Correspondence. Surnames, 'Avery' to 'Buxton'

Contributors

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Wellcome Collection
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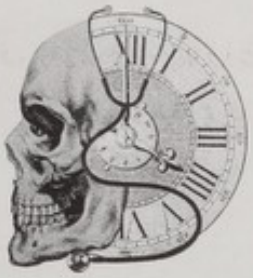

The Wellcome Trust Centre for the History of Medicine at University College London

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

UCL

Dr Mary Ellen Avery
Children's Hospital Boston
300 Longwood Avenue
Boston
MA 0211
USA

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

11 March 2004

Dear Dr Avery

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

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

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

Continued/... Page 2

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

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

atts.

HARVARD MEDICAL SCHOOL
DEPARTMENT OF PEDIATRICS

MARY ELLEN AVERY, M.D.
Thomas Morgan Rotch Distinguished Professor of Pediatrics

Children's Hospital, Hu 432
300 Longwood Avenue
Boston, Massachusetts 02115
Tel.: (617) 355-8330
FAX: (617) 730 0486
mary.avery@tch.harvard.edu

March 22, 2004

Dr. Daphne Christie
Wellcome Trust Centre for History of Medicine
University College
24 Eversholt Street
London NW1 1AD
England

Dear Dr. Christie:

Thank you for your letter of March 11, 2004 with the invitation to join you Tuesday June 15, 2004 in the Wellcome Building in London. I accept with great pleasure and knowledge that I shall pay my travel expenses.

I have vivid memories of the early days of surfactant therapy, documented on the enclosed reprints or copies of our studies. My own interest dates from the studies of Florence Moog (1962) who demonstrated acceleration maturation of the fetal intestinal epithelium with hydrocortisone. (She and I were members of an NIH study section, and discovered our mutual interest during a coffee break.) I enclose copies of our first studies, 1970 and 1972.

The 1985 Conference at NIH was pivotal in convincing others that hydrocortisone's effect was indeed life-saving. The rest of the story is well documented in many reviews, some of which I enclose with this letter. I do not need to have them returned.

Thanks again for the opportunity of joining you on June 15th.

Sincerely,

Mary Ellen

Mary Ellen Avery, MD

MEA:erc
Enclosure

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

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

UCL

Dr Mary Ellen Avery
Children's Hospital Boston
300 Longwood Avenue
Boston, MA 02115
USA

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

26 April 2004

Dear Dr Avery

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

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

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

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

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

Yours sincerely

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

enc.

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Wendy Kutner

To: mary.avery@tch.harvard.edu
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Professor Avery, I would be grateful if you could let me know whether you are able to join Dr Tansey and Dr Christie for supper after the meeting on 15th June. 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

Dr Daphne Christie

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 13 May 2004 09:24
To: mary.avery@tch.harvard.edu
Subject: witness seminar prenatal corticosteroids 15 June 2004

averyltrstartballrolli ng1305.d...

CORTI -NAMEPROG_1305.

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

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

Dr Daphne Christie

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 13 May 2004 09:31
To: mary.avery@tch.harvard.edu
Subject: FW: witness seminar prenatal corticosteroids 15 June 2004

averyltrstartballrolling1305.d... CORTI-NAMEPROG_1305.

Dear Dr Avery
I've embedded my letter in this e-mail - some fields may have been left blank? My apologies if this was the case.
Best wishes,
Daphne Christie

Dr Mary Ellen AveryChildren's Hospital Boston300 Longwood Avenue Boston, MA 02115USA
Dr Daphne Christied.christie@ucl.ac.ukwww.ucl.ac.uk/histmedTel: +44 (0) 20 7679 8125Fax: +44 (0) 20 7679 8193

12 May 2004

Dear Dr Avery

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

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

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

As you already know, we do not have the funds to assist with your travel from overseas, but whilst you are in the UK, The Wellcome Trust Centre for the History of Medicine at University College London will reimburse your return travel costs to the meeting only if supported by suitable receipts. They are inflexible in this matter.

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

Continued/ Page 2 …

Dr Tilli Tansey and I would like to invite you to join us for an early supper at a

local restaurant after the meeting. We should be finished by 9pm. Please let me know whether you are able to attend the supper (d.christie@ucl.ac.uk). You may also contact Mrs Wendy Kutner (w.kutner@ucl.ac.uk) 0044 207679 8106 or myself if you have any queries on the above or would like any further information.

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 13 May 2004 09:24
To: mary.avery@tch.harvard.edu
Subject: witness seminar prenatal corticosteroids 15 June 2004

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

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

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 14 May 2004 08:23
To: Avery, Mary
Cc: Wendy
Subject: RE: witness seminar prenatal corticosteroids 15 June 2004

Dear Dr Avery
Thank you for your reply. We have noted that you do not require the Ibis London reservation for the night of the meeting.
We look forward to seeing you at the meeting.
Yours sincerely
Daphne Christie

-----Original Message-----
From: Avery, Mary [mailto:Mary.Avery@childrens.harvard.edu]
Sent: 13 May 2004 17:18
To: d.christie@ucl.ac.uk
Subject: RE: witness seminar prenatal corticosteroids 15 June 2004

I have previously booked a room at the Sheraton in Picadilly so there is no need for the Ibis London reservation. I do not expect reimbursement.

Thank you.

Mary Ellen Avery

From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: Thu 5/13/2004 4:30 AM
To: Avery, Mary
Subject: FW: witness seminar prenatal corticosteroids 15 June 2004

Dear Dr Avery
I've embedded my letter in this e-mail - some fields may have been left blank? My apologies if this was the case.
Best wishes,
Daphne Christie

Dr Mary Ellen AveryChildren's Hospital Boston300 Longwood Avenue Boston, MA 02115USA Dr Daphne Christied.christie@ucl.ac.ukwww.ucl.ac.uk/histmedTel: +44 (0) 20 7679 8125Fax: +44 (0) 20 7679 8193

12 May 2004

Dear Dr Avery

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Continued/ Page 2 ...

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

-----Original Message-----
From: Dr Daphne Christie [mailto:d.christie@ucl.ac.uk]
Sent: 13 May 2004 09:24
To: mary.avery@tch.harvard.edu
Subject: witness seminar prenatal corticosteroids 15 June 2004

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

Tel 020 7679 8125
Fax 020 7679 8193
Mobile 07810 541812

Wendy Kutner

From: Avery, Mary [Mary.Avery@childrens.harvard.edu]
Sent: 07 June 2004 12:22
To: w.kutner
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dr. Avery is in London and can be reached at Novartis from June 5-8 (636-9456) and at the Park Lane Hotel in Picadilly (499-1965) from June 9-16.

Thank you

Ellen Collins

(w) acc 7/6/04

From: Wendy Kutner [mailto:w.kutner@ucl.ac.uk]
Sent: Thu 6/3/2004 10:51 AM
To: Avery, Mary
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Dear Professor Avery, I would be grateful if you could let me know whether you are able to join Dr Tansey and Dr Christie for supper after the meeting on 15th June. Yours sincerely, Wendy Kutner

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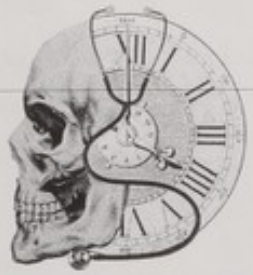
www.ucl.ac.uk/histmed



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

UCL

Dr Mary Ellen Avery
Children's Hospital
Boston
300 Longwood Avenue
Boston, MA 02115
USA

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

16 June 2004

Dear Dr Avery

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

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

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

We particularly want to thank you for travelling from Boston to attend the meeting. You are an integral part of the story and your personal contribution added to the success of the meeting.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

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

HYALINE MEMBRANE DI

Lecture

Prepared as hand-out
for Harvard Medical Students

You may use these
notes in any way you
wish - No need to
return. No copyright -
They are my own lecture
notes as of Apr. 2002.
MEG

1. Review natural history of HMD - (early 1950 progressive increase in respiratory rate, severe grunting, retractions, progressive cyanosis, metabolic acidosis, death within hours or a few days in about half the infants, or full recovery.

2. Pathology Liver-like lungs.
   No foam in airways.
   Widespread atelectasis, over distention of alveolar ducts
   "Swiss cheese" pattern
   Distensible with saline (or kerosene) with
   normal architecture -- thus not dysplastic.

   The membrane is not the cause of the atelectasis
   rather it follows from over distention (injury)
   to aerated areas. It consists of fibrin, nucleoproteins,
   heme, etc. (Gitlin and Craig).

3. Significant right-to-left shunts, through the foramen ovale, ductus arteriosus, and from perfusion of poorly ventilated lung. Reduced compliance of lung

4. Role of pulmonary surfactants in alveolar stability
   (anti-atelectasis factor).
   LaPlace Law.
   Pressure-volume relationships.

5. Composition - lipids.

   Pulmonary surfactant proteins (A, B, C, D), knock-out mice.

"Genetic and phenotypic complexity has been described for diseases of varied etiology. Groups of patients with varied phenotype can be used in association studies as an initial approach to identify contributing loci. Although association studies have limitations, their value is enhanced by using candidate genes with functions related to disease. Surfactant proteins have been studied in the etiopathogenesis of neonatal pulmonary diseases. SP-A a,d SP-B polymorphisms are

HYALINE MEMBRANE DISEASE

Lecture April 2002

Prepared as hand-out for Harvard Medical Students

Mary Ellen Avery, M.D.

1. Review natural history of HMD - (early 1950s) onset "shortly" after birth - progressive increase in respiratory rate, severe grunting, retractions, progressive cyanosis, metabolic acidosis, death within hours or a few days in about half the infants, or full recovery.

2. Pathology Liver-like lungs.
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"Genetic and phenotypic complexity has been described for diseases of varied etiology. Groups of patients with varied phenotype can be used in association studies as an initial approach to identify contributing loci. Although association studies have limitations, their value is enhanced by using candidate genes with functions related to disease. Surfactant proteins have been studied in the etiopathogenesis of neonatal pulmonary diseases. SP-A a,d SP-B polymorphisms are

found at a higher frequency in certain groups of patients with respiratory distress syndrome (RDS), and SP-B mutations are linked to the pathogenesis of congenital alveolar proteinosis (CAP). Phenotypic heterogeneity is observed for both CAP and RDS. The available data suggest that a number of factors contribute to the etiology of CAP and RDS and, therefore, a multidisciplinary approach of clinical, genetic, epidemiologic, and statisticai considerations is necessary for an in-depth understanding of the pathophysiology of these and other pulmonary diseases."

Please see below, "Historical Overview of Antenatal Steroid Use".

Abstracted from Commentary: "Historical Overview of Antenatal Steroid Use". Pediatrics 95:133, 1995.

The important and ever-accelerating basic science supports the fact that giving antenatal glucocorticoids in the event of pre-term labor could be considered a physiologic rather than a pharmacologic intervention, in as much as one role of the fetal adrenal cortex is to increase the cortisol levels in the weeks before term birth. In fact the adrenal gland at birth is 10 to 20 times larger than in the adult, relative to body weight.

Hormonal influences in the timing of organ maturation date from Moog in 1953, and were pursued by Liggins in 1969, with his publication on the influence of glucocorticoids and the timing of parturition in fetal lambs. He observed that the lungs of a lamb delivered at 117 to 123 days appeared to be functioning normally and the premature lamb was viable at an earlier stage than would have been the case in the absence of maternal glucocorticoids. The observation was of particular interest, since the glucocorticoids stimulated both the onset of labor in the lambs, as well as precocious maturation of the lung. Much evidence accumulated since then makes it clear that glucocorticoids do not have the same effect on the initiation of labor in the human, but fortunately, do indeed accelerate maturation of the lung and some other organs as well.

