes very well.

difficult

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

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

of a 'lost' completed and published more than five years ago, they can still find the original raw paper work?

one of

Hey: The answer for Gill Gyte was that the data was there but 20 years later, it had still not even been analysed. Who can put their hands up and say that ~~a trial that we did five years ago, and has now been reported, we could find the results.~~ And one of the things, I mean the most amazing thing, that I found in just reading around before today's meeting, was to come across this paper by a Jane Harding in the *American Journal of Obstetrics and Gynecology* on just this subject, published in 2001, and this is control trial data, and it has sat there all that time.

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

If I could just go onto the other issue that was raised, what about the women who get steroids and don't deliver? We have been concerned about this with respect to the repeat steroid issue. There's been a randomized trial, multi-centre randomized trial being run by Caroline

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 ~~in~~ hypertension?'.
mother with

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?
Could

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

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

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

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

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

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

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

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

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

care, and they are willing to pay for the benefits of having survivors. So it's not just that they need to save money, it's that there's a willingness to pay for the benefits and that 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 cost 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.

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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 ^{about} 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.

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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

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 1972¹ 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

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.

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 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

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.

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.

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 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

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.

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.

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

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

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.

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 recognise the crucial importance of systematic reviews of clinical trials for patient benefit, I

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)

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**]

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.

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

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.

for a
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 ^{while} ~~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 *about* it?

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

unexplained deaths in hypertensive women from Liggins's original report which turned out to spurious.

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

Hanney: We have been looking at the benefits from health research for about ten years now, and this particular stream of work seems to us to have been one of the most interesting, and I have worked on it with Miranda and Martin Buxton and Jonathan Grant, and I apologise for I will check on my notes from time to time, because I am trying to pick up on what various people have said today on what I think is an interesting session. For instance, John, 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 researchteam, 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 disconsensus statement, the college statement, had more impact than most of them. An implementation project found that after a year just passive dissemination, in fact implementation of college guidelines went up from 33 to 58 per cent, which is quite substantial. But after active dissemination it went up from 33 to 68 per cent. So it does seem that there are many elements of this whole stream of research that have produced benefits and perhaps the key thing from our work, use of research, is different from some other perspectives in the debate about research utilization, is that our work has been concentrated on showing that benefits have been achieved even though the uptake level has been less than optimum.

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

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

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

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

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

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

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

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

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

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

looked at the cost of babies going home on oxygen. And it was terrific. Parents gave up their whole careers to look after their children and again if we redid 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.

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

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

American Journal of Obstetrics and Gynecology by Alan Jones and Roger 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 decrease 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.

added to them as a preservative, but

recall

study

should require

The preparation he used was also preservative-free.

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~~ ^{were} 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 core 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,

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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.

now go
away
and

This has
just been a

Biographical notes

Dr Mary Ellen (Mel) Avery

Sir Christopher Booth

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

Dr Peter Brocklehurst

Sir Iain Chalmers

Kt FRCPE FFPHM FMedSci (b. 1943) has been Director of the UK Cochrane Centre in Oxford, since 1992. With the NHS Centre for Reviews and Dissemination in York, the Centre is part of the

information system supporting the NHS Research and Development Programme and a component of the Cochrane Collaboration – an international organization that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. Before taking up his current post, he was Director of the National Perinatal Epidemiology Unit in Oxford (1978–92).

Professor Patricia Crowley

Professor John Gabbay

Professor Harold Gamsu

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

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27th August 2005

Dear Mrs Reynolds,

Here are the marked up proofs for the Witness Seminar. For clarity I have typed out the answers to some of the queries Dr Tansley has raised. I am sorry to see that so many of the questions you asked the two overseas contributors are still unanswered. I did offer to help you with the editing process more than once and could have helped you clarify most of these issues had you so wished

Page 4. Note 2. The live interview of Sir Peter was conducted by **David Wilson**. The book you refer to was published by Oxford University Press in 1990, but I was quoting from pages 5 to 7 of the paperback edition published in 1991. The paperback edition had xix + 291 pages. I can't speak for the 1990 edition. ✓

Page 25 Note 36. This footnote is wrong – it is the fetus not the ewe that is hypophysectomised. See Liggins *Am J Obstet Gynecol* 1967;98:1080-6. ✓

Page 36 lines 11 -15. These two sentences are obviously garbled. Try "I think it might be sensible to break and explore something of the debate that went on between 1976, when Liggins presented an update of his findings* at the 70th Ross Conference on Pediatric Research (a meeting devoted the topic of lung maturation and the prevention of hyaline membrane disease),** and 1994 when we end up with the NIH sponsored Consensus Conference. It is a long period of time. Mel, you were a witness to much of this."

* Mont Liggins was by now able to report on the outcome of 884 spontaneous preterm births rather than the 226 births described in the paper published in 1972. (fn) ✓

**See footnote 58

Page 49 I will answer this query when I have had a chance to get to the RSM library. ✓

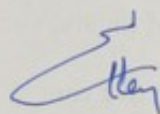
Page 92, Note 160. The book to which I was referring was "A guide to effective care in pregnancy and childbirth" the first edition of which was published by Enkin, Keirse and Chalmers in 1989 (as noted in your list of references). There have been two further editions published since then with a varying editorial panel, the most recent having appeared in 2000. The book provides a synoptic summary in non-technical language of the many systematic reviews first published in the two volume book edited by Chalmers, Enkin and Keirse also published by the OUP in 1989 (as also noted in your list of references). ✓

Page 98. See note 172 The abstract to which Dr Peter Brocklehurst was referring appeared in *Arch Dis Child* 2004;89(Suppl1);A5. However the full paper reporting the trial was published on-line ahead of publication in the print version of the *BMJ* on August 22nd, as doi 10.1136/bmj.38547.416493.06. I think it is worth recording that the whole ASTECS trial involving the randomization of 998 women from ten ✓

different maternity units over a seven year period (1995 to 2002) was undertaken with the support of a single £10,000 grant from the Welsh R&D Office. The original trial by Liggins and Howie was also managed on a shoe string of external funding, but the regulatory requirements that have come into operation in the last few years mean that any trial of this nature could now almost certainly cost at least ten times as much as this.

Page 99 line 18. The two key papers pointing to the possibility that a sulfite excipient in some formulations of parenteral dexamethasone may be neurotoxic are Baud O, Foix-L'Hélias L, Kaminski M, *et al.* Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very preterm infants. *N Eng J Med* 1999;341:1190-6 and Baud O, Laudénback V, Evrard P, *et al.* Neurotoxic effects of fluorinated glucocorticoid preparations on the developing mouse brain. *Pediatr Res* 2001;50:706-11.

Final Note I see that others have added comments to the transcript as well as correcting their entries, whereas all that I did in January was check my personal contribution to the raw transcript. There is therefore one comment I would add – a comment that I tried, unsuccessfully, to get others to make during the actual meeting. The brief note on page 99 is perhaps the right place to add this footnote. “Interestingly no drug company has, even now, sought a license from the regulatory authorities to recommend betamethasone, or any other steroid, for use in cases of threatened early labour. As a result such use remains an unlicensed use of a licensed product – a situation that the general public find quite baffling. It is easy to see why the drug companies have not spent the money necessary to get their licenses modified when the basic product is no longer patent protected, but less easy to see why the regulators (the FDA in America and the MHRA in the UK) have not pressed to get this anomaly rectified. Look up the use of steroids in pregnancy in the otherwise excellent British National Formulary (BNF) and the most that it is prepared to offer is the negative comment that ‘there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome)’.” Lack of action by the regulatory authorities must have contributed, over the years, to the under-use, and the over-use, of this drug.



Edmund Hey

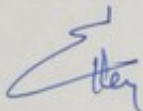
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27th August 2005

Dear Mrs Reynolds,

You ask if there is any way that contributors can help to see that the publication of this Witness Seminar triggers a few comments and notices in some of the medical journals. As it happens I may be able to get a brief mention of this Wellcome publication into a future issue of Archives of Disease in Childhood. However, if I am to do that, it would be of help if I could be given two more copies of last December's issue of Wellcome News, told exactly when the proceedings are going to appear, and told how precisely how to cite the forthcoming publication, how it can be obtained, and at what cost.



Edmund Hey

Please note my
change of address ✓ 9/9/05

ow due postage 94p.

✓ by email.
need + ask 9/9/05.

Heys

please see pages

3-5, 7-8, 14-16, 21, 25-27, 36, 44, 48-9, 52,
54-5, 59, 61-2, 70, 72-3, 84, 89, 92, 99, 100-01
big note on p 115

ACCEA

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

I can't find anything on
pages 72-3 that I
need to address. Please

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

clarify

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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11.8.05

please return by 7 Sept 05

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

Participants

Dr Mary Ellen (Mel) Avery	Dr John Hayward
Sir Christopher Booth	Dr Edmund Hey (Chair)
Dr Peter Brocklehurst	Dr Ian Jones
Sir Iain Chalmers	Professor Richard Lilford
Dr Patricia Crowley	Professor Miranda Mugford
Professor John Gabbay	Mrs Brenda Mullinger
Professor Harold Gamsu [†]	Professor Ann Oakley
Dr Dino Giussani	Dr Sam Richmond
Mrs Gill Gyte	Dr Roger Verrier Jones
Dr Stephen Hanney	Professor Dafydd Walters
Professor Jane Harding	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 Robertson, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

[†]Died 31 August 2004

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

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

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

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

Medawar's

873

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

⁶ ??1962 paper from your laboratory??

⁷ Liggins (1969).

⁸ Liggins and Howie (1972).

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

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

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

⁹ Buckingham *et al.* (1968).

This was an American NIH sponsored trial. Its outcome was the corporately authored paper quoted at the bottom of page 104. I suspect this deserves a cross-reference for clarity

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

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

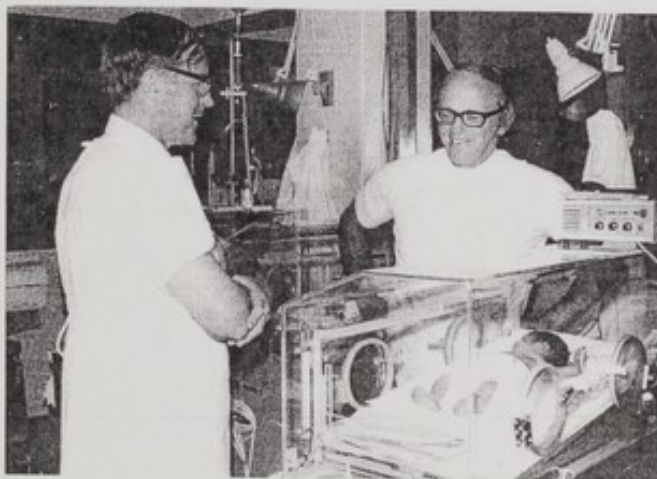


Figure 1: Ross Howie and Mont Liggins, c. 1972

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

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

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

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

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

Ross describes presenting the results of the completed study – not the initial part of the study that was published in 1972, but the completed study – at a symposium hosted by the Royal College of Obstetricians and Gynaecologists of the UK in 1977.²⁰ He said to me, 'They didn't really want to hear'. He also

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

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

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

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

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

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

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

²² Follow-up studies here.

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

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

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

Harding: Twelve hundred. The real number was 1218.

Hey: Still the biggest trial.

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

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

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

Harding: That's correct.

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

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

²⁴ 1976 results?

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?

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

SHH unpublished ✓

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

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

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

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

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

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

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

³⁵ Hanney and Wellcome funding

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

³⁷ See Appendix xx, page xx.

No. This is incorrect. It is the
pituitary of the fetal sheep that is removed
(ablated). See: Lygner GC, Kennedy PC, Holm LH
Failure of initiation of parturition after electrocoagulation
of the pituitary of the fetal sheep American Journal of Obstetrics
and Gynecology 1967; 98: 1080-6.

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

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

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

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

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

trial, which we will no doubt come to, and the follow up was still going on at the time that the Auckland trial follow up was completed.³⁸ I asked Ross if he knew about this and he said he couldn't remember if he had known about it, but if he had he certainly would have encouraged them to proceed, because again he thought it was important that other groups replicated the trial under other circumstances, and check what specifically was and wasn't helpful about this treatment.

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

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

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

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

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

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

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

Prenatal Corticosteroids for Reducing Morbidity and Mortality

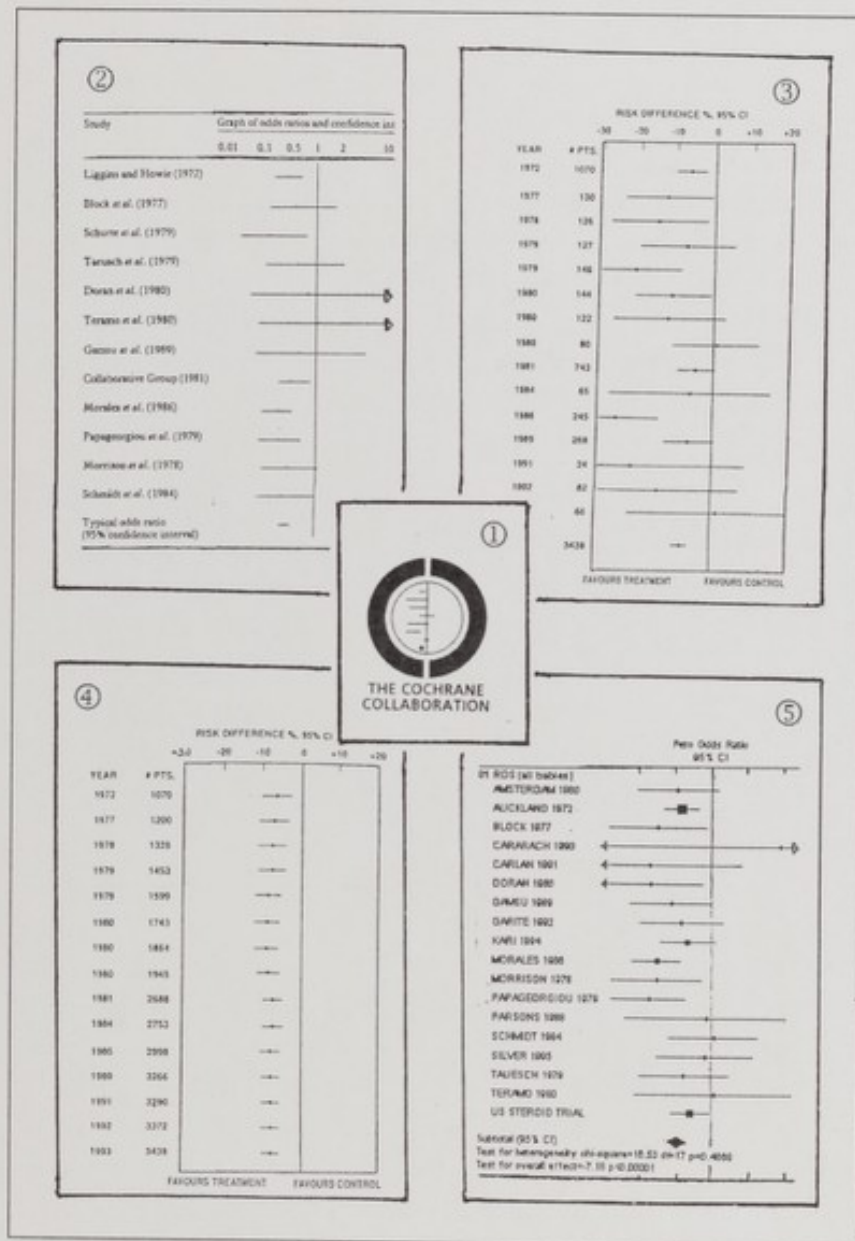


Figure 4: Patricia Crowley meta-analyses, 1992-2004.