Some of the surprising observations are that much of the basic science was understood, and the beneficial effect on the lungs of animals thoroughly documented in the 1970s. Numerous, well-designed, prospective, randomized, clinical trials to evaluate prenatal glucocorticoids on lung maturation have on the whole confirmed the very first one, that of Liggins and Howie published in 1972.

In reviewing the chronology of events, it was clear to Florence Moog, the anatomist from Washington University, St. Louis, that the timing of the appearance of phosphatase in the duodenum of the suckling mouse was accelerated by cortisol. Published in the **Journal of Experimental Zoology** in 1953, the article did not evoke any great interest on the part of physicians looking after premature infants. It was, in fact, ignored.

The reawakening appeared in the form of an insight by Sue Buckingham working with pathologists at Presbyterian Hospital in New York, who was an avid reader and came upon the article by Moog. She was aware that the developing lung was an outpouching of the primitive gut and that the question occurred to her that it might be an analog of Moog's developing intestine. She demonstrated this in 1968 with the precocious appearance of phosphatase in the lungs of fetal rabbits. Unfortunately, her premature death prevented her from completing this important study.

After reading Liggins' paper published in 1969, we tested his hypothesis in pre-term lambs. We found lungs of fetal lambs less than 125 to 127 days were unable to retain air. Lambs treated with cortisol had aerated lungs at 117 to 123 days, thus, strongly supporting the likelihood that his administration of cortisol to the fetal lamb had indeed induced precocious maturation. With Robert deLemos, and later Robert Kotas, we carried out studies in the fetal lambs and confirmed Liggins findings of precocious maturation, using measurements of pressure-volume curves and surface tension properties of lung extracts. Liggins proceeded with his colleague, Ross Howie, to carry out a controlled trial of antepartum glucocorticoid treatment for premature infants, published as a now classic article, in **Pediatrics** in 1972.

At this point, with an obstetrician in New Zealand, and pediatricians from Johns Hopkins writing about these remarkable findings, the way was open for both obstetricians and pediatricians to contribute further to our understanding of the timing of lung maturation and the role of glucocorticoids.

In the National Institutes of Health-sponsored collaborative study on antenatal steroid therapy (1977-1981), 7893 pregnant women were screened for eligibility to enroll; only 696 were thought eligible for randomization in the study. Of course, we know that entry into the study was at the discretion of an obstetrician, and Liggins assures us that easily half, if not more, women in labor can have a long enough period of time (about 24 hours) for combined tocolysis and prenatal glucocorticoids to have an effect.

The appearance of a new and effective therapy makes a still controversial therapy more likely to be abandoned. It was clear from 1980 with Fujiwara's publication in **Lancet**, that surfactant replacement therapy would have a protective effect, when administered as a liquid through an endotracheal tube, in the early hours of life in infants at risk of respiratory distress syndrome. Subsequently multiple prospective controlled clinical trials have confirmed the safety and efficacy

of the now-licensed surfactant preparations. The comment frequently made by obstetricians was "well now that we have surfactant therapy we don't need to fuss with tocolytics and prenatal glucocorticoids anymore." The evidence that that was not an isolated comment comes from the fact that in some multicenter controlled trials to evaluate exogenous surfactants, only approximately 10% of mothers received prenatal glucocorticoids, when we can assume at least half of them would have been eligible.

The consensus development conference statement on **"Effect of corticosteroids for fetal maturation on perinatal outcomes,"** (March, 1994) provides convincing evidence of efficacy and safety in the acceleration of lung maturation, a 40% reduction in neonatal mortality, and a reduction in intraventricular hemorrhage of even greater magnitude (odds ratio of 0.5, 95% confidence interval 0.3 to 0.9). Their conclusion is that "all fetuses between 24 to 34 weeks gestation threatened with premature delivery are candidates for treatment with antenatal steroids." A review of the greater efficacy of combined antenatal steroid and postnatal surfactant replacement was another step forward.

Recommended Reading:

Lanman JT. The fetal zone of the adrenal gland. Its developmental course, comparative anatomy, and possible physiological functions. Medicine 32:389, 1953.

Moog F. The influence of the pituitary-adrenal system on the differentiation of phosphatase in the duodenum of the suckling mouse. J Exp Zool 124:329, 1953.

Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol 45:515, 1969.

Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatr 50:515, 1972.

Fujiwara T, Chida S, Natobe Y, et al. Artificial surfactant therapy in hyaline membrane disease. Lancet 1:55, 1980.

Collaborative Group on Antenatal Steroid Therapy. Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome. Am J Obstet Gynecol 141:276, 1981.

Jobe AH, Mitchell BR, Gunkel JH. Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant on pre-term infants. Am J Obstet Gynecol 168:508, 1993.

More Recent Recommended Reading:

Hawgood S. SP-A and SP-D knock-outs. (Abstract) J Clin Invest 99:2992, 1997.

Floros F, Kala P. Surfactant Proteins: Molecular genetics of neonatal pulmonary diseases. Annu Rev Physiol 60:365 -84, 1998.

Clements JA, Avery ME: Lung surfactants and neonatal respiratory distress syndrome. Am J Respir Crit Med 157:559-566, 1998.

Spragg R. et al. First clinical and early clinical experience with a recombinant SP-C based surfactant. Appl Cardiopulmonary Pathophysiology 9:301, 2000.

Wright J R, et al. Surfactant protein A: Regulation of innate and adaptive immune responses in lung inflammation. Am J Respir Cell Mol Biol 24:513-517, 2001.

Floros J, Fan R. Surfactant Protein A and B genetic variants and respiratory distress syndrome: Allele interactions. Biol Neonate 80(suppl 1)22-25, 2001.

Golioto A, Wright JR. Effects of surfactant lipids and surfactant protein A on host defense functions of rat alveolar macrophages. Pediatr Res 51:220-227, 2002.

TABLE 1

Hyaline Membrane Disease (HMD): Selected Historical Aspects

DATE	OBSERVATION
1903	Initial description of pulmonary hyaline membrane (PHM) considered by Hochheim to represent aspirated amniotic fluid.
1923	First English description of PHM in association with neonatal pneumonia.
1925 - 49	Prevailing view was that PHM resulted from aspirated amniotic sac contents ("vernix" membrane). Other causes considered include degenerated alveolar epithelium and anomalous development.
1950	An interval of air breathing was proposed as prerequisite to development of PHM, which are especially associated with prematurity, fetal anoxia, maternal diabetes, and cesarean section.
1950	Description of the clinical presentation of respiratory abnormalities in association with PHM.
1951	PHM results from tissue damage and transudation of plasma protein, and are therefore secondary phenomena; atelectasis proposed as the significant factor in HMD.
1953 - 55	Radiographic descriptions of the reticulogranular pattern in generalized neonatal atelectasis, as distinguished from the radiographic appearance in cases of aspirated amniotic debris.
1953 - 57	PHM further attributed to transudation after injury and shown to consist principally of fibrin and entrapped cellular debris.
1955 - 56	Clarification of the clinical pattern as the respiratory distress syndrome with characteristic symptom complex permitting quantification of severity.
1955 - 56	Discovery of surfactant in pulmonary edema foam and lung extracts.
1954 - 59	Major pulmonary function abnormalities in HMD elucidated.
1959	Demonstration of pulmonary surfactant deficiency in infants who died of HMD. The term was changed at an International Conference, to that of Idiopathic Respiratory Distress Syndrome - IRDS, then RDS has been used synonymously with HMD ever since.
1961	Decreased mortality with intensive care directed toward meeting metabolic needs.
1965 - 67	Demonstration of reduced lung phosphatidylcholine in HMD.
1967	Description of chronic lung disease following respiratory therapy.

Continued ...

1965 - 70	Improved survival in severe HMD with assisted ventilation.
1971	Predictability of respiratory distress from the ratio of lecithin to sphingomyelin in amniotic fluid as an index of lung maturity.
1971	Markedly reduced mortality and severity with continuous positive airway pressure.
1971	Effectiveness of regional perinatal care demonstrated.
1972	Description of surfactant-associated proteins initiated.
1973	Prevention of HMD with antenatal corticosteroid administration.
1980	Artificial surfactant replacement therapy was effective (bovine preparation, Fujiwara).
1984	Immunochemical characterization of surfactant-associated proteins.
1985	Calf lung-derived surfactant administered at birth prevents pulmonary hyaline membrane disease - HMD.
1985 - 89	Structures of surfactant apoproteins described.
1987	Surfactant-protein A deficiency in lungs of infants who died from pulmonary hyaline membrane disease - HMD.
1988	Metabolic and developmental aspects of surfactant system elaborated.
1988	Evaluation of surfactants for replacement therapy in the United States.
1989	Multicenter randomized trial of surfactant therapy.
1991	Clinical trial of protein-free surfactant (dipalmitoylphosphatidyl choline) with additives.
1993	Beneficial effects of combined use of prenatal corticosteroids and surfactant replacement.
1993	Deficiency of surfactant protein B in congenital alveolar proteinosis.
1997	Anti-inflammatory effects of surfactant lipids.
1997	Sp-A (Surfactant-protein A) can mediate Mycobacterium tuberculosis entry into alveolar macrophages, and can be an opsonin for some viruses and bacteria.
2001	Role of Surfactant protein A in regulation of innate and adaptive immune responses in lung inflammation.
2001	Surfactant protein D demonstrated in all secretory epithelial cells - skin, saliva, tears, G-I tract, etc.

Children's Hospital Boston

A teaching affiliate of Harvard Medical School

Division of Newborn Medicine
Hunnewell 430
300 Longwood Avenue
Boston, Massachusetts 02115
phone 617-355-6027 | *fax* 617-730-0486

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1. NAME Dr Mary Ellen Avery

2. ADDRESS Children's Hospital Boston
300 Longwood Avenue
Boston, MA 02115, USA

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

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Signed Mary Ellen Avery Date June 20 '05

2nd 9/6/05

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

210 Euston Road • London • NW1 2BE
www.ucl.ac.uk/histmed • +44 (0) 20 7679 8100

Dr Mary Ellen Avery,
Children's Hospital Boston,
300 Longwood Avenue,
BOSTON, MA 02115
USA

Dr Daphne Christie
d.christie@ucl.ac.uk
www.ucl.ac.uk/histmed
Tel: +44 (0) 20 7679 8125
Fax: +44 (0) 20 7679 8192

9 Dec 11

7 December 2004

Dear Dr Avery

Witness Seminar: Prenatal Corticosteroids for reducing Morbidity and Mortality

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

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

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

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

sBvass 27/6/05
Yes, thanks.

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

I look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

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June 17 '05

CURRICULUM VITAE Revised 10/2004

Name: Mary Ellen Avery

Date of Birth: May 6, 1927

Place of Birth: Camden, New Jersey

Office Address: 300 Longwood Avenue
Boston, MA 02115
(617) 355-8330
FAX #(617) 730-0486
E-MAIL: mary.avery@tch.harvard.edu

Home Address: 65 Grove Street
Wellesley, MA 02482-7804

Social Security No. 138-22-0651

Education:

1948 A.B.	Wheaton College, Norton, Massachusetts (summa cum laude)
1952 M.D.	Johns Hopkins University School of Medicine Baltimore, Maryland

Post Doctoral Training:

Internship and Residencies:

1954	Intern, Pediatrics, Johns Hopkins Hospital
1954-55	Jr. Assistant Resident, Pediatrics, Johns Hopkins Hospita
1955-57	Sr. Assistant Resident, Pediatrics, Johns Hopkins Hospita

Research Fellowships:

1957-59	Research Fellow, Pediatrics, Harvard Medical School
1959-60	Fellow, Pediatrics, Johns Hopkins University

Academic Appointments:

1960-64	Assistant Professor of Pediatrics Johns Hopkins University
1964-69	Associate Professor of Pediatrics Johns Hopkins University
1965-69	Eudowood Associate Professor Pulmonary Disease of Childre
1969-74	Professor and Chairman, Department of Pediatrics McGill University
1974-85	Thomas Morgan Rotch Professor of Pediatrics Harvard Medical School
1996-	Thomas Morgan Rotch Distinguished Professor of Pediatrics Harvard Medical School

Hospital Appointments:

1961-69	Pediatrician-in-Charge, Newborn Nurseries Johns Hopkins Hospital
1969-74	Physician-in-Chief Montreal Children's Hospital
1974-84	Physician-in-Chief The Children's Hospital, Boston
1985-	Physician-in-Chief Emeritus The Children's Hospital, Boston

Honorary Degrees:

1974	Honorary Master of Arts Degree, Harvard University
1974	Honorary Doctor of Science Degree, Wheaton College
1975	Honorary Doctor of Science Degree, University of Michigan
1976	Honorary Doctor of Science Degree, Medical College of PA
1976	Honorary Doctor of Science Degree, Trinity College, Hartford

✓
17/6/05.

1977	Honorary Doctor of Science Degree, Albany Medical College
1978	Honorary Doctor of Science Degree, Medical College of Pennsylvania
1978	Honorary Doctor of Science Degree, Radcliffe College
1979	Honorary Doctor of Humane Letters Degree, Emmanuel Colleg
1981	Honorary Doctor of Humane Letters Degree, Northeastern Un v.
1983	Honorary Doctor of Science Degree, Russell Sage College
1993	Honorary Doctor of Science Degree, Memorial University of Newfoundland
1999	Honorary Doctor of Humane Letters, Johns Hopkins Universi y
2000	Honorary Doctor of Laws, Queens University, Toronto
2003	Honorary Doctor of Science, University of Southern Califo nia

Other: 2004 " " Harvard University

1986-1993	Member, Council, Institute of Medicine
1989-1993	Board of Directors, American Association for the Advance ent of Science
1990-1991	President, American Pediatric Society
1991	National Medal of Science
1991	Virginia Apgar Award, American Academy of Pediatrics
1993-2001	Board of Directors, Burroughs Wellcome Fund
1994-	Member, National Academy of Sciences
1997-2000	Member of Council, National Academy of Sciences
1998	The Marta Philipson Award for Pediatric Research, Karolins ka Institute, Stockholm
1999	Lifetime Achievement Award, Massachusetts Medical Society
2000	Walsh McDermott Medal, Institute of Medicine
2001	First-Vice President, Johns Hopkins Medical,Surgical Asso .
2002	President-elect American Association for the Advancement of Science (AAAS)
2003	President American Association for the Advancement of Sci nce
2004	Chairman of the Board American Association for the Advancement of Science

2005 John Howland Award, American Pediatric Society

Books:

1. Avery ME, Pletcher BD: **The Lung and Its Disorders in the Newborn Ins ant** WB Saunders, Philadelphia, 1964; 2nd ed. 1968, 3rd ed. 1974, 4th ed. 1981.

2. Schaffer AJ, Avery ME, eds.: **Diseases of the Newborn.** WB Saunde rs, Philadelphia, 4th ed. 1977.

3. Avery ME, Litwack G: **Born Early: The story of a premature baby.** Litt le, Brown and Company, Boston, 1983.

4. Avery ME, Taeusch HW Jr, eds.: **Schaffer's Diseases of the Newborn.** WB Saunders, Philadelphia, 5th ed. 1984.

5. Taeusch HW Jr., Ballard R, Avery ME: **Schaffer and Avery's Diseases of the Newborn.** WB Saunders, Philadelphia, 6th ed. 1991.

6. Taeusch HW Jr, Ballard R, Avery ME: **Avery's Diseases of the Newborn.** WB Saunders, Philadelphia, 7th ed., 1998.

7. Avery ME, First LR, eds.: **Pediatric Medicine.** Williams & Wilki ns, Baltimore, 1989; 2nd ed. 1994.

8. Taeusch HW, Ballard R, Gleason CA: **Avery's Diseases of the Newborn.** WB Saunders, Philadelphia, 8th ed. 2004.

Author of over 100 scientific publications, mostly on respiratory disorders of newborn infants.

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

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

Edited by L A Reynolds and E M Tansey

Dr Mary Ellen Avery: I bring you a personal view of the discovery of aspects of maturation of the lung of the preterm infant by antenatal glucocorticoids. The story really begins as you have noticed with Professor G.C. Liggins (Mont) an obstetrician in Auckland. I am happy to acknowledge that he has been a most generous supporter and friend and we have been 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 babies were initiated largely, I think, in this country (England), with Barcroft and Barron in combination with Maureen Young. I was finishing a fellowship supported by the National Institutes of Health in 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 admiration for English research and animal research in particular, and, of course, that was followed within a month with Leonard Strang at University College Hospital. My research fellows at Johns Hopkins set out to map the course of events in the developing ewe lung, the animal of choice. (I have often wondered why, and I think it's because babies and lambs are about the same size at birth and the equipment you had for one

corrected 27/6/05

worked for the other. I don't know if that's 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, embryologist who was studying the intestine of mice 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 told 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.

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 our laboratory (which then numbered 15 or 20) produced a paper about the timing was of various enzymes and other events in the normal lamb lungs. I went to New Zealand 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, Mont said, 'Well, what if I told you we can identify accelerated maturation in the lambs' lungs 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 glucocorticoids could accelerate lung maturation of lambs.

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

would also like to pay tribute to Sue Buckingham, a fellow at the Columbia Presbyterian medical school in New York City, probably well known to you. She presented at a federation meeting on the effects on the mice. In 1969 she made that point, and I thought it was frivolous. Then we had a series of observations over and over, that glucocorticoids accelerated maturation, not only of the Moog's intestine, but also of the fetal lung. I, by then, had finished my Fellowship (Sue, alas, died shortly after that meeting, which was a great tragedy, but her contribution was invaluable). 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 outcome of anything that's invasive. 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 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.

Second Comment

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

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

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

✓ 27/6/05

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

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

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

Avery: The meeting was a combined meeting of obstetricians and pediatricians. They had invited me over as a visiting speaker. It was the first meeting with Liggins who told me of these findings.

...

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

Avery: It was frustrating.

Hey: Well I mean you banged the drums quite hard.

Avery: I cannot begin to organize my thoughts for this period. I was not centrally engaged, I am not an obstetrician, I didn't want to tell obstetricians what to do and what not to do. In fact, I didn't have that kind of self-confidence. I wanted long-term follow up. I spent hours with Ross Howie, urging him to please keep track because the Swiss were talking about inhibiting lungs seriously, and even brains weren't growing well if little animals got big steroid doses during pregnancy. You probably know that. It's kind of scary. All animal. It was done by the group in Bern, I think it is Burri who is the fellow who is still publishing on beware, beware, and I cannot counter that. I'm glad he's looking at it, and I just think we have to be vigilant and those of us who spend more time with babies, have to keep track of the babies.

...

Avery: I think we have to think in terms of 1970s versus the 1990s and over 2000, because up until the 1970s the controlled trials were very supportive of efficacy of prenatal glucocorticoids, but that was an era when we didn't have lots of babies under 800g. Now the story's different. We have babies of 600g and 700g and 800g, who are getting

glucococorticoids, and we assumed that they wouldn't have any serious toxicity. But along came Petra Huppi from Geneva who worked with us at Harvard and who had developed a great experience with imaging studies of the brains of these babies. There is no question that there can be white matter problems which she has documented and published. I'm not prepared to take a stand, I'm only saying this is one group, where there could be toxicity, and where we really don't know the cost–benefit of accelerating the lung versus some white matter problems in the baby. This is a new frontier, and I just wanted to put this on the table. I don't know any more about it than I have just said.

...

Thank you. First there is definitely a difference between male and female and white and non-white. The Asian population is more advanced and yet when you look at these differences they are real even into 20 weeks. I don't think they are big enough to swamp all the other things that are going on, but it's a very interesting issue, I think about taking into consideration the chance that you might have more girls and look at the output in terms of scoring.

Richmond: I fully respect that there is a difference in survival based on race and sex, but I didn't think there would necessarily be a difference in response to steroids based on that. It just means that you get more informative clients if you choose the ones with the higher risk, but is there a differential response to steroids based on sex or race?

Avery: I cannot give you chapter and verse, I think there is a difference. Maybe somebody else has a reference.[1]

...

[1] Could you suggest an appropriate refcrence??

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. [2]

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

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

....

Hey: So are everybody's, but if people have kept their data, there's 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.

...

Dr Mary Ellen (Mel) Avery
Xxx (b. 1927) was Professor of Paediatrics at Harvard Medical School, Boston, MA, from 19xx to xxxx and Physician-in-Chief, later Emeritus, at the Children's Hospital, Boston, from xxxx to xxxx. See Avery and Mead (1959); Avery (2000).

[2] 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.' 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.

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****

1. NAME Dr Mary Ellen Avery

2. ADDRESS Children's Hospital Boston
300 Longwood Avenue
Boston, MA 02115, USA

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

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Signed Mary Ellen Avery Date June 20 '05

2nd 9/6/05

Medark 30/6/05
Please sign and return by 25 June 2005

Children's Hospital Boston

A teaching affiliate of Harvard Medical School

Division of Newborn Medicine
Hunnewell 430
300 Longwood Avenue
Boston, Massachusetts 02115
phone 617-355-6027 | *fax* 617-730-0486

Facsimile Transmission

Date: 6.21.05

To: Dr. Daphne Christie

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Tel No. (Recipient)

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MARY ELLEN AVERY
65 GROVE STREET • WELLESLEY, MASSACHUSETTS 02482

Errors:

p1, 2nd ¶ 2nd line - studies of sheep (not babies)

3rd line from bottom - developing fetal, (not ewe)

Approx. refers - foot note p6.

Male infant has 1.5 to 2.0 times ~~The risk~~ the risk of fatal hyaline membrane disease.

~~in males compared to fatal hyaline membrane disease~~

Wood Wood and Farrell. Pediatr. Research 8 452, 1974.

email query

corrected 3/8/05

MARY ELLEN AVERY
65 GROVE STREET • WELLESLEY, MASSACHUSETTS 02482

My apologies to whoever struggled with this transcript. If you find other mistakes — please feel free to correct them, or E-mail me for clarification.

MARY ELLEN AVERY, M.D.

PROFESSOR OF PEDIATRICS
HARVARD MEDICAL SCHOOL
CHILDREN'S HOSPITAL, HU 432
BOSTON, MASSACHUSETTS 02115

HOME:
65 GROVE STREET
WELLESLEY, MASSACHUSETTS
02482-7004

OFFICE: 617-355-6330
FAX: 617-730-0486
HOME: 781-235-7160
mary.avery@tch.harvard.edu

Lois Reynolds

No response by 10/8/05 - included in package of 2nd corrections.

From: Lois Reynolds [ucgarey@ucl.ac.uk]
Sent: 03 August 2005 17:33
To: Mary.Avery@childrens.harvard.edu
Subject: Witness Seminar: Prenatal Corticosteroids : query

Dear Prof Avery,

May I check your suggested reference included in your fax of 21 June for the following exchange:

Avery: Thank you. First there is definitely a difference between male and female and white and non-white. The Asian population is more advanced, yet when you look at these differences they are real, even into 20 weeks. I don't think they are big enough to swamp all the other things that are going on. It's a very interesting issue, I think, taking into consideration the chance that you might have all girls and look at the output in terms of scoring.