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

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

Hey: I think it might be sensible to break and explore some of theation 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

there was this attitude and that was one of the reasons why there had been a lower [?slower?] [prenatal/antenatal steroid] uptake.⁶¹ I am very interested, Patricia, when you raised the issue of the role of the NIH Collaborative Group trial because we were trying to trace through uptake levels and it did seem to us that in the 1970s there had been some increase in uptake: there was a supportive review in the *Lancet* for example in 1979,⁶² and there had been the survey of use by Members and Fellows of the Royal College [??RCOG??] which showed that quite a lot of them were using it in 1980.⁶³ It then seemed that things happened in the 1980s, as I think you were saying, that did seem if anything to increase the opposition, and there was, for example, the editorial in the *British Medical Journal (BMJ)* written by Cliff Robertson, based on the NIH Collaborative Group sub-group analysis that's got criticized.⁶⁴ So I would just like to ask you how far you think that sub-group analysis perhaps did reduce usage?

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

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

⁶² Ritchie and McClure (1979).

⁶³ Lewis *et al.* (1980).

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

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

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

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

⁶⁵ See note 64.

⁶⁶ Lewis *et al.* (1980).

⁶⁷ Lewis *et al.* (1980).

⁶⁸ Ten Centre Study Group (1987).

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

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

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.

⁷⁴ See biographical note on page xx. Sir Iain Chalmers provided an audiotape of the James Young Simpson Lecture given by Mont Liggins at the Silver Jubilee Congress of Obstetrics and Gynaecology in London, 4–7 July 1989, which will be deposited along with the records and tapes from this meeting in GC/253, Archives and Manuscripts, Wellcome Library, London. Sir Ian wrote: 'Liggins notes that Joseph Barcroft's work on fetal physiology was largely ignored by obstetricians until the mid-1960s, when Geoffrey Dawes' Nuffield Institute became the "hub of the universe" in terms of fetal physiology.' E-mail to Edmund Hey, copy to Tilli Tansey and Daphne Christie, 17 April 2004.

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

Avery: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically told Dawes that he would not allow anyone to do any work, even discuss, surfactants for the whole time that Mont was there.⁷⁵

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

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

Hey: I will just interject that in the Ross conference report that you mentioned in 1976, there are five papers from the US saying that they tried to do a trial

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 Prometheus Press, NY, 1992.

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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

⁷⁶ See note 58. Dr Hey, could you list the five papers?  NB

⁷⁷ Kenyon *et al.* (ORACLE Collaborative Group) (2001a and b).

⁷⁸ See Kenyon *et al.* (2001a, b).

rupture of membranes, because you may, in doing something good for the baby, increase the risk of the mother developing a generalized septicaemia. So presumably the people [authors?] couldn't see the unanswered question there.

Gyte: I went to *Effective Care in Pregnancy and Childbirth*⁷⁹ to read Patricia's chapter to find an NCT perspective, and I remember thinking that there were some areas of uncertainty, but certainly that randomization was removed from the study.

Dr Peter Brocklehurst: I suppose I was just thinking about how we now approach the use of antenatal steroids, how we have heard today that it was very difficult to get antenatal steroids used in clinical practice, particularly in the UK, and then, within a very short space of time, we were throwing them around like Smarties. I suppose what nobody has mentioned yet is that in order to get 90 per cent coverage of babies admitted to the neonatal unit exposed to antenatal steroids, you have to give them to an awful lot of pregnant women. I have heard it said that in some hospitals a pregnant woman under 34 weeks only has to burp to be given antenatal steroids. And then there was the use of multiple courses of steroids that is becoming very frequent. Now, of course, what is being considered more and more in the literature are the potential adverse effects, not just of multiple courses of steroids, but the potential long-term hazardous effect of a single course of antenatal steroids on brain development, as John Newnham's group at Perth are coming up with evidence about.⁸⁰

I think a lot of what is difficult about this issue is that we are not very good at predicting preterm birth, and if we were better at predicting who was going to deliver preterm we would probably feel much more comfortable about using steroids in a more targeted way. The concern is that currently at least 50 per

⁷⁹ See note 43.

⁸⁰ Their earlier work includes Newnham and Moss (2001); Newnham *et al.* (2002).

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

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

⁸⁵ McLaughlin *et al.* (2003).

⁸⁶ Gamsu *et al.* (1989). See? Protocol and case record, in Figure ??? Dr Clive Dash wrote: 'The retention of clinical trial data in the 1970s-80s was poor. This has changed in recent years. When Harold Gamsu persuaded us to do a detailed analysis of the UK study, the computer software had changed and so had most personnel acquainted with the prior system. Luckily, Alex Paton at Glaxo was able to interrogate the database and through her efforts we were able to meet Harold's expectations and answer his critical questions. Also, Harold volunteered to keep safe the original case record forms and other study documentation when Brenda Mullinger and I left Glaxo to pursue other career opportunities. I believe Harold always hoped to trace the babies in adult life to address the question of the long-term safety. It is due to his diligence and enthusiasm that he persuaded us (again, pleasantly) in 2001 to begin the process towards a 30+ years follow-up. His untimely death occurred in August 2004, soon after this Witness Meeting. We hope to continue this project with the support of NPEU in Oxford provided external support can be mobilized and plan to dedicate any outcomes to his memory.' E-mail to Dr Daphne Christie, 10 January 2005.

the adults, and in fact things haven't turned out that way, but that's still available for people to do if they would like to.

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

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

Hey: So are everybody's, but if people have kept their data, there are more that can be analysed that has not yet been done. Could anybody find the NIH data? Would the NIH people share their data?

Avery: I have no idea.

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

Brocklehurst: I cannot tell you very much more, because I heard it presented in Glasgow about six weeks ago, but I have seen nothing in the press yet.⁸⁷ My recollection is that it was in animals, but we'll be able to explore this further

⁸⁷ Professor John Newnham from the King Edward Memorial Hospital, University of Western Australia, Perth, Australia, delivered the Society Lecture, 'Antenatal Steroids and Outcome', at the British Maternal and Fetal Medicine Society's Ninth Annual Conference, 1-2 April 2004, held at the Scottish Exhibition and Conference Centre (SECC), Glasgow. He presented results from human and animal studies where infants had been exposed to steroids before birth. See the full report by Dr Margaret M Ramsay, Honorary Secretary, BMFMS at www.bmfms.org.uk/presssummaryofglagow04.doc (visited 18 July 2005).

when the study is published.⁸⁸ Having tried to do one of the large trials of multiple courses of steroids, I think one of the issues with clinicians about the use of multiple courses of steroids is that their threshold for starting antenatal steroids is lower, because if they are wrong, and the woman doesn't deliver soon, they have felt that they can always give a second course. If people are restricted to giving a single course of steroids they may delay starting until there is stronger evidence, if you like, of impending preterm birth. So the groups of women selected into these trials is likely to be quite different from the multiple steroids group and that will make the interpretation of the results interesting.

Lilford: I recently had a debate with my 14-year-old daughter Philippa about whether history is just an interesting thing to read, or whether it helps us to design our own futures. Listening to Jane speak makes me think that there really are occasions when history has a lesson for the future. Hearing you speak about finding these records has been very interesting, but I suspect that many people in this room were amazed that you really could find those source materials after 30 years, that you could find the trial documents and so on. When Harold Gamsu moves the documents from his office, goodness knows where they might go. So the lesson that we might want to learn from this is the importance of some sort of systematic paid for-archive for trial information and I don't know if you might want to comment. I know that the Economic and Social Research Council (ESRC) archive their most precious data and build the cost of so doing into the grant.⁸⁹ The more I hear the more I think this might be something we ought to try to take forward as a matter of some urgency.

⁸⁸ The lecture will be published in 2006 as: Newnham J P. (in press) The steroid story: iconic advance or ticking bomb? *Yearbook of Obstetrics and Gynaecology*, vol. 12. London: The College.

⁸⁹ The Economic and Social Data Service (ESDS) Qualidata is a specialist service of the ESDS led by the UK Data Archive (UKDA) at the University of Essex. The service provides access and support for a range of social science qualitative datasets. Established in 1967 the UKDA holds the largest collection of digital data in the social sciences and humanities in the UK, funded by the ESRC.

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

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

Mugford: My background is a degree in economics. I graduated from the University of Stirling in 1972 and the relevance of that is that health economics as a discipline didn't exist then. I think the first Penguin book of readings for students of health economics was published in 1973.⁹² I looked at it and wished that I had studied health economics. There wasn't at that stage even postgraduate training in it. I finished my economics [degree?] quite disillusioned with the subject, because it was very much centred on the formal economy, that is how people trade goods and services using the money mechanism and adjustments of it through the public services as a method. So I finished a Masters in Monetary Economics and then dabbled in bits of health of economics research and had some children. And this is very personally indulgent, and I shall go on, but I joined the NPEU in Oxford, as a researcher in statistics, medical statistics, with Alison Macfarlane, but also to work in the unit on other topics, including incorporating economics alongside randomized trials with Adrian Grant, this very new notion of building economic evaluations using evidence from syntheses of evidence of effectiveness, building

⁹² Cooper M H, Culyer A J. (1973) *Health Economics: Selected readings*. Harmondsworth: Penguin.

on the work that Iain Chalmers and others were pioneering in the Oxford Database of Perinatal Trials, as it later became but wasn't when I first joined the unit in 1981.

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

At that time health economics was emerging and that's another whole historical story which has been documented elsewhere.⁹³ My connection with it was really through Professor Alan Williams at York who was probably the founding father of health economics in the UK, and his visit to the unit. I think he was examining a dissertation in Oxford with Iain and I asked him how I could qualify as a health economist? He replied, 'What you have to be able to do if you are a graduate economist is to stand up and say that you are a health economist in front of a bunch of doctors.' So I girded my loins and worked on subjects that seemed to be relevant to our brief in the NPEU to the enthusiasms of people within the unit, including the systematic review of steroids. I remember the day when the results were being worked through by Patricia and Iain before it was published. The coffee room was buzzing and this was very exciting. At the same time I was host and supervisor to a series of students from York where they had a new health economics Master's degree and they looked for placements for their students during the summer to do dissertations. One of them, James Piercy, came to me with his topic on the economics of antenatal corticosteroids and he did some observational work in the neonatal unit in Oxford to try to assess the costs of treating babies at risk of preterm delivery and eligible for steroids. In fact, the surfactant question was also, I was going to say bubbling around at that time. He and I with Iain wrote

⁹³ Prof Mugford, was this Croxson (1998).

a paper which was a modelling exercise, a very, very simple decision modelling exercise, based on different assumptions about initial birth weight and mortality risk, based on the cost data, which James had gathered for his dissertation, and the evidence of effectiveness from the systematic review. That was published by *Archives of Disease in Childhood*, having been rejected by the *British Medical Journal*, in 1991, after the systematic review.⁹⁴ So as far as I am concerned, that wasn't quite the end of the story because the Oxford Regional Health Authority had introduced the Getting Research Into Practice Programme [?and Purchasing?] (GRIP).⁹⁵ We are going to hear more about that later, I think.

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

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

⁹⁴ Mugford *et al.* (1991).

⁹⁵ Dopson and Gabbay (1995).

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

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

Mugford: No. There's just one other thing which I think Mary Ellen Avery referred to, and Patricia too, and that was the analysis we did was quite unsophisticated, but we did make some effort to model the impact in the smaller babies and the more preterm babies, and in those cases there wasn't a predicted cost saving. One of the problems we had with people was the assumption that that is not then cost effective, which isn't true, because society has shown that it is willing to pay for neonatal care, and they are willing to pay for the benefits of having survivors. So it's not just that they need to save money, it's that there's a willingness to pay for the benefits and that it can go beyond the straight, evident cost savings. But it is ridiculous that anyone should just not look at this. Economists, it's not very fashionable to look at areas where in fact there is a win-win situation. The exciting academic work goes on at the fringes, where benefits perhaps might not be worth the costs.

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

Yes
please
make
all these
suggested
changes
as
marked.

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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 subject⁹⁶ – 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

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 Robertson N R C, Rennie 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

⁹⁹ Chalmers (1999).

¹⁰⁰ Glass (1976).

¹⁰¹ Chalmers (1979).

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

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

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

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).

✓ 22/9/05

Jack

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

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

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

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

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

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

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

May I just mention the main conclusions from this particular piece of work? Don't expect this sort of study to get it into the *British Medical Journal*. It won't be accepted. Secondly, advocates are really important when it comes to getting guidelines adopted and I think opinion leaders are really important within institutions, but the important thing is that the guidelines have got to be written in such a way to be usable, understandable and accessible to those who are going to implement them. That means clear inclusion and exclusion criteria. Another important agent for change are the users, and if you have women asking these sorts of questions, after a while people do get a bit embarrassed coming up with the same answers that clearly won't be supported by evidence or by colleagues. I would like to see women users being far more involved in ways in which we can encourage the implementation of best practice. I am not surprised that there was no sign of managers actually implementing any change in Richard's study. It's a scary business. There was blood all over the carpet when we were dealing with the ECV meetings, and it required somebody – like the users who were tough, or somebody like me who's a public health specialist and who has been a GP and is not afraid of consultants – to hold the line if necessary. Managers cannot do that, and I don't think we should expect them to. I think it's exceedingly difficult. The

most important barrier, the most important influence to achieve change, is the personal experience of the person making the clinical decision. When new interventions are being rolled out we must encourage people to be at the centre of it, so they get feedback of the positive results. Then it is much easier to get change implemented.

22/9/06
7 J1
Hey: That rings true for a lot of us, I think. You went over time, but I think you said something very important. We are beginning to get very tight for time and so I am going to ask Stephen Hanney to speak next. But Harold [Gamsu], while you were out of the room we did hear that quite a lot of units said that they couldn't join your trial, because they were already using it so widely and that occurred at the time when in actual fact we know that less than 6 per cent were really using steroids nationally. Did being involved in the trials themselves influence the centres? Did the centres that had been involved in the research take up the outcome of that research more than those who only read about it?

Gamsu: I don't know the answer to that I am afraid. We didn't follow that point up, but as far as I know Brenda Mullinger might know something about it. All I can say is that there were local reasons that indicated against the use of steroids. There was quite a lot of gossip about this and we have heard some examples of this today. The risk of infection especially in ruptured membranes, and the unexplained deaths in hypertensive women from Liggins's original report which turned out to be spurious.

The other thing that I found was influencing obstetricians was the increased risk of pulmonary oedema which people widely accepted as a complication of steroid therapy. In fact it was a complication of tocolytic agents that were used, especially when those agents were given in large volumes of fluid. As far as I know, steroids given alone were not tocolytic agents and did not result in pulmonary oedema. So I think we had quite a lot of persuading to do even in

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

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

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

¹⁵⁸ More about patient???

had different policies. I was learning what those policies were and then I was passing on this information to the junior members of their team, so that they could also practice non-evidence-based medicine. That was a long time ago, but I think it is still the case that many people believe that doctors and other experts know what they are doing.

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

Crowley: As an obstetric senior registrar in 1985, I took over the care of a woman who was having an antepartum haemorrhage at 37 weeks gestation. We thought she was 37 weeks because of an error in estimating the dates made earlier in the pregnancy. Because of continuing antepartum haemorrhage I induced labour following consultation with a supervising consultant. She had not had antenatal steroids. She was, in fact, only 33 weeks gestation and the baby went on to develop severe RDS and after prolonged ventilation survived with severe cerebral palsy. His mother sued the hospital, my consultant colleague and myself. The patient was awarded Euros 4000 million compensation in an out-of-court settlement because I had failed to give her antenatal steroids. The decision by the protection society and the legal team was that whereas other obstetricians might be able to defend themselves against not giving antenatal steroids in 1985, the papers I had published demonstrating the evidence in favour of antenatal steroids prior to 1985 rendered my failure to prescribe antenatal steroids indefensible. So a very disabled 20-year-old man and his parents have suffered a lot as a result. This

medico-legal event contributed a further chapter to my 30-year personal involvement with the antenatal steroid story.¹⁵⁹

Hey: One of the good things was that came out of the book, *Effective Care in Pregnancy and Childbirth*, was a version which has been widely read by parents, wasn't it?¹⁶⁰ Not many other branches of medicine have pursued it through to that point yet, have they?