Richmond: I fully respect that there is a difference in survival based on race and sex, but I didn't think there would necessarily be a difference in response to steroids based on that. It just means that you get more informative clients if you choose the ones with the higher risk, but is there a differential response to steroids based on sex or race?

Avery: I cannot give you chapter and verse, I think there is a difference. (FN) Maybe somebody else has a reference.

FN: Professor Mel Avery wrote: 'A male infant has 1.5 to 2.0 times the risk of fatal hyaline membrane disease. See Wood and Farrell (1974).' Fax to Dr Daphne Christie, 21 June 2005.

I have been unable to find the reference by Wood and Farrell on Pub Med. The following by Farrell appeared in Pediatr Research. I would be grateful for an early reply to be included in the final proof to be sent next week.

Which address should be used?

(i) 65 Grove Street, Wellesley, MA 02482 USA
(ii) Children's Hospital Boston,300 Longwood Avenue, BOSTON, MA 02115 USA

Best wishes from Lois Reynolds

1: Perelman RH, Engle MJ, Palta M, Kemnitz JW, Farrell PM.
Fetal lung development in male and female nonhuman primates.
Pediatr Res. 1986 Oct;20(10):987-91.

2: Rieutort M, Farrell PM, Engle MJ, Pignol B, Bourbon JR.
Changes in surfactant phospholipids in fetal rat lungs from normal and diabetic pregnancies.
Pediatr Res. 1986 Jul;20(7):650-4.

3: Bourbon JR, Farrell PM.
Fetal lung development in the diabetic pregnancy.
Pediatr Res. 1985 Mar;19(3):253-67.

4: Farrell PM, Mischler EH, Engle MJ, Brown DJ, Lau SM.
Fatty acid abnormalities in cystic fibrosis.
Pediatr Res. 1985 Jan;19(1):104-9.

5: Manniello RL, Schulman JD, Farrell PM.
Amino acid metabolism in dysmature newborn rats--possible explanation for the antihypoglycemic effect of prenatal glucocorticoids.
Pediatr Res. 1977 Nov;11(11):1165-6.

6: Manniello RL, Adams AJ, Farrell PM.
The influence of antenatal corticosteroids on hypoglycemia in newborn rats with intrauterine growth retardation.
Pediatr Res. 1977 Jul;11(7):840-4.

7: Farrell PM, Blackburn WR, Adams AJ.
Lung phosphatidylcholine synthesis and cholinephosphotransferase activity in anencephalic rat fetuses with corticosteroid deficiency.
Pediatr Res. 1977 Jun;11(6):770-3.

8: Farrell PM, Fox GN, Spicer SS.
Determination and characterization of ciliary ATPase in the presence of serum from cystic fibrosis patients.
Pediatr Res. 1976 Feb;10(2):127-35.

9: Epstein MF, Farrell PM.
The choline incorporation pathway: primary mechanism for de novo lecithin synthesis in fetal primate lung.
Pediatr Res. 1975 Aug;9(8):658-65.

10: Klagsbrun M, Farrell PM.
The methylation of transfer and ribosomal ribonucleic acid in human fibroblasts: normal methylation of ribonucleic acid in cystic fibrosis.
Pediatr Res. 1974 Mar;8(3):205-11.

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

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

210 Euston Road • London • NW1 2BE
www.ucl.ac.uk/histmed • +44 (0) 20 7679 8100

05

Professor Mary Ellen Avery,
Children's Hospital Boston,
300 Longwood Avenue,
BOSTON, MA 02115
USA

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

10 August, 2005

Dear Professor Avery,

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

Enclosed is the final proof of the transcript, *Prenatal Corticosteroids for Reducing Morbidity and Mortality in Preterm Birth* to which you contributed, for your final approval. Please note that only typographical corrections are allowed at this stage.

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

Please look very carefully at your own contribution on pages 5-7, 22-24, 36-37, 39 and your biographical note on page 112 to check that the added footnotes are correct. In particular, I would like to ask:

- **footnotes on pages 5–7, 36–7, 39, 46:** please check references and if incorrect, suggest appropriate citation(s);
- **if you would suggest appropriate phrase for missing text on pages 7 and 37 ;**
- **two queries on pages 46 and 48.**

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

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

Yours sincerely,

Lois Reynolds.

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey

enc. Wit25 final

Avery

Thanks for the opportunity to review these pages -

I tried to ans. your questions on the appropriate pages

MEA

Rec'd 22.8.05 to DC

Final queries Rec'd by LR: 7.9

please see pages 5-7, 22-24, 36-37, 39 46, 48, 55, 112 (please check biog note).

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

Please return by 7 September 2005

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 [redacted]

From: ME Avery 8/17/05

see p 1. (query 1)

-3 10.3.05; -4 7.07.05; -5 28.7. [redacted] d: 5 August 2005

o:\data\witness\25-corticosteroids\cortico6-040805.doc

2 queries:

- pg. 46 I could find nothing for Word and Farrell (1974) in FN 73. See list attached.
- pg 48 See FN 75 - Did Liggins dispute your remark about his time in the Bowes lab. Would you like to reply?

Please delete my comment re Liggins. MEA

Sent to DC - Rec'd in office 22/8/05.

Rec'd by LR 7/9/05: spare pgs removed 19/9/05

Corrections finished 20/9/05

Avery

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Corrections finished 20/9/05

Prenatal Corticosteroids for Reducing Morbidity and Mortality In Preterm Birth

Participants

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

Among those attending the meeting:

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

Apologies include:

Professor Sir Robert Boyd, Dr Clive Dash, Professor Geoffrey Chamberlain, Dr Pamela Davies, Professor Sir Liam Donaldson, Professor Peter Dunn, Dr Jonathan Grant, Professor Aidan Halligan, Professor Mark Hanson, Professor Ross Howie, Professor Frank Hytten, Professor Marc Keirse, Professor Sir Graham Liggins, Dr Jerold Lucey, Professor Sally MacIntyre, Dr Jonathan Mant, Professor Jim Neilson, Dr Cliff Roberton, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

†Died 31 August 2004

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

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

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

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

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

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

Prof. Maureen Young was in the audience - she lives in Cambridge UK
see p 117
19/9/05

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

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

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

[7] Liggins (1969).

[8] Liggins and Howie (1972).

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

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

United States National Institutes of Health (NIH) Collaborative Group

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

Buckingham, S. Avery ME. The time of appearance of lung surfactant in the foetal mouse Nature 1962; 193: 688-689.

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.

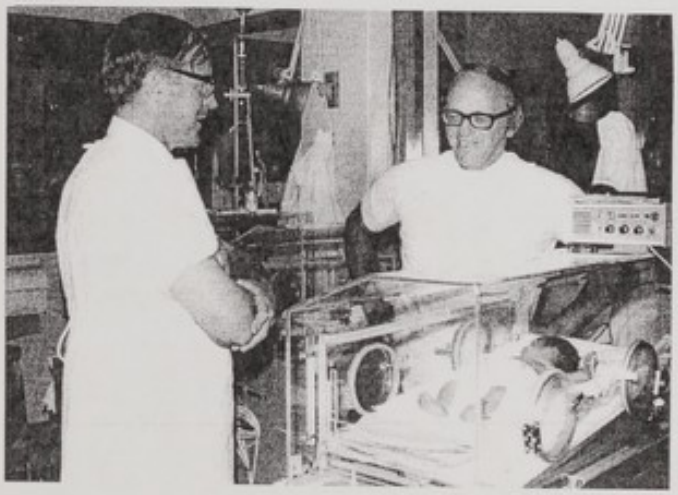

Figure 1: Ross Howie and Mont Liggins, *c* 1972

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

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

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

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

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

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

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

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

[22] Follow-up studies here.

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

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

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

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

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

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

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

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

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

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

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

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

Lois Reynolds

From: Avery, Mary [Mary.Avery@childrens.harvard.edu]
Sent: 24 August 2005 15:35
To: ucgarey@ucl.ac.uk; l.reynolds@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal corticosteroids: your comment, page 48

To: Mrs. Lois Reynolds

The reference you were looking for is: Not Published.

Wood, RE, Farrell, PM. Epidemiology of respiratory distress syndrome (RDS). Ped. Res.(8) 452.1974.

Thank you for all of your good work. checking at UCL Lib

Dr. Mary Ellen Avery Ordered, 2019/05.

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

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

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

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

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

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

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

Harding: The short answer is no, I cannot, but I could go back and ask him. He commented about who gave him the money and I think probably he simply asked for research funding to look at preterm labour.[33] I cannot tell you more details about how much it was, not his personal salary, it must have been working expenses. It was for some considerable period of time, because he worked on this for several years.

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

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

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

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

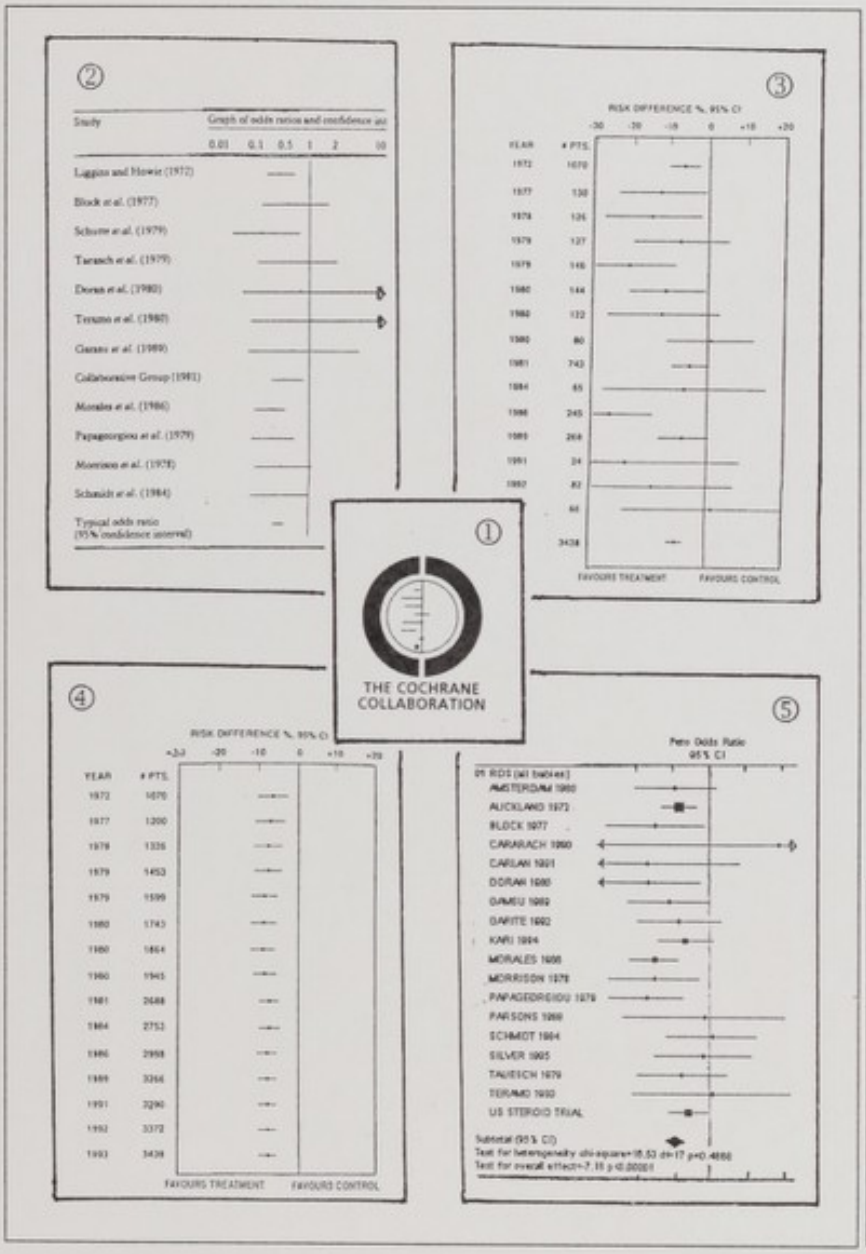

Figure 4: Patricia Crowley' meta-analyses, 1992–2004.

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

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

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

Avery: It was frustrating.

Hey: Well, you banged the drums quite hard.

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

Note: Performing your original search, ***bubble stability test***, in PubMed will retrieve *30* citations.

☐ **1:** Med J Zambia. 1977 Aug-Sep;11(4):109-12. Related Articles, Links

The prediction of fetal maturity: a comparison between the bubble stability test and cytological evaluation of maturity.

Dowd MJ, Zeigler O.

Amniotic fluid from fifty women soon to be delivered, or already in labour, was analysed in the Obstetric unit of University Teaching Hospital, Lusaka. A Bubble Stability Test (Clements et al, 1972) and cytological screening for maturity (Sharma & Trussell, 1970) was carried out on each specimen. The latter test has been routinely used in the Obstetric unit for three years. The intent was to discover which test was the most useful indicator of fetal maturity.

PMID: 579013 [PubMed - indexed for MEDLINE]

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

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

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

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

Ref refs to Pattle, Richard Parton. Wilts UK who devised The bubble stability test – sometimes called the "shake" test for lung maturity.

see Permissions of Avery + Pattle. for photo

Mrs Brenda Mullinger: At the time of the UK multicentre trial, I was working for Glaxo and I coordinated the trial in the UK.[55] What I wanted to say relates to what Professor Crowley said about uptake. Although we originally coordinated the study after different clinicians had approached Glaxo, we found that we needed more centres to join the study, and so we did actually try approaching [?approach?] other centres in the UK. Looking at the paper [now?] we got underway in mid-1975, but I was told by Dr Clive Dash, the medic at Glaxo who unfortunately cannot be here, that many of the UK centres who were approached wouldn't join the study because they were already using betamethasone and they felt that it wasn't ethical to have control groups. So that although your uptake maybe was only 10 per cent, certainly the research centres, the sort of centres that might have joined the study, were starting to think about using it by the mid-1970s in the UK.[56]

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

[56] Dr Clive Dash wrote: 'The UK multicentre study [Gamsu *et al.* (1989)] was designed in 1974, largely stimulated by the publication of Liggins and Howie (1972) and their prior animal studies. The idea for a UK study was an amalgam of interest from some obstetricians and neonatal paediatricians and from within the Medical Department of Glaxo in the UK because of the organizational link with the Antipodes. A taxing question in the design and analysis of the UK study was the imprecision in estimating gestational age at the time of recruitment. Maternal dates and obstetrical palpation were the only antenatal assessments available then – so different from the current techniques! The clinicians documented both estimates for the analysis. These were augmented (or confounded) by neonatal assessment [Farr *et al.* (1966); Dubowitz *et al.* (1970)], which was also recorded. Clinicians' views can change during the planning and conduct of long-term studies (about 4 years to plan and complete recruitment and follow-up for the UK study). All the clinicians involved in the early planning recognized that more clinical work was needed to confirm the results from New Zealand. Everyone involved in the study's planning recognized that it was important to have commitment from an obstetrician and paediatrician at each participating hospital. By the time the study recruitment started (about one year later), some of the clinicians did not wish to recruit patients to the study for various reasons, even after Ethics Committee approval.' E-mail to Dr Daphne Christie, 10 January 2005.

Lois Reynolds

From: Avery, Mary [Mary.Avery@childrens.harvard.edu]
Sent: 30 August 2005 15:55
To: ucgarey@ucl.ac.uk; l.reynolds@ucl.ac.uk
Subject: RE: Witness Seminar: Corticosteroids : corrections received

Lois,

I wasn't sure if you had seen this article: ✓ checked 20/9/05.

Stefan A. Tschanz, Andrew N. Makanya. Beat Haenni, and Peter H. Burri. Effects of Neonatal High-Dose Short-Term Glucocorticoid Treatment on the Lung: A Morphologic and Morphometric Study in the Rat. Pediatric Research. 2003 Vol 53(1): 72

Mary Ellen Avery

Avery: We have to think in terms of the 1970s versus the 1990s and up to 2000, because up until the 1970s the control trials were very supportive of the efficacy of prenatal glucocorticoids, but that was an era when we didn't have lots of babies under 800g. Now the story is different. We have babies weighing 600g, 700g and 800g, who are getting glucococorticoids, and we assumed that they wouldn't have any serious toxicity. But along came Petra Huppi from Geneva, who worked with us at Harvard and had developed a great experience with imaging studies of the brains of these babies. There is no question that there can be white matter problems which she has documented and published.[57] I'm not prepared to take a stand, I'm only saying this is one group where there could be toxicity, and where we really don't know the cost–benefit of accelerating the lung versus some white matter problems in the baby. This is a new frontier, and I just wanted to put this on the table. I don't know any more about it than I have just said.

Crowley: Through all the systematic trials we have kept an eye on intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL). There is good evidence that these adverse outcomes are reduced by antenatal steroids across the gestational ages. The use of early postnatal steroids is associated with an increased risk of adverse outcome. Antenatal steroids are protective in terms of neonatal neurology, whether you look at the brain at autopsy or with imaging techniques for PVL. Would you agree with that, Jane?

Harding: If I could come back briefly to address Richard Lilford's point and then go back to some of the reasons perhaps why steroids weren't used. I have just dragged out the report of the 70th Ross Conference on Paediatric Research, which was I think about 1979, but I don't have a date on the paper.

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[57] ~~Prof Avery, is the correct Huppi reference??~~ Murphy B P, Inder T E, Huppi P S, Warfield S, Zientara G P, Kikinis R, Jolesz F A, Volpe J J. (2001) Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. *Pediatrics* **107**: 217–21.

[From the floor: 1976].[58] It was one of the places where Mont Liggins reported the outcomes of the Auckland trial. He also reports the outcomes of ratios in amniotic fluid before and after steroid treatment, and points out that they don't change consistently, so that amniotic testing for fetal lung maturation did not reflect clinical lung maturation. I was reminded of his concluding paragraph, which is why I dragged it out:

> We have not attempted to select patients on the basis of assessment of pulmonary maturation from amniotic fluid analyses. In pregnancies beyond 34 weeks, in which the risk of respiratory distress syndrome (RDS) is low, a strong case can be made for giving glucocorticoids only when the results of amniocentesis indicate pulmonary immaturity. Before 32 weeks the likelihood of RDS is so high, and finding a mature pattern in amniotic fluid is so low that treatment without prior amniocentesis is probably justified.[59]

So back then, they had considered the phenomenon, had picked the subjects to uinclude, and concluded that it wasn't worth doing, except perhaps in pregnancies more than 34 weeks.

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

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[58] Liggins G C. (1976) Prenatal glucocorticoid treatment: prevention of RDS by maternal betamethasone administration. Moore T D. (ed.) *Lung Maturation and the Prevention of Hyaline Membrane Disease.* Report of the 70th Ross Conference on Pediatric Research. Columbus, OH: Ross Laboratories, 97–103. [highlighted title differs from Ross Howie's list]

[59] Page number of quote??

Some hospitals approaching 25 to 30 per cent usage, and others, by far the majority, scarcely reaching 10 per cent.

I wanted to ask two other things. A number of the sub-analysis [?which sub-analyses?] that I think were useful from my perspective at that stage as a paediatric registrar interested in neonates and the business of steroids, was with the sub-analyses and the long-term outcome worries were one of the major concerns, sub-analysis in the US Collaborative Group study.[71] What I found interesting was two aspects of that study. One was the vast number of mothers who were eligible but excluded, 88 per cent of those thought to be eligible to be considered but not actually entered, they were excused for various reasons, the vast majority being excluded because they weren't thought to be delivering within the time frame. I wondered what actually happened, whether they did or they didn't deliver within the time frame, I cannot find evidence to show what happened. But the other issue is was there ever any biological plausibility to the reasons for the subject analysis. Why would we expect betamethasone to work differently according to sex of the fetus? I wondered if anyone had any clues as to that. I am not a laboratory person, but I cannot see any particular reason why one should divide on the basis of the sex of the fetus in relation to likely outcome. I could be completely wrong. But that seemed to be one of the major issues that unless you were expecting a black female baby, it was a waste

[71] Dr Sam Richmond wrote: 'I was particularly interested in the sub-analyses of the collaborative study [Collaborative Group on Antenatal Steroid Therapy (1981)] because of the general felt concern over possible long-term adverse effects in babies exposed to antenatal steroids and the possibility of being able to be more discriminating in which mothers were offered steroids based on these sub-analyses. What concerned me and significantly undermined the trust one might place in these sub-analyses were two things: firstly the vast proportion of eligible mothers (7197/7893=91 per cent) who were excluded from the study, which must raise some questions, and secondly the illogical interpretation of some of the sub-analyses. While I can understand that one might expect that a medication will have a greater effect among a subgroup at greater risk – such as among Caucasians rather than American blacks of equivalent gestation, or among male babies rather than females of equivalent gestation – however, that does not translate to the conclusion that steroids don't work in the low risk group – it merely means that one requires a larger sample of the low-risk group to show an effect.' Note on draft transcript, 26 June 2005.

of time, and that's clearly incorrect.[72] But why did anyone think to look in the first place?

Avery: First there is definitely a difference between male and female and white and non-white. The Asian population is more advanced, yet when you look at these differences they are real, even into 20 weeks. I don't think they are big enough to swamp all the other things that are going on. It's a very interesting issue, I think, taking into consideration the chance that you might have all girls and look at the output in terms of scoring.

Richmond: I fully respect that there is a difference in survival based on race and sex, but I didn't think there would necessarily be a difference in response to steroids based on that. It just means that you get more informative clients if you choose the ones with the higher risk, but is there a differential response to steroids based on sex or race?

Avery: I cannot give you chapter and verse, but I think there is a difference.[73] Maybe somebody else has a reference.

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[72] Dr Sam Richmond wrote: 'I know of no reason why one might expect any such difference (other than the well-known fact that girls of an equivalent gestation are at less risk of death than boys) and thus I could not understand why the sub-analyses by sex were made in the first place – nor why this aspect was so vigorously pursued. If one undertakes a large number of sub-analyses of any dataset one will find some statistically significant differences purely by chance – it therefore behoves one to limit sub-analyses to those with some biological plausibility. However, what was suggested by the Roberton editorial [Roberton (1982)] was that steroids were only effective in white male babies (even though the Collaborative Group study [Collaborative Group on Antenatal Steroid Therapy (1981)] showed an effect only in females).' Note on draft transcript, 25 June 2005.

[73] Professor Mel Avery wrote: 'A male infant has 1.5 to 2.0 times the risk of fatal hyaline membrane disease[also known as respiratory distress syndrome (RDS)]. See Wood and Farrell (1974).' Fax to Dr Daphne Christie, 21 June 2005. See also Avery (2000).