Mugford: Following on from Patricia's story and also what I was saying earlier, that the impacts on the economic side that we measured were purely the health services facts and many economic studies are just cost-effectiveness analyses from the point of view of the health service for the efficient running of the health services. But the impact on family is terrific and there's a long-term impact of children with cerebral palsy.¹⁶¹ We did a study in the NEPU with another York MSc student who looked at the cost of babies going home on oxygen. And it was terrific. Parents gave up their whole careers to look after their children and if we redid the steroid analysis taking account of family and household impact it would just emphasize the same answer, it's even more of a 'win-win'. We don't really need to do the study, but sometimes you have to do the study to have the impact.

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

¹⁵⁹ May we have a date on this?

¹⁶⁰ Dr Hey, could you elaborate?

¹⁶¹ Prof Mugford, could you provide a reference here?

perfectly reasonable justification for raising the age at which you can vote.¹⁷⁴ But babies develop, they develop for a long, long time and something like steroids has an enormously potent effect on all the systems of the body, and yet we think we can just look at RDS and ignore the potential long-term effects. I think we are beginning to realize that we cannot do that, that interventions which show short-term benefits, like neonatal dexamethasone, may be countered by long-term harm. Not that there is no benefit in the long term, but that the long-term effects may be in the opposite direction. This means that long-term follow up studies of these trial cohorts become essential and yet the current situation [?of funding??] in the UK, I would suggest, is making it more and more difficult and more and more expensive in terms of being able to follow-up people.

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

Brocklehurst: I think there is an issue here about preparations, because I remember [??who??, from??] the Canadian study got in touch with us about our TEAMS trial, and asked, 'How [?Where?] did you get a placebo for your betamethasone, because ours is cloudy?' We replied that ours was completely clear. The original trial doesn't specify what the betamethasone preparation was and we were using the betamethasone that was available in this country, and in the UK you can only buy betamethasone in a solution, not a suspension.

¹⁷⁴ Wallis (2004).

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

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

Gamsu: It did cross but in much smaller quantities.

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

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

To come back to Peter Brocklehurst's point about how come they chose the best dose and the best drug, I don't think we know that they did. Nobody's looked and almost all of the issues that Peter has raised – the repeat steroids, which dose, which drug, how often, at what gestation, to which pregnancy – all

of those things were raised by Liggins and Howie in their original publications and said these were the things that needed work, including long-term follow up. When Stuart Dalziel, the key person in the 30-year follow up, presents this data, he starts off by saying, 'Why do we do this?' He then puts up a quotation from the original papers, and says, 'Because they told us we had to 30 years ago'.¹⁷⁵ To complete that story, recently at a meeting at the National Women's Hospital, Stuart said, 'I expect that it will be my PhD student in 20 years time who will have to do the 50-year follow up'.

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

¹⁷⁵ Dalziel *et al.* (2005).

Appendix

If permission to reproduce is granted, appendices will include:

'Prenatal glucocorticoids in preterm birth: a paediatric view of the history of the original studies', a memoir by Roos N Howie, 2 June 2004, circulated at the meeting.

A letter from G C (Mont) Liggins to Iain Chalmers, 6 April 2004, with three slides.

A history of the Wellcome Trust grant support for G C Liggins research group at the Postgraduate School of Obstetrics and Gynaecology, University of Auckland, 1968–76

Neonatal pharmacokinetics ✓ 22/9/05

Prenatal Corticosteroids for Reducing Morbidity and Mortality

He was Director of Public Health in Newham, London, from 2002 until 200x. See Hayward (2001).

Dr Edmund Hey

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

Professor Ross Howie

Mr Ian Jones

(b. 1945) has been Publisher at the Wellcome Trust since 19xx.

Dr William ('Bill') Henry Kitchen

AM, MD BS FRACP FRACOG (b. 1926) trained at the University of Melbourne Medical School who joined the Children's Hospital in 1953 as a Junior Resident and the following year was Research Registrar for a year under Drs Howard Williams and Charlo Anderson. Until 1965 he combined work as an Outpatient Physician at the Hospital with a private paediatric practice. In 1965 he was appointed to a

full-time position as First Assistant (equivalent to Associate Professor) in both the University of Melbourne Department of Paediatrics and the Department of Obstetrics and Gynaecology, continuing in this post until 1991. See www.cshs.unimelb.edu.au/programs/jnmhu/witness/references1.html (visited 2 August 2005).

Professor Sir William Liley

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

Professor Sir Graham (Mont) Liggins

FRCOG FRCS (Edin) PhD (b. 19xx) graduated in medicine at University of Otago in 1949. He was appointed to a personal chair at the Postgraduate School of Obstetrics and Gynaecology,

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

Professor Richard Lilford

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

Professor Miranda Mugford

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

incorporated into economic evaluation techniques. See Macfarlane and Mugford (1984).

Mrs Brenda Mullinger

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

Professor Colin Normand

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

Professor Ann Oakley

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

Lois Reynolds

From: Edmund Hey [shey@easynet.co.uk]
Sent: 06 September 2005 19:19
To: l.reynolds@ucl.ac.uk
Subject: Witness seminar on antenatal corticosteroid use

I think I can get an annotation on this publication into *Archives of Disease in Childhood*, but if I am to do this it would be good if I could have a copy of the final proofs back (I returned the only copy you sent me a week ago). I am presuming that volume 25 will now appear by November - no doubt you will warn me if there is any last minute delay.

E Hey

Lois Reynolds

From: Edmund Hey [shey@easynet.co.uk]
Sent: 22 September 2005 20:06
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal corticosteroids : query

You will find the comment in every recent issue of the BNF. It appears on page 359 of the most recent issue [that is in BNF 49] published jointly by the British Medical Association and the Royal Pharmaceutical Society of Great Britain in March 2005. If we are to be punctilious I would merely comment that while the quote I gave you was almost word perfect the acronym "RDS" really ought to be replaced by the words "Respiratory Distress Syndrome"
E

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

From: "Lois Reynolds" <ucgarey@ucl.ac.uk>
To: <shey@easynet.co.uk>
Sent: Thursday, September 22, 2005 5:42 PM
Subject: Witness Seminar: Prenatal corticosteroids : query

> Dear Dr Hey,
> Thanks for your corrections. There is a query on your 'final note', which
> has been added on to the footnote on page 99, as you suggested. I would be
> grateful if you could give the page number and edition of the BNF for the
> quote.
> Many thanks and best wishes from Lois
>
> 0-0-0-0-0
>
> Dr Edmund Hey wrote: "The two key papers pointing to the possibility that
> a
> sulfite excipient in some formulations of perenteral dexamethasone may be
> neurotoxic are: Baud et al. (1999, 2001). Interestingly no drug company
> has,
> even now, sought a license from the regulatory authorities to recommend
> betamethasone, or any other steroid, for use in cases of threatened early
> labour. As a result such use remains an unlicensed use of a licensed
> product - a situation that the general public find quite baffling. It is
> easy to see why the drug companies have not spent the money necessary to
> get
> their licenses modified when the basic product is no longer patent
> protected, but less easy to see why the regulators (the Food and Drug
> Administration (FDA) in the US and the Medicines and Healthcare products
> Regulatory Agency (MHRA) in the UK) have not pressed to get this anomaly
> rectified. Look up the use of steroids in pregnancy in the otherwise
> excellent British National Formulary (BNF) and the most that it is
> prepared
> to offer is the negative comment that "there is no evidence of
> intra-uterine
> growth restriction following short-term treatment (eg prophylactic
> treatment
> for neonatal RDS)".(FN) Lack of action by the regulatory authorities must

> have contributed, over the years, to the under-use, and the over-use, of
> this drug.' Note on draft transcript, 27 August 2005.
>
> FN: BNF: number xx (date), page.
>
> 0-----0
>
>
> Mrs Lois Reynolds
> Research Assistant to Dr Tilli Tansey
> History of Twentieth Century Medicine Group
> Wellcome Trust Centre for the History of Medicine
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> www.ucl.ac.uk/histmed
>
> The Wellcome Trust Centre is supported by the Wellcome Trust, a registered
> charity, no. 210183.
>
>
>

corrected +
checked 22/9/05
✓

Footnote 76

If you want a full answer to this query then I would refer you to the report of the Ross Conference in 1976 (footnote 58). In introducing the contribution by Prof Liggins the Chairman, Professor TD Moore, said "The information which is most likely to reduce the uncertainty associated with decisions dealing with the safety and effectiveness of drugs is obtained from tightly controlled, double-blind clinical studies. As you will learn from subsequent discussion sessions such studies are extremely difficult to execute. Not only must the clinical investigator have the blessing of the Human Research Committee, he must also have complete cooperation from his medical patients and their patients. You say impossible? Most of the time, yes. However, on rare occasions someone will pull it off. When that happens we have a classic piece of research on which many others can build."

Clinicians from centres from Quebec in Canada, from San Francisco, from Texas, and from two medical schools in Boston, America all indicated during the subsequent discussion that they had not found it possible to undertake such a study. As Dr Killam, said [a little confusingly] (p 119) "Research guidelines in federal hospitals as they apply to non-consenting fetuses have become very strict. The only studies that our Human Research Committee will approve are those in which the potential for fetal benefit is unquestionably clear. If there is a drug or procedure that is presumed to be beneficial, then we must go to great lengths to justify withholding the treatment from a patient. There is no way we could get approval for a double-blind study of prenatal treatment with glucocorticoids."

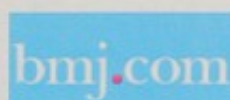
E

Lois Reynolds

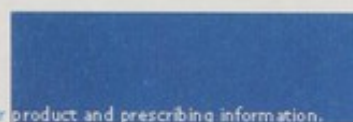
✓ 23/9/05

From: Edmund Hey [shey@easynet.co.uk]
Sent: 23 September 2005 12:00
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal corticosteroids : query

Can I just alert you to the fact that the research by Stutchfield that was mentioned during the seminar by Peter Brocklehurst, has now been published in full in today's issue of the BMJ (pp662-4) as has a second important 30+ year follow-up paper relating to the original Liggins and Howie trial (pp665-8).
E Hey.



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BMJ 2005;331 (24 September), doi:10.1136/bmj.331.7518.0-b

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Antenatal steroids may have no long term side effects

Another study looks at the long term effects of antenatal exposure to betamethasone and finds that a single course does not alter psychological functioning in adult life. Dalziel and colleagues (p 665) followed up 192 babies of mothers in the Auckland, New Zealand steroid trial conducted in the early 1970s. An editorial by Steer (p645), however, warns that although the immediate benefits of antenatal steroids in reducing respiratory distress are clear, the long term effects of repeated courses continue to be debated.



Credit: BIOPHOTO/SPL

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Stuart R Dalziel, Vanessa K Lim, Anthony Lambert, Dianne McCarthy, Varsha Parag, Anthony Rodgers, and Jane E Harding

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Giving steroids before elective caesarean section

Philip J Steer

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Saturday 24 September 2005

BMJ

Giving steroids before elective caesarean section

Neonatal respiratory morbidity is halved, but they may be harmful in the long term

Papers pp 662, 665

In recent years the caesarean section rate in developed countries has been rising. This may be because improved techniques to control haemorrhage, infection, and thromboembolism have increased the safety of the procedure. As a result obstetricians and pregnant women have a reduced threshold for choosing it. However, although maternal risks have decreased, the effects on the baby of surgical delivery before the due date continue to be debated.¹

In this issue (p 662), Stutchfield et al confirm previous reports that elective caesarean section before 40 weeks' gestation increases neonatal admissions to the special care unit for respiratory distress (mainly for transient tachypnoea of the newborn).^{1,2} In the control group of the randomised controlled trial, 11.4% were admitted at 37 weeks, 6.2% at 38 weeks, and 1.5% at 39 weeks. If women were given two intramuscular injections of 12 mg of betamethasone in the 48 hours before delivery the rates of admission were 5.2% at 37 weeks, 2.8% at 38 weeks, and 0.6% at 39 weeks. Although none of the babies in the control group died, admission will have increased parental anxiety and the cost to the NHS and may have long term sequelae. Giving mothers betamethasone before elective caesarean section halved neonatal respiratory morbidity, so should we give steroids to all mothers before delivery?

We need to know what the potential harms for the fetus are. Lawson has summarised the growing number of reports of adverse long term effects associated with antenatal steroids.³ Animal studies show that maternal corticosteroid administration delays myelination in the fetal brain (which in humans normally continues up to the age of 2 years) and reduces the growth of all fetal brain areas, particularly the hippocampus.⁴ There may be long term effects on the setting of the hypothalamo-pituitary axis and glucose homeostasis.⁵ In preterm infants, antenatal corticosteroids have been associated with higher systolic and diastolic blood pressures in adolescence, possibly leading to clinical hypertension.⁶ Other studies suggest that repeated courses of antenatal steroids reduce neonatal head circumference and birth weight.^{7,8} Multivariate analyses of the behaviour of children in the Western Australian preterm infant follow-up study have shown that increasing the number of antenatal exposures to glucocorticoids is associated with reduced birth weight and an increase in behavioural disorders at age 3.⁹

In 2000, the National Institutes for Health reported that the current benefit and risk data are insufficient to support routine use of repeat or rescue courses of

antenatal corticosteroids in clinical practice.⁸ Clinical trials are in progress to assess potential benefits and risks of various regimens of repeat courses. Until data establish a favourable ratio of benefit to risk, repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials.⁸ This conclusion is supported by the American College of Obstetricians and Gynecologists and a Cochrane review.^{10,11}

Currently, the evidence for harmful effects is strongest for repeated courses of steroids. The effect of a single course on cognitive function, however, is more reassuring, as shown by Dalziel et al in this issue (p 665).¹² However, in their companion paper in the *Lancet* they report small but significant increases in insulin resistance which "could signify a raised risk of diabetes and cardiovascular disease as this cohort ages."¹³ We should not forget that more than 2 million children were born with abnormalities of the genital tract before it was realised that these were caused by diethylstilbestrol given to their mothers as an (ineffective) treatment for threatened miscarriage,¹⁴ and more than 10 000 babies were born with phocomelia before we realised that this was caused by the use of thalidomide in pregnancy.¹⁵

The data presented by Stutchfield et al show that delaying non-urgent elective caesarean section until 39 weeks is much more effective in avoiding neonatal admission than giving steroids.¹ For the 15% or so of such women who will go into labour between 37 and 39 weeks, the inconvenience of having their caesarean "out of hours" is likely to be less than that of having their baby admitted to special care. Most will only be in early labour, avoiding the complications of an acute intrapartum emergency.

A single course of steroids reduces neonatal mortality in babies born before 34 weeks and this perhaps justifies the small risk of long term side effects. However, no such substantial benefit has been shown after this gestation. Delaying delivery until 39 weeks, unless necessary, would seem a more prudent option than giving steroids whose long term safety, even as a single course, remains questionable.

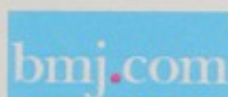
Philip J Steer, professor of obstetrics

Imperial College, Chelsea and Westminster Hospital, London SW10 9N1
(p.steer@imperial.ac.uk)

Competing interests: None declared.

References w1-w3 are on bmj.com

BMJ 2005;331:645-6



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BMJ 2005;331 (24 September), doi:10.1136/bmj.331.7518.0-a

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Antenatal steroids reduce respiratory distress in babies

Antenatal steroids and delaying delivery until 39 weeks reduce respiratory distress in babies born by elective caesarean section. Stutchfield and colleagues (p 662) randomised nearly 1000 women from 10 maternity units in Wales to receive two intramuscular doses of 12 mg of

betamethasone 48 hours before delivery or to get usual care. Fewer children from mothers who had had betamethasone were admitted to a special care baby unit with respiratory distress. The rate of such admission fell with increasing gestation, supporting the recommendation to delay elective section until 39 weeks.



Credit: MAURO FERMARIELLO/SPL

Related Article

Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial

Peter Stutchfield, Rhiannon Whitaker, Ian Russell on behalf of the Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team

BMJ 2005 331: 662. [\[Abstract\]](#) [\[Full Text\]](#)

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A new FREE service for UK GPs

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Lois Reynolds

From: Edmund Hey [shey@easynet.co.uk]
Sent: 26 September 2005 09:55
To: ucgarey@ucl.ac.uk
Cc: Iain Chalmers
Subject: Re: Witness Seminar: Prenatal corticosteroids

Lois,

I told you on Friday that two key papers that got a mention during this seminar as 'in the pipe line' finally emerged from that pipe line on Saturday. Sadly the accompanying editorial was lamentably bad and will call for comment.

Doing that will give me a chance to mention the fact that the report of last year's Witness Seminar should see the light of day quite soon now. Your people in the History unit asked me if there was anything I could do to publicise that event. Well now there is! However you will need to tell me EXACTLY how I cite this in a way that will allow readers to find either a paper or an electronic copy for themselves if they so wish, and do so this week.

E Hey

Lois Reynolds

From: Edmund Hey [shey@easynet.co.uk]
Sent: 26 October 2005 12:11
To: ucgarey@ucl.ac.uk
Subject: Getting that footnote right

Lois,

Sulfite is the way the Americans speak of this excipient (and I was quoting from a paper in the New England Journal of Medicine). The English spelling is **sulphite**

A few words seem to have gone missing a little further down this footnote (see below).

E

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

From: "Lois Reynolds" <ucgarey@ucl.ac.uk>
To: "Edmund Hey" <shey@easynet.co.uk>
Sent: Wednesday, October 26, 2005 11:09 AM
Subject: RE: Witness Seminar: Prenatal Corticosteroids

> Many thanks, Dr Hey. A near final version will be sent to you by the end of
> November.
> May I also ask about the following footnote: Till queried 'sulfite
> excipient'.
> Best wishes from Lois

FN197: Dr Edmund Hey wrote: 'The two key papers pointing to the possibility that a sulfite excipient in some formulations of perenteral dexamethasone may be neurotoxic are: Baud et al. (1999, 2001). Interestingly no drug company has, even now, sought a license from the regulatory authorities to recommend betamethasone, or any other steroid, for use in cases of threatened early labour. As a result such use remains an unlicensed use of a licensed product - a situation that the general public find quite baffling.

It is easy to see why the drug companies have not spent the money necessary to get their licenses modified when the basic product is no longer patent protected, but less easy to see why the regulators (the Food and Drug Administration (FDA) in the US, and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK) have not pressed to get this anomaly rectified. The use of steroids in pregnancy receives hardly a mention in the otherwise excellent British National Formulary (BNF). The most that it is prepared to offer is the negative comment that "there is no evidence of intra-uterine growth restriction following short-term treatment (eg prophylactic treatment for neonatal RDS)". [BNF 49 (2005): 359.] Lack of action by the regulatory authorities must have contributed, over the years, to the under-use, and the over-use, of this drug.' Note on draft transcript, 27 August 2005.

Stutchfield + Dalziel

Lois Reynolds

To: Edmund Hey
Cc: Tili
Subject: RE: Witness Seminar: Prenatal corticosteroids

Thanks, Dr Hey, for the warning on Friday about the publication of Stutchfield and the second paper on the 30-year follow-up, both will be added to the text.

The citation of volume 25 follows. We are glad of a mention.

Best wishes from Lois

Reynolds L A, Tansey E M. (eds) (2005) Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth. Wellcome Witnesses to Twentieth Century Medicine, volume 25. London: The Wellcome Trust Centre for the History of Medicine at UCL. ISBN: 0854841024

On publication in ^{? say in December?} November 2005, Volume 25 will be freely available to download at www.ucl.ac.uk/histmed, following the links to Publications/Wellcome Witnesses. A hard copy of volume 25 can only be ordered at £6/\$10 plus postage from www.amazon.co.uk; www.amazon.com and through all good booksellers quoting the ISBN.

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

From: Edmund Hey [mailto:shay@easynet.co.uk]

Sent: 26 September 2005 09:55

To: ucgarey@ucl.ac.uk

Cc: Iain Chalmers

Subject: Re: Witness Seminar: Prenatal corticosteroids

Lois,

I told you on Friday that two key papers that got a mention during this seminar as 'in the pipe line' finally emerged from that pipe line on Saturday. Sadly the accompanying editorial was lamentably bad and will call for comment.

Doing that will give me a chance to mention the fact that the report of last year's Witness Seminar should see the light of day quite soon now. Your people in the History unit asked me if there was anything I could do to publicise that event. Well now there is! However you will need to tell me EXACTLY how I cite this in a way that will allow readers to find either a paper or an electronic copy for themselves if they so wish, and do so this week.

E Hey

Dr Edmund Hey,
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Lois Reynolds
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www.ucl.ac.uk/biomed
Tel: 020 7679 8123
Fax: 020 7679 8192

27 September 2005

Dear Dr Hey,

Thank you very much for your e-mail of 6 September concerning the *Archives of Disease in Childhood*. A mention would be terrific.

Enclosed are two copies of the December 2004 issue *Wellcome News*, which included a piece on the Corticosteroids meeting. Unfortunately there was an error, so the erratum slips are included.

The transcript of *Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth*, will not be available for another four weeks, as there have been a number of additional appendices. I will send you a copy when it is nearly ready to be typeset.

The publication date has been somewhat delayed by the lack of an indexer, but the volume should be in print by Christmas.

Yours sincerely,

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey

enc. 2 x *Wellcome News*, December 2004: Corticosteroid article on page 8.

Lois Reynolds

From: Edmund Hey [shey@easynet.co.uk]
Sent: 16 November 2005 23:21
To: ucgarey@ucl.ac.uk
Subject: Re: Getting two footnotes right : 15 Nov, urgent
Importance: High

*in email
17/11/05*

Lois,

I now have the answers you were wanting. The statement about "six per cent nationally" needs marginal modification. For a start it looks as though I am saying 6% of hospitals were using steroids when I had intended to imply that only about 6% of the mothers likely to benefit were getting steroids antenatally

The fact is that some 15% of all the mothers delivered before 32 weeks gestation in the units that recruited into the Osiris trial in the UK in 1990 had received steroids. However, that is a self-selected and not a representative sample of units of course. A survey of *all* units in the north of England came up with a figure of 11% for 1990 but if the returns from the two large teaching hospital units in Newcastle are excluded the average for all the *other* units in the north of England in 1990 falls to 7%.

I leave you to rephrase this as you think best. What I probably should have said was that "... at a time when we know that, in most maternity units in the UK, less than 10% of the mothers meriting steroid treatment were getting it." The reference in justification that you want for footnote 166 is Khanna R, Richmond S. Osiris Trial. [Letter] *Lancet* 1993;**341**:174. This contains a graph summarising much of what I have just said.

I am happy with the truncation you have suggested to footnote 87 on page 40.

E Hey

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

From: Lois Reynolds

To: Edmund Hey

Sent: Tuesday, November 15, 2005 2:09 PM

Subject: Getting two footnotes right : 15 Nov, urgent

Dear Dr Hey,

One last time -- two queries. Urgent, by 16 November, if you can. Hope all is well with you. Best wishes from Lois

0-0-0-0

(i) Your statement about 6 per cent nationally. Do you have a source for that? That figure was mentioned by no-one else at the meeting. I have left a footnote for it and time is getting short now.

Hey: That rings true for a lot of us, I think, you said something very important. Harold [Gamsu], while you were out of the room we did hear that quite a lot of units said that they couldn't join your trial, because they were already using it so widely, at a time when we know that fewer than 6 per cent were really using steroids nationally.(FN166) 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?

(ii) Cuts needed from following footnote: need to lose about 60 words without

introducing too manys.

Footnote 87, page 40:

(a) Original: 281 words

87 Dr Edmund Hey wrote: 'In introducing the contribution by Professor Liggins, the Chairman, Professor T D Moore, said: "The information which is most likely to reduce the uncertainty associated with decisions dealing with the safety and effectiveness of drugs is obtained from tightly controlled, double-blind clinical studies. As you will learn from subsequent discussion sessions, such studies are extremely difficult to execute. Not only must the clinical investigator have the blessing of the Human Research Committee, he must also have complete co-operation from his medical colleagues and their patients. You say impossible? Most of the time, yes. However, on rare occasions someone is able to pull it off. When that happens, we have a classic piece of research on which many others can build. Such is the case with Dr Liggins' studies of the effect of prenatal treatment with betamethasone on the prevalence of RDS." Clinicians from centres in Quebec, Canada, San Francisco, Texas and from two medical schools in Boston, all indicated during the subsequent discussion that they had not found it possible to undertake such a study. As Dr A P Killam said: "Research guidelines in federal hospitals as they apply to non-consenting fetuses have become very strict. The only studies that our Human Research Committee will approve are those in which the potential for fetal benefit is unquestionably clear. If there is a drug or procedure that is presumed to be beneficial, then we must go to great lengths to justify withholding the treatment from a patient. There is no way we could get approval for a double-blind study of prenatal treatment with glucocorticoids." Liggins (1976): 97, 119.' Note on draft transcript, 27 August 2005.

(b) Suggested cut to lose the material from: As Dr AP Killam said:

".....glucocorticoids."

: down to 192 words

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

0--0-0-0

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

From: Edmund Hey [mailto:shey@easynet.co.uk]

Sent: 26 October 2005 12:11

To: ucgarey@ucl.ac.uk

Subject: Getting that footnote right

17/11/2005



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25 March 2004

Dear Dr Hicks

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

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

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

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

Continued/... Page 2

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

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.



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21 April 2004

Dear Dr Hicks

**The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality
associated with preterm birth
Tuesday 30th March 2004 2.00 pm – 6pm**

We wrote to you on 25th March, inviting you to attend the above meeting. As we have not had a reply, but have been experiencing difficulties with our post, our original letter, or your reply, may therefore have gone astray. We enclose a copy of that letter and look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 27 April 2004 08:49
To: Wendy
Subject: FW: Honorary contract

Norman/Neonatal

Ben Williams (7/13)

I thought we had sent an update to Chalmers? Let's discuss this morning. Thanks, Daphne

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

From: Iain Chalmers [mailto:ichalmers@jameslindlibrary.org]
Sent: 24 April 2004 14:56
To: Daphne Christie (E-mail)
Cc: Nicholas Hicks (E-mail); 'GARDINER SUE (5CQ) MILTONKEYNES-PCT'; Edmund Hey (E-mail)
Subject: RE: Honorary contract

Dear Daphne

Nick Hicks' name was among those on the first list I sent to you last month because he was actively involved in promoting the uptake of prenatal steroids within the NHS. Was an invitation sent to him? If so, to which address was it sent? I would be sad to find that he had committed himself to other responsibilities because an invitation hadn't reached him for some potentially avoidable reason.

So that I can look over others who have not yet responded, please would you send me and Ed Hey the names of those who have now accepted; the names, addresses and dates on which the invitation was sent of those who have been approached who have not yet responded; and the names of those whom I or others have suggested should be approached, but who haven't yet been formally invited.

Thank you in anticipation of your help in clarifying the situation.

Iain

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

From: GARDINER SUE (5CQ) MILTONKEYNES-PCT [mailto:sue.gardiner@mkpct.nhs.uk]
Sent: 23 April 2004 08:49
To: 'Iain Chalmers'
Subject: FW: Honorary contract

From Nick - todate we have not had an invitation to the Wellcome Trust Witness Seminar but unfortunately that date at the moment does not look good in the diary.

With regards
 Sue Gardiner

Sue Gardiner
 Personal Assistant/Project Officer
 to Dr Nicholas Hicks & Dr Vasco Fernandes
 Milton Keynes Primary Care Trust

email: sue.gardiner@mkpct.nhs.uk
 Tel No: 01908 243084
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 MK PCT Intranet: <http://mkpct>
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27/04/2004

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From: HICKS NICHOLAS (5CQ) MILTONKEYNES-PCT
Sent: Thursday, April 22, 2004 06:17
To: GARDINER SUE (5CQ) MILTONKEYNES-PCT
Subject: FW: Honorary contract

From: Iain Chalmers[SMTP:ICHALMERS@JAMESLINDLIBRARY.ORG]
Sent: Thursday, April 22, 2004 6:19:43 PM
To: 'HICKS NICHOLAS (5CQ) MILTONKEYNES-PCT'
Subject: RE: Honorary contract
Auto forwarded by a Rule

Thanks very much Nick. After you read the things I sent, give me a call at home (554949) so that we can discuss when to meet up.

On another matter. Have you received an invitation to attend a Wellcome Trust Witness Seminar on the afternoon of 15 June? You should have received one some weeks ago, but I don't think they've received a response from you yet.

Aye, Iain

-----Original Message-----
From: HICKS NICHOLAS (5CQ) MILTONKEYNES-PCT [mailto:Nicholas.Hicks@mkpct.nhs.uk]
Sent: 22 April 2004 17:07
To: 'Iain Chalmers'
Subject: RE: Honorary contract

Thanks - I will get things going. Hopefully you should hear next from Richard or Jane McVey. Let me know if you don't hear soon or if there are any problems (not that I anticipate any).

I'd welcome the chance of exploring what this might mean for MK - but I've not yet read the things you attached. You and I might be able to meet in Oxford. (Jane McVey has indicated that she and the HR team should be able to do all their bit by e-mail).

with all best wishes

Nick

Dr Nicholas Hicks

Director of Public Health

Milton Keynes Council and Milton Keynes PCT

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From: Iain Chalmers[SMTP:ichalmers@jameslindlibrary.org]

Sent: 22 April 2004 12:50

To: Nicholas Hicks (E-mail); Nicholas Hicks (E-mail); Richard White (E-mail)

Subject: Honorary contract

<<File: BAMM Newsletter IC 1.doc>><<File: Reprint.pdf>>

Dear Nick and Richard

As you will have seen from the email copied to you just now, Anne-Marie Coriat has advised me to take up your kind offer of an honorary contract backdated to 1 July last year - in one sense, therefore, to carry on (in an honorary capacity) where I left off when I came off the MKPCT payroll at the end of June last year!

I would like the arrangement you have kindly offered to me to be more than token, and would like to meet with Nick or both of you to discuss this. I am attaching two things which will give you a feeling of what I'm up to at the moment.

I would be happy to come to Milton Keynes to have this discussion if appropriate. Please would you give me a call to explore possibilities.

Best wishes, Iain

SIR IAIN CHALMERS

Editor, James Lind Library

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27 April 2004

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associated with preterm birth
Tuesday 15th June 2004 2.00 pm – 6pm

We wrote to you on 21st April, enclosing our original invitation letter to the above meeting, but the date of the meeting on the reminder letter was incorrect. Please note that the date of the meeting is Tuesday 15th June 2004.