Chalmers: I want to comment on extrapolation from data in animals, pathophysiological data in humans, and observational data in humans. One of the most remarkable things about the Auckland story is that Mont and Ross went directly from hypotheses they had tested in animals to assess the relevance of the hypotheses to women and their babies. People working with animals who generate hypotheses – whether it's about brain damage in the long term or some other matter – too often fail to exercise the scientific self-discipline shown by Mont Liggins and Ross Howie. I'll give you an example. Geoffrey Dawes was one of the hubs of perinatal physiological research in this country.[74] He and I often had arguments about the behaviour that I have just been complaining about. I had the impression that he was very annoyed that he hadn't made the discovery that Mont and Ross had made. I remember how in the 1990s he telephoned me in some glee to say that he had discovered – in an observational study – that prenatal steroid administration was associated with a pattern of fetal breathing movements that he regarded as worrying. I said to him, 'So what? You have now a mass of data from women and babies. If you have a hypothesis that is worth testing in terms of the relevance of your observations to human health, then test it, using the mass of data that's now available from human experiments'. There is this bizarre lack of scientific self-discipline among people who know how to design experiments in animals, but actually don't know how to design, or even exploit, experiments in human beings.

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

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

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

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

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

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

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[75] Professor Mont Liggins wrote: 'I spent a sabbatical with Geoffrey in 1970 but I certainly made no such statement about surfactant. I can't imagine where Mel got that idea. It should be deleted unless it can be validated. I was aware of the suggestion about the relative efficacy of batamethasone and dexamethasone [see note 144]. I think the evidence deserves your critical comment. I recall that Peter Nathanielsz reported that beta was more active than dex in an effect on a kidney function (I think) in fetal sheep. I don't have the reference but I could get it from Peter if you would like me to.' E-mail to Professor Ross Howie, 11 January 2005. Prof Liggins wrote: 'Mel Avery's comment …is news to me and I cannot imagine where she got this idea from. I had no reason to make such a statement. I think it should be deleted unless it can be validated.' E-mail to Dr Daphne Christie, 8 January 2005. See Nathanielsz P W. (1996) *Life Before Birth: The challenges of fetal development*. New York, NY: W H Freeman. First published by Promethean Press, NY, 1992.

would you like to reply?

I regret that I cannot recall the source - perhaps Maureen will remember that

I hope you do not include this off-hand remark

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

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

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

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

Avery: I have no idea.

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

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

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

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

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

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

[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,

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

Hanney: We at Brunel have been looking at the benefits from health research for about ten years now, and this particular stream of work seems to us to have been one of the most interesting, and [that] I have worked on ~~it~~ with Miranda, Martin Buxton and Jonathan Grant. I apologize for checking my notes from time to time, because I am trying to pick up what various people have said today in what I think is an interesting session.

For instance, John [Hayward], we at least read your work. There is a paper that sets out most of this in detail in press and will be published in *Social Science and Medicine*.[147] I will just highlight all the key points for now. Perhaps it's just worth spending a minute, going over our payback framework so you can see how we tried to drop this stream of work into a frame [?model?] that we had already developed. Apologies to those who have already heard this many times before. Basically, there are two aspects to our payback framework: a multidimensional categorization of benefits, and a model to examine how they arrive. The categories which we suggest are five: knowledge production; the targeting of future research and building research capacity; better informing policies, with the term policies being widely interpreted; health gain and benefits to the health sector; and the broad economic benefits. There's a series of stages in the model in which we think these various benefits can be identified. A key feature of our model is to attempt to identify actual levels of uptake so that we can then say what the benefit has been, and this, of course, links with previous discussions.

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

There's always a problem when doing this type of analysis as to where you start. Various initial presentations today showed clearly that research builds on previous research etc., and so whenever one makes [?chooses?] a start[ing] point, it is always artificial. On the other hand I do think the nature of the discussions [?today?], and what Mary Ellen says, does provide [?has provided?] a realistic basis for saying we will start by looking at the work of Liggins and Howie. In terms of knowledge production clearly the 1969 paper from Liggins, [and] the 1972 paper from Liggins and Howie, were very important.[148] There are lots of weaknesses in citation analysis, but it does indicate whether people have taken notice, and these are two very highly cited papers, especially the 1972 paper which has been cited over 1200 times.[149]

There has been some bibliometric analysis in this field undertaken by the Policy Unit here at the Wellcome Trust.[150] Various generations of papers were traced backwards and showed again that this was the most important work in this field in several generations. Clearly knowledge production [is] very high. In terms of affecting future research, again citations indicate that it has influenced much subsequent work. It's also interesting that many of the other pieces of work, trials etc., actually start with a reference to the work of Liggins and Howie, which again I think emphasizes their importance for further work. And it's also been mentioned that Ross Howie felt that further trials should be undertaken rather than necessarily saying that people should act on the findings. Nevertheless, there was quite an uptake in some places, on the basis of this very important trial and the ensuing publications from it. In the UK the

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

[149] Dr Stephen Hanney wrote: 'The article pre-dated the start of the electronic record of citations, therefore I calculated this figure from the post-1981 electronic data plus hard copies of ISI data from earlier years [Hanney *et al.* (2005)]. Mont Liggins had an article in the *Citation Classics* series in March 1982 and by then the number of citations for the 1972 paper was already 565.' Note on draft transcript, 12 July 2005. See Mont Liggins' article of 29 March 1982 freely available at www.garfield.library.upenn.edu/classics1982/A1982NF37800001.pdf (visited 14 June 2005).

[150] Grant *et al.* (2003).

*Biographical notes**

* Contributors are asked to supply details; other entries are compiled from conventional biographical sources

Dr Mary Ellen (Mel) Avery

MD (b. 1927) was Thomas Morgan Rotch Professor of Paediatrics at Harvard Medical School, Boston, MA, and Physician-in-Chief, later Emeritus, at the Children's Hospital, Boston from 1974 to 1985. She was awarded the Virginia Apgar Award by the American Academy of Pediatrics in 1991 and the John Howland Award from the American Pediatric Society in 2005. She served on the Board of Directors of the Burroughs Wellcome Fund from 1993 to 2001; has been a member of the National Academy of Sciences since 1994, and was President of the American Association for the Advancement of Science for 2003, and Chairman of its board in 2004. See Avery and Mead (1959); Avery (2000).

Sir Joseph Barcroft

Kt CBE HonFRSE HonFRCOG FRS (1872–1947) was Reader (1919) and Professor of Physiology (1926–1937) in Cambridge, and was appointed Director of the Unit of Animal Physiology, Agricultural Research Council, in 1941. His research interests included studies of the properties of blood, especially blood gases and the oxygen-carrying function of haemoglobin, and studies on the physiology of the fetus. See, for example, *The Respiratory Function of the Blood* (1914) and *Researches on Prenatal Life* (1946). See also Roughton (1948–49).

Sir Christopher Booth

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

Dr Peter Brocklehurst

MBChB FRCOG MSc(Epidemiology) (b. 1962) trained as an obstetrician and gynaecologist, and an epidemiologist in London. He joined the National Perinatal Epidemiology Unit (NPEU), Oxford, as a Research Fellow in 1994, became consultant epidemiologist in 1996 and was appointed Director in 2002. See www.npeu.ox.ac.uk/npeu_home.php (visited 18 July 2005).

Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds) (1997) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 1. London: The Wellcome Trust.

Ten Centre Study Group. (1987) Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. *British Medical Journal* **294**: 991–4.

Wallis C. (2004) What makes teens tick? *Time Magazine* (10 May 2004). See pay-for-view at www.time.com/time/archive/preview/0,10987,994126,00.html (visited 26 July 2005).

Wilson B, Thornton J G, Hewison J, Lilford R J, Watt I, Braunholtz D, Robinson M. (2002) The Leeds University Maternity Audit Project. *International Journal for Quality in Health Care* **14**: 175–81.

Lois Reynolds

From: Avery, Mary [Mary.Avery@childrens.harvard.edu]
Sent: 26 October 2005 18:16
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal Corticosteroids: further queries

Lois,

My statement should say "Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically was told by Dawes that he would not allow anyone to do any work..."

If you have further questions, please let me know.

Thank you,
Mica

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: Wed 10/19/2005 12:09 PM
To: Avery, Mary
Subject: Witness Seminar: Prenatal Corticosteroids: further queries

Dear Prof Avery,
(1) In the discussion below you mention the Swiss. Could you suggest a reference that would help those who are not familiar with everyone involved in the early story?

(2) We would like to retain your comment on page 48 (also reproduced below) on Geoffrey Dawes and Liggins, for the reasons suggested earlier, that we cannot censor what was said at the meeting. It would, however, be helpful to know if you meant: (a) Liggins told Dawes xxx? OR (b) Dawes told his staff that Mont had said xxx?

Best wishes from Lois

0-0-0-0
(1) 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.(FN1) You probably know that. It's kind of scary. It was done by the group in Berne, I think it is Burri at the Université de Paris, the fellow who is still publishing on 'beware, beware,' and I cannot counter that.(FN2) I'm glad he's looking at it, and I just think we have to be vigilant and that those of us who spend more time with this have to keep track of the babies.

FN1. Dr Ross Howie wrote: '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 [Ballard et al. (1975)]. 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 follow-up 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.' E-mail to Mrs Lois Reynolds, 26 August 2005.

FN2. Tschanz et al. (2003).

(2) 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.

0-0-0-0

-----Original Message-----
From: Avery, Mary [mailto:Mary.Avery@childrens.harvard.edu]
Sent: 29 August 2005 15:26
To: ucgarey@ucl.ac.uk; l.reynolds@ucl.ac.uk
Subject: quick question

To Lois Reynolds,

Have you seen this report? NIH Consensus Development report - Am J Ob Gyn 173, 413, 1995.

Mary Ellen

FN 42 VII/05

Lois Reynolds

From: Avery, Mary [Mary.Avery@childrens.harvard.edu]
Sent: 31 October 2005 15:58
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal Corticosteroids: further queries

Lois,

Yes, please send to the Wellsley address. I believe the reference she is referring to is "Rokos J, Vaeusorn O, Nachman R, Avery ME. (1968) Hyaline membrane disease in twins. Pediatrics 42: 204-5." Please let me know if you need any further information.

Mica Astion

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: Wed 10/26/2005 1:55 PM
To: Avery, Mary
Subject: RE: Witness Seminar: Prenatal Corticosteroids: further queries

Thank you, Mica. Any suggestions for the Swiss reference in query (1)?
I'm please to be able to clarify what Dawes said. I'll send a copy of her pages by post tomorrow, for final approval. To the Wellsley address?
Best wishes from Lois

-----Original Message-----
From: Avery, Mary [mailto:Mary.Avery@childrens.harvard.edu]
Sent: 26 October 2005 18:16
To: ucgarey@ucl.ac.uk
Subject: RE: Witness Seminar: Prenatal Corticosteroids: further queries

Lois,

My statement should say "Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically was told by Dawes that he would not allow anyone to do any work..."

If you have further questions, please let me know.

Thank you,
Mica

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: Wed 10/19/2005 12:09 PM
To: Avery, Mary
Subject: Witness Seminar: Prenatal Corticosteroids: further queries

Dear Prof Avery,
(1) In the discussion below you mention the Swiss. Could you suggest a reference that would help those who are not familiar with everyone involved in the early story?

asking re FN 63
Rokos is FN 42.

(2) We would like to retain your comment on page 48 (also reproduced below) on Geoffrey Dawes and Liggins, for the reasons suggested earlier, that we cannot censor what was said at the meeting. It would, however, be helpful to know if you meant: (a) Liggins told Dawes xxx? OR (b) Dawes told his staff

√

that Mont had said xxx?

Best wishes from Lois

0-0-0-0
(1) 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.(FN1) You probably know that. It's kind of scary. It was done by the group in Berne, I think it is Burri at the Université de Paris, the fellow who is still publishing on 'beware, beware,' and I cannot counter that.(FN2) I'm glad he's looking at it, and I just think we have to be vigilant and that those of us who spend more time with this have to keep track of the babies.

FN1. Dr Ross Howie wrote: '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 [Ballard et al. (1975)]. 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 follow-up 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.' E-mail to Mrs Lois Reynolds, 26 August 2005.

FN2. Tschanz et al. (2003).