Yours sincerely

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey

Dr Nicholas Hicks FFPHM FRCP
Director of Public Health
Milton Keynes, Primary Care Trust
Hospital Campus, Standing Way
Eaglestone
Milton Keynes
MK6 5NG

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

29 April 2004

Dr Hicks

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

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

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

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

Continued/... Page 2

Wendy Kutner

To: nicholas.hicks@mkpct.nhs.uk; sue.gardiner@mkpct.nhs.uk
Cc: Daphne; Chalmers, Sir Iain
Subject: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth



WHATIS--april2004rCORTIHicksinvltr.doDRAFTcorticoFLYER
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Dear Dr Hicks, Please find attached an invitation to the above meeting. A previous invitation was sent to the wrong address. A hard copy of the letter and attachments will be sent to you in the post today. We do hope you will be able to attend. Yours sincerely, Wendy Kutner

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

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

Wendy Kutner

To: GARDINER SUE (5CQ) MILTONKEYNES-PCT
Cc: Daphne Christie; Edmund Hey; Chalmers, Sir Iain
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Thank you very much for letting us know. Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
The Wellcome Trust Centre
for the History of Medicine at UCL
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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: GARDINER SUE (5CQ) MILTONKEYNES-PCT [mailto:sue.gardiner@mkpct.nhs.uk]
Sent: 10 June 2004 15:56
To: 'Wendy Kutner'
Cc: 'Iain Chalmers'
Subject: FW: Witness Seminar: Prenatal corticosteroids - 15th June 2004

I write to inform you that Nick Hicks is unable to attend on the 15th June. He has to attend an all day meeting for Milton Keynes South Midlands Group whereby the day includes interviews for the main consultant.

With kind regards,
Sue Gardiner

Sue Gardiner
Personal Assistant/Project Officer
to Dr Nicholas Hicks & Dr Vasco Fernandes
Milton Keynes Primary Care Trust

email: sue.gardiner@mkpct.nhs.uk
Tel No: 01908 243084
Fax No: 01908 243517
MK PCT Intranet: <http://mkpct>
MKPCT Website: <http://www.mkpct.org.uk>

This e-mail is confidential and privileged. If you are not the intended recipient please accept our apologies; please do not disclose, copy or distribute information in this e-mail or take any action in reliance on its contents: to do so is strictly prohibited and may be unlawful. Please inform us that this message has gone astray before deleting it. Thank you for your co-operation.

From: Iain Chalmers[SMTP:ichalmers@jameslindlibrary.org]
Sent: Wednesday, June 09, 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

--

Wendy Kutner

From: Iain Chalmers [ichalmers@jameslindlibrary.org]
Sent: 10 June 2004 20:58
To: GARDINER SUE (5CQ) MILTONKEYNES-PCT; 'Wendy Kutner'
Cc: Nicholas Hicks (E-mail); Nicholas Hicks (E-mail); Nicholas Hicks (E-mail 2); Muir Gray (E-mail); Edmund Hey (E-mail)
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Thanks for copying me in to this, Sue. I'm sorry Nick won't be able to make it. Please would you ask him to brief Muir Gray, who is able to attend the meeting, about the GRIP work done in Oxfordshire in the early-mid-1990s. Thanks, 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: GARDINER SUE (5CQ) MILTONKEYNES-PCT [mailto:sue.gardiner@mkpct.nhs.uk]
Sent: 10 June 2004 15:56
To: 'Wendy Kutner'
Cc: 'Iain Chalmers'
Subject: FW: Witness Seminar: Prenatal corticosteroids - 15th June 2004

I write to inform you that Nick Hicks is unable to attend on the 15th June. He has to attend an all day meeting for Milton Keynes South Midlands Group whereby the day includes interviews for the main consultant.

With kind regards.
Sue Gardiner

Sue Gardiner
Personal Assistant/Project Officer
to Dr Nicholas Hicks & Dr Vasco Fernandes
Milton Keynes Primary Care Trust

email: sue.gardiner@mkpct.nhs.uk
Tel No: 01908 243084
Fax No: 01908 243517
MK PCT Intranet: <http://mkpct>
MKPCT Website: <http://www.mkpct.org.uk>

This e-mail is confidential and privileged. If you are not the intended recipient please accept our apologies; please do not disclose, copy or distribute information in this e-mail or take any action in reliance on its contents: to do so is strictly prohibited and may be unlawful. Please inform us that this message has gone astray before deleting it. Thank you for your co-operation.



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Dr Nicholas Rooke Hicks FFPHM FRCP
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Old Road
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Fax: +44 (0) 20 7679 8193

28 April 2004

Dr Hicks

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

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

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

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Continued/... Page 2

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.



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

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Dr Alison Hill
Buckinghamshire Health Authority
Vernley House
Gatehouse Road
Aylesbury HP19 8ET

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

25 March 2004

Dear Dr Hill

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

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

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Continued/... Page 2

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

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

To: alison.hill@phru.nhs.uk
Cc: Daphne; Chalmers, Sir Iain
Subject: Witness Seminar: 15 June 2004 - Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth



CORTI Hill invltr.doc DRAFT cortico FLYER WHATIS--april2004r
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Dear Dr Hill, Please find attached an invitation to the above meeting. A previous invitation was sent to the wrong address on 25th March. A hard copy of the letter and attachments will be sent to you in the post today. We do hope you are able to attend. Yours sincerely, Wendy Kutner

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

Tel: 020 7679 8106
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21 April 2004

Dear Dr Hill

The Wellcome Trust's History of Twentieth Century Medicine Group
Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality
associated with preterm birth
Tuesday 30th March 2004 2.00 pm – 6pm

We wrote to you on 25th March, inviting you to attend the above meeting. As we have not had a reply, but have been experiencing difficulties with our post, our original letter, or your reply, may therefore have gone astray. We enclose a copy of that letter and look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.



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27 April 2004

Dear Dr Hill

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Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality
associated with preterm birth
Tuesday 15th June 2004 2.00 pm – 6pm**

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Yours sincerely

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey



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

24 Eversholt Street • London • NW1 1AD
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Dr Alison Hill
Director, Public Health Resource Unit
Institute of Health Sciences,
Old Road,
Headington,
Oxford OX3 7LF

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

29 April 2004

Dr Hill

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Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality
associated with preterm birth
Tuesday 15th June 2004
2.00 pm – 6.00 pm**

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Continued/... Page 2

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

The Wellcome Trust Centre for the History of Medicine at UCL
UNIVERSITY COLLEGE LONDON
24 Eversholt Street, London, NW1 1AD
The Wellcome Trust History of Twentieth Century Medicine Group

Professor Ross Howie
2 Matata St
Blockhouse Bay
Auckland
NEW ZEALAND

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

20 April 2004

E-Mail h.r.howie@xtra.co.nz

Dear Professor Howie

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

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Continued/... Page 2

As a colleague of Professor Mont Liggins, we feel that your attendance would greatly enhance the success of the meeting. I am writing, therefore, to enquire whether, in principle, you would be able to travel to England to participate as a main witness on Tuesday 15th June 2004. Unfortunately, we do not have the funds to assist with travel from overseas. However, we are able to fund your travel within the UK to and from the meeting and to offer you accommodation for the night of the meeting at the Ibis Hotel London Euston and will reserve an extra night's accommodation if you require it.

We are hoping that Professor Jane Harding will be able to attend. If so, you may prefer to ask her to speak on your behalf, given the distances involved.

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

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

atts.



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Professor Ross Howie
2 Matata St
Blockhouse Bay
Auckland
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Dr Daphne Christie
d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8193

22 April 2004

E-Mail h.r.howie@xtra.co.nz

Dear Professor Howie

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

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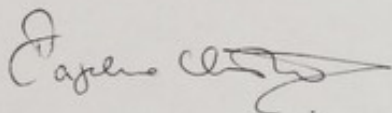
Continued/... Page 2

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We are hoping that Professor Jane Harding will be able to attend. If so, you may prefer to ask her to speak on your behalf, given the distances involved.

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

Yours sincerely

A handwritten signature in dark ink, appearing to read 'Daphne Christie', with a stylized flourish at the end.

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

atts.

Wendy Kutner

To: h.r.howie@xtra.co.nz
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth



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EASinvltr.doc 190404.doc evdc.DOC

Dear Professor Howie, I attach an invitation letter with attachments, inviting you to the above meeting. We very much hope you will be able to attend. Yours sincerely, Wendy Kutner pp Dr Daphne Christie

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

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

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 27 April 2004 11:09
To: h.r.howie
Cc: Wendy
Subject: witness seminar 15 June 2004

Dear Professor Howie

Thank you for your e-mail. We are very sorry that you are unable to attend the witness seminar on 15 June.

We are grateful for your offer to provide something in writing for the seminar. As you know we are hoping that Professor Jane Harding will be able to attend. If so, you may like to ask her to speak on your behalf.

We will of course keep you informed about publication of the subsequent witness seminar transcript.

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

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E-mail d.christie@ucl.ac.uk

www.ucl.ac.uk/histmed

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 28 April 2004 13:04
To: Howie
Cc: Wendy
Subject: RE: Witness Seminar: prenatal corticosteroids

Dear Professor Howie

Thank you for your reply. We are sorry that you will be unable to attend the meeting but understand the difficulties involved. We were sorry to hear the news about your wife's injury and hope that with time things will become a little easier.

We look forward to receiving an account of the steroid work with Mont Liggins and have noted that this might need to be revised in the future as documents come to light. We'll let you have the report of our meeting - we should have a first draft, fresh from the transcriber, about two months after the meeting.

I have forwarded your request for Vol. 5, on obstetric ultrasound, Vol. 9, on neonatal intensive care, Vol. 10, on Africa and Vol. 12, on maternal care to Tracy Tillotson at the Wellcome Trust, who will deal with your order.

Mary Ellen Avery can be contacted by e-mail: mary.avery@tch.harvard.edu

Thank you for your help.

With best wishes

Daphne Christie

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

From: Howie [mailto:h.r.howie@xtra.co.nz]
Sent: 27 April 2004 21:04
To: d.christie
Cc: Jane Harding
Subject: Witness Seminar: prenatal corticosteroids

Dear Dr Christie,

Thank you for your email and also for the airmail packet which arrived yesterday, containing Volume 1 of the Wellcome Witnesses.

I should very much like to attend the seminar, especially as I have been made aware of a number of misconceptions about the early history of the project. But circumstances make it very difficult and I regret having to decline. I should explain that my wife injured her back 7 years ago, has a resulting chronic pain disorder, is in a wheelchair and needs fairly constant attention. Added to this we have had 2 house moves in the last 15 months, one temporary pending the building of a house purpose-designed for her needs. Not an easy time, but the new house works very well for my wife and she has noticeably improved in it. Most of my papers are still in storage but we are slowly getting organised.

In my earlier email I offered a paper: I note the volume you sent me has no formal papers, so presumably it would not be published. This suits me well as there would then be no restriction on length. I have already been writing on aspects of history that I have been associated with, not to publish but to deposit in our national historical library (the Turnbull Library, Wellington), whose curator expressed interest.

My next project was going to be some account of the steroid work with Mont Liggins, so the timing suits well - except for the fact that I have no easy access at present either to my papers or to a medical library. This places rather heavy demands on a failing memory, but to test it I have written drafts on two matters before seeing the relevant papers and have found my memory totally accurate on one (a minor issue) and reasonably so on the other (with some interesting exceptions). So I feel confident that I could provide you with a fair draft, albeit one that would need to be revised in the future as documents come to light.

In this revision it would be very helpful for me to have the report of your meeting, as it will certainly tell me of things I don't know (I have been largely out of touch for many years), and almost certainly things I disagree with.

I am delighted to know that Mary Ellen Avery will be attending. She was of course in at the very beginning of the surfactant story. I think I last saw her nearly 20 years ago and would very much like to get in touch again. Can you tell me her email address?

Am also delighted to know Jane Harding may be attending to give some New Zealand presence. I left her the trial papers and was especially pleased that she was able to organise the 30-year followup. I think she will have enough to say on her own account and will still plan to send you a paper.

I note that Ian McDonald is a member of your Programme Committee. Is he the contemporary I remember as the life and soul of the party at Knox College, Dunedin in the 1950s? If he is, please give him my warmest greetings.

Your list of published meetings was especially interesting. There was no note of prices or availability, but I wondered if copies of 4 of them are still available:

- * Vol. 5, on obstetric ultrasound
- * Vol. 9, on neonatal intensive care
- * Vol. 10, on Africa
- * Vol. 12, on maternal care

I should very much like to have copies and of course would be happy to pay.

Best wishes,
Ross Howie

Wendy Kutner

From: Howie [h.r.howie@xtra.co.nz]
Sent: 22 April 2004 20:49
To: w.kutner
Subject: Re: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Dear Mrs Kutner,

This is a brief but immediate reply to thank you for your message: it is very kind of the Wellcome Trust Centre to invite me. I shall reply in more detail later, but in short (a) regretfully I shall be unable to come, and (b) if you wish I can try to provide something in writing for the seminar. I hope it goes well.

Best wishes
Ross Howie

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

From: "Wendy Kutner" <w.kutner@ucl.ac.uk>
To: "h.r.howie" <h.r.howie@xtra.co.nz>
Cc: "Daphne Christie" <ucgachr@ucl.ac.uk>
Sent: Friday, April 23, 2004 1:47 AM
Subject: Witness Seminar: Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

> Dear Professor Howie, I attach an invitation letter with attachments,
> inviting you to the above meeting. We very much hope you will be able to
> attend. Yours sincerely, Wendy Kutner pp Dr Daphne Christie

>
> Mrs Wendy Kutner
> Secretary to Dr Tilli Tansey
> The Wellcome Trust Centre
> for the History of Medicine at UCL
> Euston House
> 24 Eversholt Street
> LONDON NW1 1AD
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> Tel: 020 7679 8106
> Fax: 020 7679 8193
> w.kutner@ucl.ac.uk
> www.ucl.ac.uk/histmed
>
>

Dr Daphne Christie

From: Howie [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

08/06/2004

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.

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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 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.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 08 June 2004 09:14
To: Wendy
Subject: FW: Witness Seminar: prenatal corticosteroids
Follow Up Flag: Follow up
Flag Status: Flagged

Wendy

I've sent a copy to Ed and Iain, and copied to Tilli. We should make copies for the 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

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

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Ross N Howie
Auckland, New Zealand
2 June 2004

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But I welcomed Patricia Crowley's meta-analysis and the stimulus the history gave to the work of Iain Chalmers and others in setting up the Cochrane Collaboration. This was a major advance and long overdue, even if I think rather too much has come to be expected of 'evidence-based medicine'. More recently I have welcomed another development, the 30-year 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.

Wendy Kutner

To: h.r.howie@xtra.co.nz
Cc: Daphne Christie
Subject: Witness Seminar - 15th June 2004

Dear Professor Howie

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

This is just to let you know that the meeting was held yesterday and was a splendid occasion.

Thank you for sending us the draft text 'Prenatal glucocorticoids in preterm birth: a paediatric view of the history of the original studies', which was distributed to all participants at the meeting.

We hope to send you a draft manuscript in about three month's time, which we ultimately intend to publish. We hope to be able to include your script in the final papers of the meeting.

Everyone who attended the Witness Seminar felt it was a very interesting and worthwhile meeting and we are grateful to you for your contribution.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

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

Wendy Kutner

From: Howie [h.r.howie@xtra.co.nz]
Sent: 17 June 2004 20:38
To: w.kutner
Cc: Daphne Christie
Subject: Re: Witness Seminar - 15th June 2004

Dear Mrs Kutner,

Thank you very much for the message. I am pleased to know the meeting went well, and look forward to seeing the transcript.

Best wishes,
Ross Howie

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

From: "Wendy Kutner" <w.kutner@ucl.ac.uk>
To: <h.r.howie@xtra.co.nz>
Cc: "Daphne Christie" <ucgachr@ucl.ac.uk>
Sent: Thursday, June 17, 2004 2:32 AM
Subject: Witness Seminar - 15th June 2004

> Dear Professor Howie
>
> The Wellcome Trust History of Twentieth Century Medicine Group
> Witness Seminar: Prenatal corticosteroids for reducing morbidity
> and mortality associated with preterm birth
>
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> Yours sincerely
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> Dr Daphne Christie
> Senior Research Assistant to Dr Tilli Tansey
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> Mrs Wendy Kutner
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Professor Ross Howie
2 Matata St
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7 December 2004

Dear Professor Howie

Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality

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

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

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

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

I look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

Dr Daphne Christie

From: Howie [h.r.howie@xtra.co.nz]
Sent: 31 December 2004 04:50
To: d.christie
Subject: Witness Seminar: Prenatal corticosteroids

Dear Dr Christie,

Many thanks for the draft transcript, which arrived only today having been postmarked in London on 8 December. I look forward to reading it. Given the slowness of the mail to and from this part of the world I cannot hope to return it to you by 10 January but shall try to email comments by that date or shortly after.

Best wishes for the new year and for your new premises. I am sure you will have been very well organised in your move, unlike me, still disoriented after mine!

Ross Howie

Dr Daphne Christie

From: Howie [h.r.howie@xtra.co.nz]
Sent: 06 January 2005 14:12
To: d.christie@ucl.ac.uk
Subject: Witness Seminar: Prenatal corticosteroids

Dear Daphne,

Thank you for your email of 4 January. Open plan is still fashionable but must be hell to work in: my commiserations!

Having had a quick read of the transcript, I congratulate you and the Wellcome Trust Centre on a fascinating document. I learned a lot from it.

I shall make some more detailed comments later but in the meantime here is some typographical editing. This is probably presumptuous of me, not having been at the seminar, as it will be done by the actual speakers. But experience suggests that even the most careful review by individuals (especially of their own work) misses a lot, and in editing there is safety in numbers.

P6, line 6, 'Norman' should be 'Normand', I think.

P8, line 7: 'Gallus' should be 'Gellis' ?

P9, second line from bottom, 'Limie' should be 'Liley'

P10, line 9, also P27 line 11, 'Davies' should be 'Davis' ✓

P13, line 5, 'liquid corticoids' should probably be 'glucocorticoids' ✓
 last line, change 'should' to 'would'

P16, line 3, 'sights' should be 'cites' ✓

Pp18-19, Jane Harding: I need to comment on this further but shall do so later.)

P20, line 14, for '(?)' insert 'tocolytic' ✓
 lines 14-15, in 2 places 'epinol' should be 'ethanol'
 line 15, delete '(?)'. '1970' should read 'about 1971': the exact date will be in records I don't have, but if the exact date is thought to be important one of us could look it up.

P27, lines 4,7 and 12: the word is 'hypophysectomy' (or derivative).

P29, line 4, 'NIX' should be 'NIH'
 line 20, 'cure steroids' should probably be 'corticosteroids'

P30, line 13, 'necalictic'?? Possibly 'nihilistic'
 lines 23-24, 'Rob (?)...': did Patricia Crowley mean me, i.e. 'Ross Howie'? ✓

P32, lines 5 and 6, book title, should it not be '*Effective care in labour and delivery*'? ✓

P34, line 21, name 'Bob Kitchlin' should read 'Bill Kitchen'

P36, lines 2-3, 'between 1977 and Ross's reporting to the College in 1994'. This needs rephrasing: I reported to the College in 1977, not 1994.

P38, last line, 'imagining' should be 'imaging' ✓

P39, second line from bottom, also P48, lines 18 and 21, 'Mark' should be 'Mont' ✓

P40, line 22, 'economies' should be 'the Colonies' (with a capital C!)

P41, line 12, also P44, line 10, and P60, line 2: 'Cliff Robertson' should surely be 'Cliff Roberton'? (I particularly

07/01/2005

8/6/05

remember partly because one of his ancestors had an island named after him in NZ's Bay of Islands in early days, an idyllic one but with a tragic history.)

P44, line 2, 'referred' should surely be 'respiratory'? ✓

In the remainder, quite a lot of editing needed looks to be needed, but it seems more routine, e.g.

P84, line 20, 'ECV, st.....tic (?) version' should presumably read 'ECV, external cephalic version' ✓

P87, line 7, 'placenta eruptions': 'abruptions' surely? ✓

P98, line 5, 'win-rim' should ? be 'win-win' ✓

P102, lines 15,16,22 and 23, 'acumen' should read 'outcome' ✓

Enough for the moment. Shall try to write again soon.

Very best wishes
Ross Howie

Dr Daphne Christie

From: Howie [h.r.howie@xtra.co.nz]
Sent: 06 January 2005 14:13
To: d.christie@ucl.ac.uk
Subject: Witness Seminar: prenatal corticosteroids: illustration

Dear Daphne,

In your letter of 7 December you said you would like 'to include illustrations of early work' in the published volume. Here is one, a photo of Mont Liggins (right) and me, *circa* 1972. It was scanned by me and is sent at the highest resolution of my scanner. Apologies for any technical problems: I am technologically challenged. If you would prefer the original I can post it.

Another illustration I would have liked to send is a Kodachrome slide of the lungs of the lambs I referred to in the piece I wrote for the seminar. It shows the striking contrast between the steroid-treated lamb and the control. Unfortunately it is still with most of my papers in storage and is unlikely to emerge in any reasonable time. It is possible that Mont Liggins has a copy he may be able to send if you are interested.

Regards, Ross Howie

1
forwarded up
8/6/05

Dr Daphne Christie

From: Howie [h.r.howie@xtra.co.nz]
Sent: 11 January 2005 05:16
To: d.christie@ucl.ac.uk
Subject: Fw: Wellcome seminar June 2004: comments from Professor Liggins

Dear Daphne,

Correspondence for your information and use in editing. My reference to 'UC Davis' (**not** for use in the report unless Mont so authorises) is to the fact that, as I understand it, one of the people there used Mont's data as his own and in a subsequent inquiry was found guilty of scientific misconduct and sacked.

I suggest you delete Mel Avery's comment, and on the other matter quote me as doubting the notion that betamethasone is more effective than dexamethasone until there is better evidence than was provided in the early clinical trials.

Best wishes, Ross

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

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

Dear Ross,

I spent a sabbatical with Geoffrey in 1970 but I certainly made no such statement about surfactant. I can't imagine where Mel got that idea. It should be deleted unless it can be validated.

I was aware of the suggestion about the relative efficacy of betamethasone and dexamethasone. I think the evidence deserves your critical comment. I recall that Peter Nathaniel 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.

Regards, Mont

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

From: Howie [mailto:h.r.howie@xtra.co.nz]
Sent: Tuesday, 11 January 2005 6:53 AM
To: Mont Liggins
Subject: Wellcome seminar June 2004

Dear Mont,

I recently received the transcript, as I imagine you did. There is a lot of it that I don't fully understand, very likely because of (a) ignorance and (b) obtuseness on my part, but there are two particular matters on which I would be grateful for your comments before I write back to the organisers.

Page 48, bottom, comment by Mel Avery: '...[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.' I fail to see the point of that comment, even after several re-readings of the context. It could be interpreted as derogatory to you, although I am sure Mel would not have intended that. It seems to me that her comment should be either further explained or omitted entirely. (When was your time in Geoffrey Dawes's lab? If after UC Davis and before first publication of the steroid trials, it seems to me that the attitude imputed to you would be entirely understandable.)

Page 99, lines 9-12: '...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 ...' Is there any real evidence that betamethasone is better than dexamethasone? It seems to me much more likely that the difference is only apparent, and due to the progress of newborn care between the times betamethasone and dexamethasone were used in trials (a matter referred to in the note I sent to the organisers before the symposium), but can you comment?

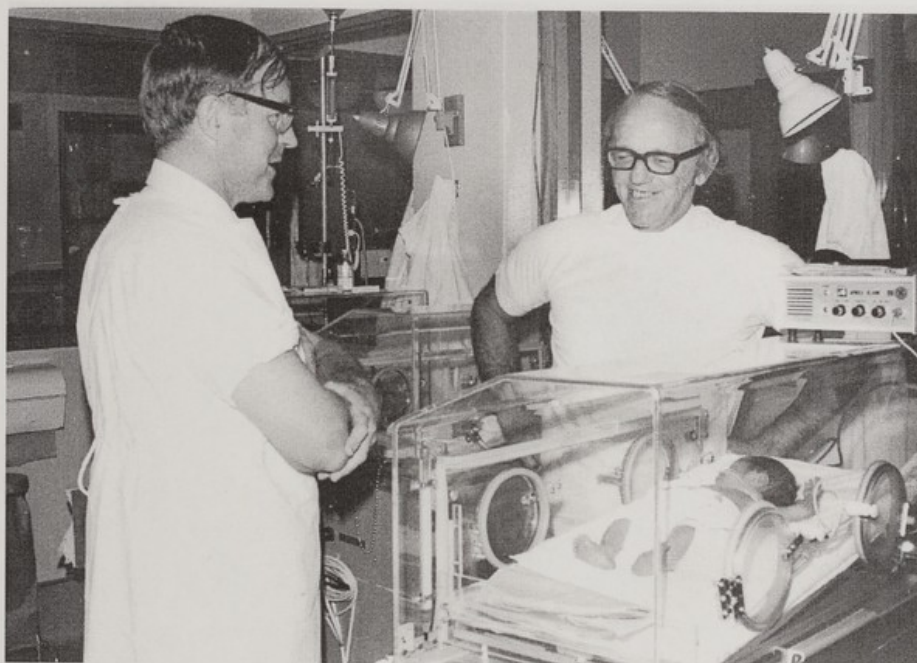
I hope this finds you well. Very best wishes for the year ahead.

Ross

No virus found in this incoming message.

Checked by AVG Anti-Virus.

Version: 7.0.300 / Virus Database: 265.6.10 - Release Date: 10/01/2005



Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 14 June 2005 22:17
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: prenatal corticosteroids : lungs

Dear Lois,

A further reply, this one about the slide you asked for. I have located my slides, at least most of them, but am sorry to say couldn't find it. As it doesn't feature in my slide index I may never have had one of my own. I remember it well but must have borrowed it from Mont Liggins. I have passed on your request to him and hope you have better luck from him.

Best wishes,
Ross Howie

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

From: "Lois Reynolds" <ucgarey@ucl.ac.uk>
To: <h.r.howie@xtra.co.nz>
Sent: Thursday, June 09, 2005 1:28 AM
Subject: Witness Seminar: prenatal corticosteroids : lungs

> Dear Prof Howie,
> I have taken over as joint editor with Tilli of volume 25 on prenatal
> corticosteroids from Daphne and would like to thank you for the
> photograph,
> which is stunning. It has been included in the transcript, which we hope to
> send out for your final comments later on in the summer.
> You mention a slide of the lungs of the lambs. We would be pleased to scan
> it here, if you would trust it to the post? Or, if it was published
> elsewhere, we could scan it from that journal.
> This is a cracking good story.
> Best wishes from Lois Reynolds
>
> Mrs Lois Reynolds
> Research Assistant to Dr Tilli Tansey
> History of Twentieth Century Medicine Group
> Wellcome Trust Centre for the History of Medicine
> at UCL
> 210 Euston Road,
> LONDON
> NW1 BE
>
> Tel: 020 7679 8123
> email: l.reynolds@ucl.ac.uk
> Fax: 020 7679 8192
> www.ucl.ac.uk/histmed/witnesses.html
>
> The Wellcome Trust Centre is supported by the Wellcome Trust, a registered
> charity, no. 210183.

Dear Ross,

Many thanks for the e-mail of 8 August.

Attached is an electronic version of the transcript without the illustrations (234KB). A hard copy will also be sent by post. Thanks for the postcode.

We would be grateful for your corrections by 7 September 2005.

I have not found an electronic version of your memoir here, so I assume that we received it as a typescript. I would be grateful if you didn't shorten it too much, as it will make a great appendix along with Mont's letter to Iain Chalmers (quoted by Jane Harding on pages 8 and 9 of the attached transcript). Tilli will provide a second appendix on the funding from the Wellcome Trust.

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

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

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

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

A further query has arisen from footnote 75 on page 48, which is Mont's comment on betamethasone and dexamethasone. Is there a Nathanielsz paper you would recommend citing, other than Nathanielsz (1996) [Life Before Birth: The challenges of fetal development. New York, NY: W H Freeman. First published by Prometheus Press, NY, 1992.]? Secondly, would you like to reply, as Mont suggested?

Best wishes from Lois Reynolds

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

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

The footnote at present reads:

Professor Mont Liggins wrote to Dr Ross Howie: 'I spent a sabbatical with Geoffrey in 1970 but I certainly made no such statement about surfactant. I can't imagine where Mel got that idea. It should be deleted unless it can be validated. I was aware of the suggestion about the relative efficacy of batamethasone and dexamethasone [see note 163]. I think the evidence deserves your critical comment. I recall that Peter Nathanielsz reported that 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. Professor Liggins also wrote to Dr Daphne Christie: 'Mel Avery's comment ... is news to me and I cannot imagine where she got this idea from. I had no reason to make such a statement. I think it should be deleted unless it can be validated.' E-mail to Dr Daphne Christie, 8 January 2005.

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

Dear Sir Graham,

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

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

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

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

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

Best wishes from Lois Reynolds

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

VERY: 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.

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

Lois Reynolds

To: Howie
Subject: RE: Witness Seminar: Prenatal Corticosteroids: query

Dear Ross,

Many thanks for the note.

I will be happy to remove the illustrations and send you an electronic version of the transcript, and send a hard copy by post. Thanks for the postcode.

I have not found an electronic version of your memoir here, so I assume that Jane gave it to us as a typescript. It would be grateful if you didn't shorten it too much, as it will make a great appendix along with Mont's letter to Iain Chalmers. Tilli will provide a second appendix on the funding from the Wellcome Trust.

You will notice the footnote on page 48 in the text, in response to Mel Avery's comments (below). My query is about beta and dex, and whether there is a Peter Nathanielsz paper you would like to use (a general reference is at the end) and if you would like to reply, as Mont suggested.

Mel Avery's attention was drawn to this 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.

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From: Howie [mailto:h.r.howie@xtra.co.nz]
Sent: 08 August 2005 19:24
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal Corticosteroids: query

Dear Lois,

It was good to hear from you. Re biographical note: I gave one to Daphne

CSD about
dissociated C bords remarks - also recorded chd obstetrics.

Christie in an email of 5 April (2nd paragraph). If you publish my memoir the two last sentences of that note could be deleted, leaving it as follows:

"FRACP (b.1933). Held various neonatal paediatric positions at National Women's Hospital and the University of Auckland from 1962 until 1995."

I think the briefer the better. Given the short length of the Sir Joseph Barcroft's in the sample you gave me, mine would warrant no more space.

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I hope all continues well with all of you, especially free of the kind of trouble you had in London recently, which must have been painfully close.