(2) 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.

0-0-0-0

-----Original Message-----
From: Avery, Mary [mailto:Mary.Avery@childrens.harvard.edu]
Sent: 29 August 2005 15:26
To: ucgarey@ucl.ac.uk; l.reynolds@ucl.ac.uk
Subject: quick question

To Lois Reynolds,

Have you seen this report? NIH Consensus Development report - Am J Ob Gyn 173, 413, 1995.

Mary Ellen

Lois Reynolds

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

Good afternoon Lois,

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

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

Cheers,
Mel

Lois Reynolds

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

Dear Mrs. Reynolds,

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

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

Query 2. See above

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

Best regards, Mont

Lois Reynolds

From: Lois Reynolds [ucgarey@ucl.ac.uk]
Sent: 15 November 2005 10:19
To: g.liggins@auckland.ac.nz
Subject: RE: response to queries : 15 Nov 2005

Thanks, Mont.
I'm delighted with the Binns reference, perfect timing, as the proof corrections are just being done.
Below are the paragraphs as they will appear in the published text. Best wishes from Lois

0-0-0-0-0

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

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

(2) Caption to Figure 7:

Lamb lungs showing partial infl ation after fetal infusion with cortisol at 118 days of gestation, birth at 120 days, photographed at autopsy. The pale areas are tissue inflated with air; the dark areas are uninflated lung.

(3) Query on first line of page 7 will be checked with Mel Avery. Thank you for pointing out the inaccuracy.

0-0-0-0-0

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

Dear Mrs. Reynolds,

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

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

Lois Reynolds

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

Importance: High

Thank you, Prof Avery.

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

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

Best wishes from Lois

0-0-0-0

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

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

(2) Query on following sentence:

The story of the glucocorticoids moved ahe[illegible]sed a randomized control trial [of glucocortico-ste[illegible]birth of the lamb, and it was obvious that the effe[illegible]

Footnote 86
Avery-Liggins

Would it be more accurate as follows??

The story of the glucocorticoids moved ahe[illegible]ed a randomized control trial and it was obvious [illegible]

0-0-0-0--0

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

Good afternoon Lois,

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

Lois Reynolds

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Sent: 15 November 2005 10:28
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FN86 There was some discussion between Avery, Liggins and the editors on this point. This correspondence, along with tapes and other records of the meeting, will be deposited in CG/253, Archives and Manuscripts, Wellcome Library, London.

(2) Query on following sentence:

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

Would it be more accurate as follows??

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

0-0-0-0--0

-----Original Message-----
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Sent: 14 November 2005 20:05
To: l.reynolds@ucl.ac.uk
Subject: Prenatal Corticosteroid Transcript

Good afternoon Lois,

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

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

Cheers,
Mel

Lois Reynolds

From: Avery, Mary [Mary.Avery@childrens.harvard.edu]
Sent: 15 November 2005 20:39
To: ucgarey@ucl.ac.uk
Subject: RE: Prenatal Corticosteroid Transcript : Final query 15 Nov 2005, urgent

Yes, the second one is better, but should say "controlled" instead of "control".

Thank you,
Mel

From: Lois Reynolds [mailto:ucgarey@ucl.ac.uk]
Sent: Tue 11/15/2005 5:27 AM
To: Avery, Mary
Subject: RE: Prenatal Corticosteroid Transcript : Final query 15 Nov 2005, urgent

Thank you, Prof Avery.

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

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

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0-0-0-0

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

(2) Query on following sentence: page 6. — corrected 16/11/05.

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

Would it be more accurate as follows??

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0-0-0-0--0

-----Original Message-----
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Sent: 14 November 2005 20:05
To: l.reynolds@ucl.ac.uk
Subject: Prenatal Corticosteroid Transcript

Good afternoon Lois,

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

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

Cheers,
Mel

Avery, Mary

From: Lois Reynolds [ucgarey@ucl.ac.uk] **Sent:** Fri 8/12/2005 7:23 AM
To: Avery, Mary
Cc:
Subject: Witness Seminar: Prenatal corticosteroids: your comment, page 48
Attachments:

Dear Prof Avery,

I'm sending two further copies of the final proof to your addresses in Maine and at Wellsley, as the corrections need to be in my hands by 7 September if we are to keep to our publication schedule of November 2005.

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

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

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

The published transcript of the meeting offers everyone the opportunity to comment on others' views, which we then include in an appropriate footnote (viz. the objections about Chris Booth's comments above). In this particular instance, both you and Mont could be right. You may be completely correct in saying you were told what you report you were 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.

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:

8/17/05

- Please delete it, It was a second-hand comment, and I do not recall the source.

Mary Ellen Avery

corrected 20/9/05.

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.

I agree MEA 8/17/05

Please delete my comment MEA

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

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

Avery: The meeting was a combined meeting of obstetricians and pediatricians. They had invited me over as a visiting speaker. It was the first meeting with Liggins who told me of these findings.

...

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

Avery: It was frustrating.

Hey: Well I mean you banged the drums quite hard.

Avery: I cannot begin to organize my thoughts for this period. I was not centrally engaged, I am not an obstetrician, I didn't want to tell obstetricians what to do and what not to do. In fact, I didn't have that kind of self-confidence. I wanted long-term follow up. I spent hours with Ross Howie, urging him to please keep track because the Swiss were talking about inhibiting lungs seriously, and even brains weren't growing well if little animals got big steroid doses during pregnancy. You probably know that. It's kind of scary. All animal. It was done by the group in Bern, I think it is Burri who is the fellow who is still publishing on beware, beware, and I cannot counter that. I'm glad he's looking at it, and I just think we have to be vigilant and those of us who spend more time with babies, have to keep track of the babies.

...

Avery: I think we have to think in terms of 1970s versus the 1990s and over 2000, because up until the 1970s the controlled trials were very supportive of efficacy of prenatal glucocorticoids, but that was an era when we didn't have lots of babies under 800g. Now the story's different. We have babies of 600g and 700g and 800g, who are getting

rec 12/5/04

DR.H.BARRIE
3, BURGHLEY AVENUE, NEW MALDEN, SURREY, KT3 4SW
TEL: 0208 942 2836
Fax: 020 8949 3350
e-mail: herbert@barrie97.freeserve.co.uk

V

Mrs Wendy Kuttner
The Wellcome Trust Centre for
the History of Medicine
24 Eversholt Street
LONDON NW1 1AD

5th May 2004

Dear Mrs Kutner

WITNESS SEMINAR 15th JUNE

Thank you very much for your kind invitation. I am sorry I am unable to attend.

Yours sincerely

Herbert Barrie

HERBERT BARRIE

THE WELLCOME TRUST

WITNESS SEMINARS

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****

1. NAME **Professor Sir Christopher Booth FRCP**

2. ADDRESS

The Wellcome Trust Centre
for the History of Medicine at UCL
24 Eversholt Street
London NW1 1A

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

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Signed..... Date..... 9/12/04

example

Professor Sir Christopher Booth FRCP
The Wellcome Trust Centre
for the History of Medicine at UCL
24 Eversholt Street
London NW1 1A

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

7 December 2004

Dear Sir Christopher

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 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 the 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

THE WELLCOME TRUST

WITNESS SEMINARS

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****

1. NAME **Professor Sir Christopher Booth FRCP**

2. ADDRESS

The Wellcome Trust Centre
for the History of Medicine at UCL
24 Eversholt Street
London NW1 1A

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15 June 2004

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Signed..... Date 9/12/04

Booth

Any correction S.
Please see pages. 24, 113.
Astrubhes from Lois.

OK CB

Booth –
no corrections
22/12

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

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

Edited by L A Reynolds and E M Tansey

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

o:\data\witness\25-corticosteroids\cortico6-040805.doc

Need 31/8/05 ✓
For return by 7 September

Booth

Any correction S.
Please see pages. 24, 113.
Astrishes from Lois.

OK CB

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY IN PRETERM BIRTH

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o:\data\witness\25-corticosteroids\cortico6-040805.doc

Need 3/8/05 ✓
For return by 7 September

Prenatal Corticosteroids for Reducing Morbidity and Mortality In Preterm Birth

Participants

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

Among those attending the meeting:

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

Apologies include:

Professor Sir Robert Boyd, Dr Clive Dash, Professor Geoffrey Chamberlain, Dr Pamela Davies, Professor Sir Liam Donaldson, Professor Peter Dunn, Dr Jonathan Grant, Professor Aidan Halligan, Professor Mark Hanson, Professor Ross Howie, Professor Frank Hytten, Professor Marc Keirse, Professor Sir Graham Liggins, Dr Jerold Lucey, Professor Sally MacIntyre, Dr Jonathan Mant, Professor Jim Neilson, Dr Cliff Roberton, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Peter Williams, Professor Mark Walport, Professor Jonathan Wigglesworth

†Died 31 August 2004

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

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

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

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

Harding: The short answer is no, I cannot, but I could go back and ask him. He commented about who gave him the money and I think probably he simply asked for research funding to look at preterm labour.[33] I cannot tell you more details about how much it was, not his personal salary, it must have been working expenses. It was for some considerable period of time, because he worked on this for several years.

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

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

---

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

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

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

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

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

*Biographical notes**

* Contributors are asked to supply details; other entries are compiled from conventional biographical sources

Dr Mary Ellen (Mel) Avery

MD (b. 1927) was Thomas Morgan Rotch Professor of Paediatrics at Harvard Medical School, Boston, MA, and Physician-in-Chief, later Emeritus, at the Children's Hospital, Boston from 1974 to 1985. She was awarded the Virginia Apgar Award by the American Academy of Pediatrics in 1991 and the John Howland Award from the American Pediatric Society in 2005. She served on the Board of Directors of the Burroughs Wellcome Fund from 1993 to 2001; has been a member of the National Academy of Sciences since 1994, and was President of the American Association for the Advancement of Science for 2003, and Chairman of its board in 2004. See Avery and Mead (1959); Avery (2000).

Sir Joseph Barcroft

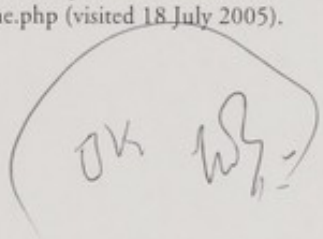
Kt CBE HonFRSE HonFRCOG FRS (1872–1947) was Reader (1919) and Professor of Physiology (1926–1937) in Cambridge, and was appointed Director of the Unit of Animal Physiology, Agricultural Research Council, in 1941. His research interests included studies of the properties of blood, especially blood gases and the oxygen-carrying function of haemoglobin, and studies on the physiology of the fetus. See, for example, *The Respiratory Function of the Blood* (1914) and *Researches on Prenatal Life* (1946). See also Roughton (1948–49).

Sir Christopher Booth

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

Dr Peter Brocklehurst

MBChB FRCOG MSc(Epidemiology) (b. 1962) trained as an obstetrician and gynaecologist, and an epidemiologist in London. He joined the National Perinatal Epidemiology Unit (NPEU), Oxford, as a Research Fellow in 1994, became consultant epidemiologist in 1996 and was appointed Director in 2002. See www.npeu.ox.ac.uk/npeu_home.php (visited 18 July 2005).



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Professor Sir Robert Boyd FRCP FPHM

rboyd@doctors.org.uk

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

1 April 2004

Dear Sir Robert

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.

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 have drawn up a list of possible participants, including clinicians and representatives from relevant organizations. We would like to include physiologists/endocrinologists from the 1960s and early 70s. Sir Graham Liggins is unable to attend but Dr Mary Ellen Avery has agreed to introduce his work. Tilli wondered whether you would be able to help with names of scientists, (preferably based in England, as we don't have the means to fund overseas travel) and if you would be interested in participating yourself.