Best wishes
Ross Howie

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To: <h.r.howie@xtra.co.nz>

Sent: Saturday, August 06, 2005 5:19 AM

Subject: Witness Seminar: Prenatal Corticosteroids: query

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- > May I ask for a copy of your brief CV, in order to produce a biographical
- > note for the back of our volume? Below is a sample version, so you can see
- > what is needed.
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 > Mrs Lois Reynolds
 > Research Assistant to Dr Tilli Tansey
 > History of Twentieth Century Medicine Group
 > Wellcome Trust Centre for the History of Medicine
 > at UCL
 > 210 Euston Road,
 > LONDON
 > NW1 BE
 >
 > Tel: 020 7679 8123
 > email: l.reynolds@ucl.ac.uk
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 >
 > The Wellcome Trust Centre is supported by the Wellcome Trust, a registered
 > charity, no. 210183.
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 > --
 > No virus found in this incoming message.
 > Checked by AVG Anti-Virus.
 > Version: 7.0.338 / Virus Database: 267.10.1/64 - Release Date: 4/08/2005
 >
 >

**Lois Reynolds**

From: Dr Tilli Tansey [t.tansey@ucl.ac.uk]
Sent: 09 August 2005 13:16
To: ucgarey
Subject: RE: Witness Seminar: Prenatal Corticosteroids: query

I have some comments on message to Ross - I think you should EXPLAIN to them both why we are apparently ignoring their wishes. Can we check when i get back from hairdressers?
well done on spotting mistakes -what were they?
t

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

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: 9 August 2005 09:51
To: Tilli
Subject: FW: Witness Seminar: Prenatal Corticosteroids: query

Hi Tilli, I was proposing to send Ross the following reply. Would you like to tinker with it? I think it is better to deal with this potential blister before it is generally distributed, and if necessary, an addendum to this footnote could be added before being put in the post. A similar note will go to Mont. Best wishes from Lois

PS. How are you? Things going well here, we found a couple of bloopers in the texts and have uploaded the corrected versions. Julie will be back from Edinburgh on Friday and will let Mike have the corrected texts for posting on the website. Corticosteroids with the photocopier and I'm preparing the letters. Also, must get to UCL at noon to renew my library card, and then pay the credit card bill before I go. Argggh. LR

Dear Ross,

Many thanks for the note.

I will be happy to remove the illustrations and send you an electronic version of the transcript, and send a hard copy by post. Thanks for the postcode.

I have not found an electronic version of your memoir here, so I assume that Jane gave it to us as a typescript. It would be grateful if you didn't shorten it too much, as it will make a great appendix along with Mont's letter to Iain Chalmers. Tilli will provide a second appendix on the funding from the Wellcome Trust.

You will notice the footnote on page 48 in the text, in response to Mel Avery's comments (below). My query is about beta and dex, and whether there is a Peter Nathanielsz paper you would like to use (a general reference is at the end) and if you would like to reply, as Mont suggested.

Mel Avery's attention was drawn to this comment, but no comment has been received.

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. 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.

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

AVERY: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically told Dawes that he would not allow anyone to do any work, even discuss, surfactants for the whole time that Mont was there. (FN1)

The footnote at present reads:

(FN1) 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 163]. 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 Prometheus Press, NY, 1992.

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- > The Wellcome Trust Centre is supported by the Wellcome Trust, a registered
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- >
- >



Appendix 2 Howie
permission

Dr Ross Howie,
2 Matata St,
Blockhouse Bay,
Auckland, 1007
NEW ZEALAND

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

10 August 2005

Dear Dr Howie,

**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 memoir that you provided for distribution at the meeting, dated 2 June 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 ordered 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 has been provided for your files.

Yours sincerely

Lois Reynolds

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
enc. Draft appendix to Volume 25.

Please sign & return

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 18 August 2005 00:00
To: ucgaray@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal Corticosteroids: query

Dear Lois,

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It would be easier for me to reply in several emails, and I shall try to do this within your deadline. On the matter of Mel Avery's comments, I am happy to defer to your editorial judgment. To save time, your query about a Nathanielsz paper might be best sent directly to Mont Liggins (g.liggins@auckland.ac.nz). Shall try to be in touch again before long.

Best wishes
Ross Howie

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From: "Lois Reynolds" <ucgaray@ucl.ac.uk>
To: "Howie" <h.r.howie@xtra.co.nz>
Sent: Thursday, August 11, 2005 3:39 AM
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> Many thanks for the e-mail of 8 August.
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> Attached is an electronic version of the transcript without the
> illustrations (234KB). A hard copy will also be sent by post. Thanks for
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> We would be glad of your corrections by 7 September 2005.
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 > comments on page 48 in footnote 75 (copied below). As you know, Mont's
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 > considered them to be inaccurate. We have not removed Mel's comment, for a
 > number of reasons.

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

>

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

>

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

>

> A further query has arisen from the same footnote 75 on page 48, which is
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✓ sent to Mont
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 the
 > Committee of Safety of Drugs (Volume 1, 1997, freely available at
 > www.ucl.ac.uk/histmed following 'Publications' link). Three different
 > versions of the origin of the yellow cards for adverse reactions (see
 pages
 > 111, 124 and 127) were revealed.

>

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

>

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

>

> A further query has arisen from the same footnote 75 on page 48, which is
 > Mont's comment on betamethasone and dexamethasone. Is there a Nathanielsz
 > paper you would recommend citing, other than Nathanielsz (1996) [Life
 Before
 > Birth: The challenges of fetal development. New York, NY: W H Freeman.
 First
 > published by Prometheus Press, NY, 1992.]? Secondly, would you like to
 > reply, as Mont suggested?

>

> Best wishes from Lois Reynolds

>

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

>
 > AVERY: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab
 > and specifically told Dawes that he would not allow anyone to do any work,
 > even discuss, surfactants for the whole time that Mont was there.
 >
 > The footnote at present reads:
 > Professor Mont Liggins wrote to Dr Ross Howie: 'I spent a sabbatical with
 > Geoffrey in 1970 but I certainly made no such statement about surfactant.
 I
 > can't imagine where Mel got that idea. It should be deleted unless it can
 be
 > validated. I was aware of the suggestion about the relative efficacy of
 > batamethasone and dexamethasone [see note 163]. I think the evidence
 > deserves your critical comment. I recall that Peter Nathanielsz reported
 > that 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. Professor Liggins also wrote to Dr Daphne Christie: 'Mel Avery's
 > comment .is news to me and I cannot imagine where she got this idea from.
 I
 > had no reason to make such a statement. I think it should be deleted
 unless
 > it can be validated.' E-mail to Dr Daphne Christie, 8 January 2005.
 >
 > Note 163: Dr Clive Dash wrote: 'Various preparations of betamethasone are
 > available in different countries. The preparations are all designed to
 > release the active sterol, betamethasone, but at different rates. The
 > soluble phosphate preparation is suitable for intravenous administration,
 > like hydrocortisone, as well as intramuscular injection. The acetate
 > preparation is not suitable for intravenous (IV) use. Some products are a
 > mixture of the acetate and phosphate derivatives (e.g. Celestone®,
 > Schering). In some countries dexamethasone is more readily available than
 > betamethasone and this is why it has featured in some studies. These two
 > steroids are isomers in which the methyl group differs in its orientation
 > (dexamethasone is 9-a-fluoro 16-a methyl prednisolone; betamethasone is
 > 9-a-fluoro 16-b methyl prednisolone)[Sweetman (2002): 1063 and 1067]. In
 the
 > usual pharmacological tests of corticosteroid potency, they are
 equivalent.
 > In general, the mode of action (pharmacodynamics) seem similar, so they
 > should be therapeutically equivalent.' E-mail to Dr Daphne Christie, 10
 > January 2005.
 >
 > 0-0-0-0-0-0
 >
 > -----Original Message-----
 > From: Howie [mailto:h.r.howie@xtra.co.nz]
 > Sent: 08 August 2005 19:24
 > To: ucgarey@ucl.ac.uk
 > Subject: Re: Witness Seminar: Prenatal Corticosteroids: query
 > [...]

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 19 August 2005 05:14
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal Corticosteroids: medical journals

Dear Lois,

In your letter of 11 August you asked if I could suggest a journal, website or information group that might be willing to review the volume. I don't know any websites or information groups, and my suggested medical journals will be fairly obvious, but here is the list of journals I have had some contact with myself (directly or indirectly):

New Zealand Medical Journal
Australian and New Zealand Journal of O&G
Pediatrics (who published our original paper)
The journal sponsored by the RCOG, whatever it is called now (used to be JOGBC)
The Lancet

It would be rather fun to send it to the last-mentioned: it rejected our original paper. See letter from Mont Liggins to Iain Chalmers (your proposed appendix). In the letter Mont said it was Nature but he queried this with me after he had written it. My firm memory is that it was The Lancet and not Nature. The latter journal in my time was not I think interested in clinical papers, but could well have been offered some of Mont's other work. The rejection letter was as I remember very prompt, courteous and brief: there would have been very little time to send it to referees.

I was, ironically, reminded of The Lancet by a circular email that I received only this morning which included this paragraph:
"Medical professionals like you subscribe to The Lancet because of our practice-changing content. They know that they can rely on The Lancet to publish the cream of the world's medical research - and to provide the news and analysis that puts that research into a clinical context."

I was pleased to read it. The Lancet must have changed its policies in the last 33 years! It has of course recently published the 30-year followup by Stuart Dalziel et al, the reference to which you have cited somewhere in the transcript.

Best wishes,
Ross Howie

Howie

✓

to mktg plan
1/9/05

✓ sent to Mont ✓
1/9/05

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 22 August 2005 04:34
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal Corticosteroids: your queries

Dear Lois,

Another reply, this time about your queries relating to specific pages in the transcript.

Pp 6-8: p6 para 3: the date was 1968 as I remember (the occasion the opening of the new Christchurch Women's Hospital), but Mel Avery will confirm. I have no other comment.

P 12, para 2: highlighted words should read '...who was able to ventilate [newborn] babies.'

P 28: no special comments.

P 36: highlighted words would read more logically (at least to me) '...between 1977, when Ross reported to the College, and 1994 ...'. The College was of course the RCOG and the paper was published in the proceedings of the meeting, reference given on p28, footnote 39.

P 42: no special comment.

P 48: your footnote 75 is confusing, as most of it is not relevant to Mel Avery's comment in the middle of the page. It may be best restricted to the email Prof Liggins wrote to Daphne Christie on 8 January 2005. The issue of the relative efficacy of betamethasone and dexamethasone is discussed on pp 93-94 and may be best dealt with in footnote 165, in which you might like to include the reference to Nathanielsz if you can get the right one. I very much doubt that the book you cite would say anything about it. Incidentally in your present footnote 65 'betamethasone' is misspelt. Also when I followed your suggestion to '[see note 144]' I found that the latter rather unhelpfully instructed me to 'see note 43'. Did you mean note 165?

Pp 69, 79, 86, 87: no special comment.

Pp 93-4, comparison of dexamethasone and betamethasone: I haven't been able to look at Jobe and Soll's paper but wonder if the supposed difference between the two drugs in effect on mortality was simply due to differing standards of newborn intensive care at the times the trials were carried out. I referred to the latter in my memoir.

P 101: no special comment.

P 115, biographical note: see my email to you of 9 August. I see no pressing reason to add to it! My email to Daphne Christie of 5 April had 2 more sentences, but their content is covered by my memoir as well as in the body of the transcript (p12, paras 2 and 3), and I doubt the need for further repetition.

Enough for the present. I plan to send at least 2 more messages, one about the appendices and one commenting further on the transcript (the parts not covered in this one).

Sincerely,
Ross Howie

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 22 August 2005 19:07
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar Prenatal Corticosteroids: appendices

Dear Lois,

A further message, about the appendices.

1. Mont Liggins's letter: can you enlarge the print to its original size?
I am rather embarrassed by the contrast between his and mine in the amount of space taken. About journal rejection (second-to-last paragraph), as I said in my message to you of 19 August I am fairly sure it was The Lancet and not Nature. I forwarded the email to Mont but haven't yet had a reply: I am sure he will correct me if I am wrong.

2. My memoir: On reflection, I would be happy for you to publish it as is: it is a bit rough, but I suppose that is in keeping with the informality of most of the rest of the transcript. If it would make it any easier for you I would be happy to send my electronic version. I shall post the consent form.

Could you make an additional note at the end, regarding my end-note 2, to the effect that Sir Iain Chalmers passed this query on to the noted US pioneer, Dr William Silverman, who replied

'...The origin of the word "perinatal" can be traced to Peller [1]: "he coined the term to mean ante-, intra-, and postpartum, the period around and including the time of birth" [2]

1. Peller S. Mortality, past and future. Population Studies 1948;1:405-
2. Silverman WA. Dunham's Premature Infants. Third Edition. 1961 page 4'.

Could I suggest yet another appendix: the list of Auckland papers I sent you on 9 April. As I said to Daphne Christie (email 5 April 2005), '[I]t may be relevant for you to have a complete list of the early Auckland publications.... Possibly no one else has one.... Most of the publications are not listed by Medline as they are in books or conference reports....' It could be important to have the list somewhere in print for the historical record. But I leave this to your judgment.

Best wishes
Ross Howie

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 26 August 2005 20:29
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal Corticosteroids: query

Dear Lois,

This is the final message in my series in reply to your letter of 11 August and emails about the transcript.

P 13, lines 5 and 6, highlighted words: I suggest simply leaving the bracketed words out. I was certainly not the only paediatrician who could look at or after premature babies, but I was the only one who had the time and interest to record and analyse the information needed for the trials. I think Jane's meaning is clear enough without elaboration. ✓

P 14, footnote 21: The 1987 reference should be deleted; it had nothing to do with the steroid work. The first one is correct. It should be followed by the second:

MacArthur BA, Howie RN, Dezoete JA, Elkins J. School progress and cognitive development of 6-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* 1982; 70: 99-105.

For consistency, you might like to put both references in your References section at the end, and let the footnote simply read 'MacArthur et al, 1981 and 1982'. ✓ FN

P 14, footnote 22: is this needed at all?

P 18, highlighted words: both the hospital and the academic unit actually started before 1964. What those of my generation called the 'new' National Women's Hospital indeed opened in that year (incidentally, it closed in 2004), but the relevant date is probably 1951 when the Postgraduate School of O&G was set up. If you want more of the story, it all started in the rather dilapidated remnants of what had been built as the 39th US Army General Hospital during World War II in a city park. After the war the buildings were taken over by the then Auckland Hospital Board, which moved both its O&G Unit and geriatric wards there, I think in 1948. This was a possibly unique pairing of services for both the beginning and end of life. I understand the O&G Unit became the National Women's Hospital in 1955, but am uncertain about this: I shall ask the historian Linda Bryder, who is currently researching the history of NWH, to check. ✓ FN

P 18, lines 9-11: Bird ventilator has a capital B. I started using CPAP in 1970 (Gregory et al's paper appeared in 1971). The idea was brought back to Auckland by Mont Liggins; I did not myself meet the San Francisco group until 1972. It was, incidentally, brilliant and possibly the greatest single advance ever made in the management of RDS, therapeutic surfactants notwithstanding. In retrospect the development was simple and logical, and I am sure I was not the only one in the field who kicked himself for not having thought of it. ✓ FN

P 19, line 14, '...how positive people were about the trial': this would have been greatly helped by the way Barton MacArthur and Anne Dezoete ✓ FN

carried out the 4- and 6-year followup studies. They were superb not only in their testing but in the way they related to their subjects and the parents. ✓

P 36, last para, '... the Swiss were talking about this treatment seriously inhibiting lungs ...': could you please add a footnote here or elsewhere about the possible hazards of steroids to the fetus. I am surprised that in all the discussions I have heard and read, little mention has been made of the work of the Ballards (J Clin Invest 1975; 56: 1548). They measured glucocorticoid levels in maternal and cord serum after prenatal betamethasone therapy, and concluded that glucocorticoid concentrations in cord serum were in the physiologic stress range and not at potentially harmful pharmacologic levels. Many people (I know not Mel Avery) in talking about hazards confuse therapy before birth with therapy after: in the course of ordinary treatment, steroid levels are many times higher in the latter case. The dose Mont Liggins gave to the mother resulted in levels in the newborn comparable to those the baby would have in the course of an illness like RDS. Has anyone ever thought of doing a 30-year followup of babies with RDS with this in mind? Of course, as Mont has suggested, there may be hazards of synthetic steroids as opposed to naturally-occurring compounds, but I know of no evidence for this. ✓
FN

P 40, footnote 58, title of citation: I try to get these right, but sometimes don't manage! I have a copy of this article somewhere in my papers but it hasn't yet surfaced. If you are unable to find one I suggest you leave the title as you have it. ✓

Pp 45-46, outcome according to sex of baby: this is something I had not analysed in the Auckland study, and when I heard of the NIH findings I went back to check. This showed that in our hands, in contrast to the NIH study, betamethasone appeared to be more effective in boys than in girls. I concluded that the difference may have been due to the fact that we are in the southern hemisphere. ✓

P 52, on retention of records: the records were kept for just this purpose, for possible future use. There was hardly enormous generosity on my part, and I was delighted that Jane and others were able to make use of them. One possible reservation: I was once told early in my career NEVER [please put this word in l.c. italics as I can't do it here] to let anyone else look at my raw data. The reason given was that there are many ways of analysing them, and some people would be only too willing to do so in such a way as to make you look a fool, or a fraud, or both. The person who told me this was one of the finest scientists I have known and no more paranoid than the rest of us. There were I confess one or two people I would not have wanted to see the material, but I had no hesitation about Jane. I imagine there would be no problem of this kind in these days of grand multiplicity of authorship, but we did not have that luxury in the early 1970s. ✓

That is all I can think of at the moment. Best wishes for your task!

Ross Howie

check
against
the report

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 26 August 2005 20:29
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal Corticosteroids: query

Dear Lois,

This is the final message in my series in reply to your letter of 11 August and emails about the transcript.

P 13, lines 5 and 6, highlighted words: I suggest simply leaving the bracketed words out. I was certainly not the only paediatrician who could look at or after premature babies, but I was the only one who had the time and interest to record and analyse the information needed for the trials. I think Jane's meaning is clear enough without elaboration.

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P 19, line 14, '...how positive people were about the trial': this would have been greatly helped by the way Barton MacArthur and Anne Dezoete

✓
✓ OK on transcript
as corrected
by L. Bryder.
checked
26/10/05

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P 36, last para, '... the Swiss were talking about this treatment seriously inhibiting lungs ...': could you please add a footnote here or elsewhere about the possible hazards of steroids to the fetus. I am surprised that in all the discussions I have heard and read, little mention has been made of the work of the Ballards (*J Clin Invest* 1975; 56: 1548). They measured glucocorticoid levels in maternal and cord serum after prenatal betamethasone therapy, and concluded that glucocorticoid concentrations in cord serum were in the physiologic stress range and not at potentially harmful pharmacologic levels. Many people (I know not Mel Avery) in talking about hazards confuse therapy before birth with therapy after: in the course of ordinary treatment, steroid levels are many times higher in the latter case. The dose Mont Liggins gave to the mother resulted in levels in the newborn comparable to those the baby would have in the course of an illness like RDS. Has anyone ever thought of doing a 30-year followup of babies with RDS with this in mind? Of course, as Mont has suggested, there may be hazards of synthetic steroids as opposed to naturally-occurring compounds, but I know of no evidence for this.

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That is all I can think of at the moment. Best wishes for your task!

Ross Howie

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 29 August 2005 02:22
To: ucgarey@ucl.ac.uk
Subject: Fw: NWH dates (Witness seminar, prenatal corticosteroids)

Dear Lois,

Could you please correct the note in my message of 27 August relating to p18, about dates. As I mentioned to you, I checked with Linda Bryder, whose reply is below. If you use my note at all, the last two dates need to be amended (the earlier dates are correct). My paragraph should now read:

"[B]oth the hospital and the academic unit actually started before 1964. What those of my generation called the 'new' National Women's Hospital indeed opened in that year (incidentally, it closed in 2004), but the relevant date is probably 1951 when the Postgraduate School of O&G was set up. If you want more of the story, it all started in the rather dilapidated remnants of what had been built as the 39th US Army General Hospital during World War II in a city park. After the war the buildings were taken over by the then Auckland Hospital Board, which moved both its O&G Unit and geriatric wards there in 1946. This was a possibly unique pairing of services for both the beginning and end of life. The O&G Unit became the National Women's Hospital about 1954."

✓
on transcript
as FN. 31/8/05

Thanks,
Ross Howie

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

From: Linda Bryder (ARTS HIS)
To: Howie
Sent: Monday, August 29, 2005 10:51 AM
Subject: RE: NWH dates

Dear Ross

It was opened in 1946 as an obstetrical and gynaecological unit, and while there seemed to be no celebration of the new name 'National Women's Hosptial' (that I have found yet anyway), it was being called that by 1954.

Best wishes

Linda

From: Howie [mailto:h.r.howie@xtra.co.nz]
Sent: Wednesday, 24 August 2005 4:37 p.m.
To: Linda Bryder (ARTS HIS)
Subject: NWH dates

Dear Linda,

Thank you for sending back my CV. I shall assemble and post back the updated version.

Can I ask you to check something for me? I was sent the transcript of the London witness seminar, which included a statement that NWH opened about 1964. This needs to be corrected, and I have sent back a message with the following statement:

31/08/2005

What those of my generation called the 'new' National Women's Hospital indeed opened in 1964 (incidentally, it closed in 2004) but the enterprise had been going for a number of years before that. If you want a fuller story, it all started in the rather dilapidated remnants of what had been built as the 39th US Army General Hospital during World War II in a city park. This was taken over after the war by the then Auckland Hospital Board and opened again I think in 1948 as both its O&G Unit and its geriatric wards, a possibly unique pairing of services for both the beginning and end of life. The Postgraduate School of O&G started in the former in 1951, and this is probably the significant date. I am told the O&G Unit became the National Women's Hospital in 1955, but am uncertain about this. The historian Linda Bryder is currently researching the history of NWH, and I shall ask her to check the dates I have given.

I know the date for the Postgraduate School only because I remember its 25th anniversary in 1976 and 50th in 2001, and am uncertain about the 1948 and 1955 dates. Could you check them and the rest of the paragraph and let me know if any corrections are needed?

Many thanks,
Ross

Lois Reynolds

From: Lois Reynolds [ucgarey@ucl.ac.uk]
Sent: 31 August 2005 11:09
To: Howie
Subject: RE: NWH dates (Witness seminar, prenatal corticosteroids)

Hi Ross,

The correction will appear as a footnote. Many thanks from Lois

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

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Sent: 29 August 2005 02:22
To: ucgarey@ucl.ac.uk
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Ross Howie

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Best wishes

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I know the date for the Postgraduate School only because I remember its 25th anniversary in 1976 and 50th in 2001, and am uncertain about the 1948 and 1955 dates. Could you check them and the rest of the paragraph and let me know if any corrections are needed?

Many thanks,
Ross

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 25 September 2005 22:56
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal Corticosteroids: your queries

Dear Lois,

Sorry to have been so very long in replying, but I have been laid low by a virus for the past 2 weeks. Thank you very much for sending me Jobe and Soll's paper (and for sending it in the body of the email: I could not access the URL). At the moment I am not in a position to make further enquiries about the points you raise, but could I simply amend the comment in my email of 22 August to read something like:

"Pp 93-4, comparison of dexamethasone and betamethasone: I wonder how much of the apparent difference between the two drugs in effect on mortality may have been due to differing standards of newborn intensive care at the times and places the trials were carried out." You could refer to my memoir, p4, paras 3 and 4. ✓

A different point : on the rejection of our initial paper, referred to by Mont Liggins in the letter you plan to include as an appendix, I can confirm that it was by The Lancet and not Nature. It says so in a piece I found recently, written by Mont himself and available online at <http://garfield.library.upenn.edu/classics1982/A1982NF37800001.pdf>. ✓

*corrected
26/9/05*

Another apology, that I overlooked sending you the consent form for publication of my memoir. This has now been signed and is out for posting.

I hope my delays have not held up the project too much, and that it is otherwise going well.

Best wishes,
Ross Howie

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

From: "Lois Reynolds" <ucgarey@ucl.ac.uk>
To: "Howie" <h.r.howie@xtra.co.nz>
Sent: Friday, September 02, 2005 3:46 AM
Subject: RE: Witness Seminar: Prenatal Corticosteroids: your queries

> Dear Ross,
> Re Jobe and Soll's 2004 paper: this can be viewed online
>
> (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=A>
> bstract&list_uids=15118606&query_hl=29) or downloaded, perhaps at your
> library.
> The text follows, if this is any help.
> Best wishes from Lois
>
> [....]

To: The History of Twentieth Century Medicine Group

I agree to the above request to reproduce the memoir^{*} described below which was distributed at the Witness Seminar on Prenatal Corticosteroids on 15 June 2004, to be described as:

'Prenatal glucocorticoids in preterm birth: a paediatric view of the history of the original studies' by Ross N Howie, 2 June 2004, a draft form of which was distributed at the Witness Seminar held on 15 June 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.

** As amended and sent with my email of 8 September 2005*

Signed *R. N. Howie* Dated *25-9-2005*

Dr Ross N Howie
2 Matata St,
Blockhouse Bay,
Auckland, 1007
NEW ZEALAND

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 25 October 2005 18:36
To: ucgarey@ucl.ac.uk
Subject: Re: Wellcome Witnesses: prenatal corticosteroids : publications list query

Dear Lois,

I can't really answer this one. The reference appears on our list, so a paper must have been prepared for it, but I didn't ever see it in print. I did not attend the Buenos Aires Congress. Our paper will be in a file I have somewhere in boxes currently inaccessible following our house move.

My list was of papers prepared for publication. I have sighted all the others in print and can vouch for them (if not necessarily the complete accuracy of the citations), but as I can't verify the publication of this one perhaps it shouldn't go on your list. That is unless you can verify it yourself. Unfortunately I have no access to the 'For a healthy child in a better world' publication you cite. If you find it I would be most grateful for a copy.

I can't understand the part of your message "Alleyne G A O, Hay R W, Picou D I, Stanfield J P, Whitehead R G. (eds) (1977) Protein-energy Malnutrition. London : Edward Arnold", and think it is unlikely to be relevant.

I don't think you should go to too much trouble to sort this out, and the simplest solution may be to omit the reference, and leave the list un-numbered. Sorry to have caused confusion!

Best wishes,
Ross

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

From: "Lois Reynolds" <ucgarey@ucl.ac.uk>
To: <h.r.howie@xtra.co.nz>
Sent: Wednesday, October 26, 2005 3:56 AM
Subject: Wellcome Witnesses: prenatal corticosteroids : publications list query

> Dear Ross,
> One last query on your publications list. Could you let me know which is
> correct? Best wishes from Lois
>
> 0-0-0-0
> Howie R N, Liggins G C. (1974) Clinical trial of betamethasone for the
> prevention of the respiratory distress syndrome. Proceedings of the XIV
> International Congress of Paediatrics, Buenos Aires, 3-9 October, 1974.
>
> ??In For A Healthy Child in A Better World: Fourteenth International
> Congress of Paediatrics, Buenos Aires, 3-9 October 1974 and five other
> recent paediatric congresses. Annales Nestlé series no. 35. Zurich: Nestlé
> Scientific Services, PAGES OR Alleyne G A O, Hay R W, Picou D I, Stanfield

Removed 31/10/05

J

> P, Whitehead R G. (eds) (1977) Protein-energy Malnutrition. London :
Edward

> Arnold, PAGES.

>

> 0-0-0-0

>

> Mrs Lois Reynolds

> Research Assistant to Dr Tilli Tansey

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>

> The Wellcome Trust Centre is supported by the Wellcome Trust, a registered

> charity, no. 210183.

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 25 September 2005 22:56
To: ucgarey@ucl.ac.uk
Subject: Re: Witness Seminar: Prenatal Corticosteroids: your queries

Dear Lois,

Sorry to have been so very long in replying, but I have been laid low by a virus for the past 2 weeks. Thank you very much for sending me Jobe and Soll's paper (and for sending it in the body of the email: I could not access the URL). At the moment I am not in a position to make further enquiries about the points you raise, but could I simply amend the comment in my email of 22 August to read something like:

"Pp 93-4, comparison of dexamethasone and betamethasone: I wonder how much of the apparent difference between the two drugs in effect on mortality may have been due to differing standards of newborn intensive care at the times and places the trials were carried out." You could refer to my memoir, p4, paras 3 and 4.

A different point: on the rejection of our initial paper, referred to by Mont Liggins in the letter you plan to include as an appendix, I can confirm that it was by The Lancet and not Nature. It says so in a piece I found recently, written by Mont himself and available online at <http://garfield.library.upenn.edu/classics1982/A1982NF37800001.pdf>.

Another apology, that I overlooked sending you the consent form for publication of my memoir. This has now been signed and is out for posting.

I hope my delays have not held up the project too much, and that it is otherwise going well.

Best wishes,
Ross Howie

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

From: "Lois Reynolds" <ucgarey@ucl.ac.uk>
To: "Howie" <h.r.howie@xtra.co.nz>
Sent: Friday, September 02, 2005 3:46 AM
Subject: RE: Witness Seminar: Prenatal Corticosteroids: your queries

> Dear Ross,
> Re Jobe and Soll's 2004 paper: this can be viewed online
>
> ([http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=A](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=A&bstract&list_uids=15118606&query_hl=29)
> [bstract&list_uids=15118606&query_hl=29](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=A&bstract&list_uids=15118606&query_hl=29)) or downloaded, perhaps at your
> library.
> The text follows, if this is any help.
> Best wishes from Lois
>
> [...]

Lois Reynolds

From: Howie [h.r.howie@xtra.co.nz]
Sent: 08 November 2005 08:11
To: ucgarey@ucl.ac.uk
Subject: Wellcome Witnesses: prenatal corticosteroids

Dear Lois,

Many thanks for your letter of 1 November with the pages of the transcript, which arrived today. In the interests of your publishing deadline, this is a quick reply. I shall read the material more carefully in the next day or two and reply further if need be, but I hope this is complete.

Rec'd 8/11/05
ack? ✓ 8/11/05
11.13 am.

P6, footnote 7: this footnote seems hardly necessary now. ✓ *OK as is*

P12, footnote 21, line 3: the correct title of the institution was I think the 'Ruakura Agricultural Research Station'.

P38, footnote 63, first sentence: this might read better if rephrased slightly: 'About the possible hazards of steroids to the fetus: I am surprised' ✓

P55, footnote 94: on further thought, to avoid some kind of witch-hunt in Auckland, could I ask you to delete sentence 6 (starting 'There were, I confess...') and replace it with 'I had no hesitation about Jane's use of the material.' ✓

P111, footnote 206: could it be made clearer at the beginning that the person wondering was me? ✓

P112, para 2, 2nd sentence and footnote 207: the first quotation mark should come two words earlier, so that the sentence starts "Babies born 'unfinished, sent before [their] time into this breathing world' form...". I am unclear which part of the sentence footnote 207 refers to. If to the quotation, it is hardly 'Anonymous (1976)'. It is of course from Shakespeare nearly 400 years before that, Richard III, Act 1, Scene 1. As I was writing for people who can be presumed to know Shakespeare much better than I do, it seemed unnecessary to reference it. The last part of the sentence ('most complex situation in human biology') is mine but very likely an unconscious echo of someone else long before 1976, and hardly worth a footnote. ✓

P113, footnote 209: thank you for the URL: I shall visit it! I marvel at your patience in unearthing all the additional references you found. ✓

I look forward to seeing the published volume. Thank you for all your very good work in editing, and very best wishes for the future (to your parents too). ✓

Ross Howie