I look forward to hearing from you.

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

Wendy Kutner

From: Wendy Kutner [w.kutner@ucl.ac.uk]
Sent: 01 April 2004 16:35
To: rboyd@doctors.org.uk
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

CortiBOYDinvltr.doc

Dear Sir Robert, Please find attached a letter about the above Witness Seminar. Yours sincerely, Wendy Kutner

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

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

Wendy Kutner

From: Robert Boyd [rboyd@doctors.org.uk]
Sent: 10 April 2004 00:23
To: w.kutner
Subject: Re: Witness Seminar: Prenatal corticosteroids - 15th June 2004

Thanks. I wasn't very involved in this issue so don't feel I would be a very contributory participant myself. I'm also therefore not a very good source of names.Possibles would include in my view:
Osmund Reynolds
Richard Olver (Dundee)
David Hull (Nottingham)
I Colin Normand(Southampton)
Richard Beard (Mary's)

Kind Regards
Robert
----- Original Message -----
From: "Wendy Kutner" <w.kutner@ucl.ac.uk>
To: "rboyd" <rboyd@doctors.org.uk>
Sent: Thursday, April 01, 2004 4:35 PM
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

> Dear Sir Robert, Please find attached a letter about the above Witness
> Seminar. 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
>
>
>
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The Wellcome Trust Centre for the History of Medicine at University College London

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

UCL

Professor Peter Brocklehurst
National Perinatal Epidemiology 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

11 March 2004

Professor Brocklehurst

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

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

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

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

Continued/... Page 2

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

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

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

npeu
National Perinatal
Epidemiology Unit

26 March 2004

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

Dear Dr Christie

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

Thank you for your letter of 11 March inviting Dr Peter Brocklehurst to attend the above meeting, which is being chaired by Dr Edmund Hey. Dr Brocklehurst is pleased to accept this invitation and would be grateful if you could let him know whether he is required to speak on a specific topic.

With best wishes.

Yours sincerely

Lynne Roberts.

Lynne Roberts
PA to Peter Brocklehurst
(e-mail: lynne.roberts@perinat.ox.ac.uk)

Wendy Kutner

To: lynne.roberts@perinat.ox.ac.uk
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15 June 2004 2pm/6pm

Thank you for your reply on behalf of Dr Brocklehurst. We are delighted he is able to attend. We are in the process of drafting a programme and will let Dr Brocklehurst know further details in due course. Yours sincerely, Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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: Lynne Roberts [lynne.roberts@perinatal-epidemiology.oxford.ac.uk]
Sent: 30 March 2004 11:32
To: w.kutner
Subject: Re: Witness Seminar: Prenatal corticosteroids - 15 June 2004 2pm/6pm

Dear Wendy

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

With best wishes

Lynne Roberts
PA to Peter Brocklehurst

****

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

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

****

>>> "Wendy Kutner" <w.kutner@ucl.ac.uk> 30/03/2004 11:22:33 >>>
Thank you for your reply on behalf of Dr Brocklehurst. We are delighted he
is able to attend. We are in the process of drafting a programme and will
let Dr Brocklehurst know further details in due course. Yours sincerely,
Wendy Kutner

Mrs Wendy Kutner
Secretary to Dr Tilli Tansey
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: Lynne Roberts [lynne.roberts@perinatal-epidemiology.oxford.ac.uk]
Sent: 30 March 2004 11:51
To: w.kutner
Subject: RE: Witness Seminar: Prenatal corticosteroids - 15 June 2004 2pm/6pm

Dear Wendy

Oh how very creepy having a friend with the same name as me. I expect you were thinking it could be a wind up. We have a courier with whom we deal and they also have a Lyn Roberts, so I guess that there are a few of us about.

Thanks for bearing timing in mind for Peter, that is much appreciated.

Best wishes

Lynne

****

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

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

****

>>> "Wendy Kutner" <w.kutner@ucl.ac.uk> 30/03/2004 11:46:34 >>>
Dear Lynne, Thank you for letting us know. We will keep this in mind when
preparing the programme. Wendy Kutner (PS I have a very good friend with
the same name as you - I had to a double take when I saw your name!)

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

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

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

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

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

UCL

Dr Peter Brocklehurst
National Perinatal Epidemiology 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

26 April 2004

Dear Dr Brocklehurst

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

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

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UCL

Dr Peter Brocklehurst
National Perinatal Epidemiology 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

12 May 2004

Dear Dr Brocklehurst

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

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

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

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

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

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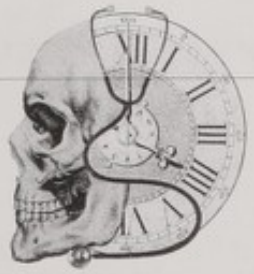
Wendy Kutner

To: peter.brocklehurst@perinat.ox.ac.uk
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004

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

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



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

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

UCL

Dr Peter Brocklehurst
National Perinatal Epidemiology 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

16 June 2004

Dear Dr Brocklehurst

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

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

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

Yours sincerely

Daphne Christie

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

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

+ack by email

rec'd 4/7/05 ✓

National Perinatal Epidemiology Unit
University of Oxford, Old Road Campus, Oxford OX3 7LF
T +44 (0)1865 289700 email: general@npeu.ox.ac.uk
F +44 (0)1865 289701 www.npeu.ox.ac.uk

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WITNESS SEMINARS

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****

1. NAME Dr Peter Brocklehurst.....

2. ADDRESS National Perinatal Epidemiology Unit, Institute of Health Sciences, Old Road, Headington, Oxford OX3 7LF.....

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

15 June 2004.....

4. ASSIGNMENT

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

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I reserve the right to make use of my Contribution, having first obtained the permission of the Trust for me to do so (such permission not to be unreasonably withheld) and I confirm that in any such use I will acknowledge the Trust.

Signed.....
Date.....22-6-05.....

Witness Seminar: PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

Dr Peter Brocklehurst: I suppose I was just thinking about how we ~~are~~ now approach~~ing~~ the use of antenatal steroids, how we have heard today that it was very difficult to get antenatal steroids used in clinical practice~~uptake~~, particularly in the UK, and then within a very short space of time, we were throwing it around like Smarties®, and I suppose what nobody has yet mentioned 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 an awful lot of women antenatal steroids. ~~I remember a lovely quote from Jacque Alferich (?) at Liverpool Women's Hospital. He said, 'If a woman under 34 weeks goes into Liverpool and burps, then she gets antenatal steroids'~~ [I know I said that but I am not happy to have this published in case it gets Prof Alfirevic into trouble in Liverpool – I realize that I should have been more discrete! Perhaps the statement could be anonin~~ly~~mised? "I have heard it said that in some hospitals a pregnant woman only has to burp to be given steroids in order to ensure 95% of babies admitted to the neonatal unit get antenatal steroids". ~~They were giving so much of it, in order to get 95 per cent of babies admitted with steroids.~~ And then the use of multiple courses of steroids which is becoming very frequent. A~~,~~ ~~a~~nd now of course what's being considered more and more in the literature are the potential adverse effects, not just of multiple courses of steroids, but John Newnam's group are~~which is~~ coming up with evidence about the potential long-term hazardous effect of a single course of antenatal steroids on brain development. ~~It's all very new stuff, but we may find ourselves going in a different direction to an extent.~~

Corrected 26/9/05

I think a lot of what is difficult about this issue, is that we are not very good at predicting preterm birth, and if we were better at predicting who was going to deliver preterm we would probably feel much more comfortable about using steroids in a much more targeted way. The concern is that currently ~~probably~~ at least 50 per cent of women who get antenatal steroids do not deliver preterm and therefore if there is long-term harm, it will be in th~~o~~ose babies that will manifest it, and if we could target our use of steroids~~it~~ better, we would probably all feel a bit more comfortable. So I just think we are beginning to go the other way, where people are actually being more cautious now with steroids than they were maybe even five years ago.

...

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 literature~~press~~ yet.[†] My recollection is that i~~But I~~t was in ~~think it is largely in~~ animals, but~~and~~ we~~you~~'ll be able to explore this~~elucidate~~ further when the study is published. ~~But I think the issue that h~~Having tried to do one of the large trials of~~, a~~ multiple courses of steroids, I think one of the issues with~~about~~ clinicians about using 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 you restrict people to giving a single course of steroids they may delay starting until there is~~are~~ stronger evidence, if you like, of impending preterm birth. So the groups of women selected into these trials is likely to be~~interestingly quite~~ different ~~I think in~~ from the multiple~~current~~

[†] ~~[Any further details on this?]~~

steroids group ~~than the single steroid group,~~ and that will make the interpretation of the results interesting.

...

Brocklehurst: I am a bit conscious that I have been asked to speak about current research and where the research 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 intend~~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 discuss~~get onto~~ the issue of the use 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 Jobe~~nes~~ and Roger Solle,[2] which ~~is~~ looked~~ing~~ at the available trials and separated~~ing~~ 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 vers~~or~~us betamethasone, which have looked at substantive neonatal outcomes. There have been trials~~ones~~ that look at antenatal fetal heart rate tracings that seem~~s~~ to be ~~hugely~~ irrelevant if they are not related to the outcome for the baby. Jobe~~nes~~ and Soll~~And they~~ suggest~~ed~~ that betamethasone is preferable to dexamethasone, because the betamethasone trials compared with placebo have a marked reduction in the

[2] ~~[A sample reference. Is this the one?] Thorp J A, Jones A M, Hunt C, Clark R. (2001) The effect of multidose antenatal betamethasone on maternal and infant outcomes. *American Journal of Obstetrics and Gynecology* 184: 196–202.~~ Jobe A, Soll R. Choice and dose of corticosteroid for antenatal treatments. Am J Obstet Gynecol 2004;190:878-881

incidence of death, and dexamethasone has no statistically significant effects on neonatal death. A~~,~~ ~~a~~lthough ~~probably~~ one of the things they reported~~invoked~~ is the fact that the number of trials using betamethasone is substantially larger than the number of trials using dexamethasone, and the numbers of participants in each trial of betamethasone are larger. However, they have suggested some biological plausibility for~~of~~ this, and I am sure we are going to see a lot more about~~on~~ what agent we should be using. I ~~and~~ interestingly, one of the issues that they brought up is that 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 oral~~all~~ steroids may be as good as intramuscular steroids and also discuss different ways of giving the steroids to the baby, whether you can give it into the intra~~.....~~ 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 after a~~of~~ ~~the~~ single dose of antenatal 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 th~~at~~ 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.

An~~The~~ other issue is one of twins and the ongoing debate about what you should do with twins and higher-order births. I was very interested when I saw the title of a paper~~research project that was presented~~ into the *American Journal of Obstetrics and Gynecology* in 2002, which was looking at twins.[3] Unfortunately it was comparing prophylactic multiple doses of steroids with a single course of 'rescue' ~~[?multiple doses of rescue doses of]~~ steroids when the women presented in preterm labour~~birth~~ and~~; which~~ showed no difference. But it certainly didn't elucidate whether the dose that they were using was appropriate or whether it was benefiting twins~~, and we are still, I think I am certain of that, although~~. Studies of ~~trials of the~~ individual patient data meta-analysis of~~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 antenatal steroids which have been brought up time and time again today.~~and~~ I think here there are~~is a bit of a~~ lessons to be learnt. As Patricia said, within a very short space of time of us using steroids, we were liberally ~~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. C~~, and c~~ertainly lots of clinicians~~users~~ were giving~~en~~ it to their triplets weekly from 20 weeks, until they goet to 34 weeks or the risk of preterm delivery was no longer~~is not~~ thought to be present. Because of this~~at~~ a great deal~~amount~~ of effort went into designing a number of trials around the world to look at the comparisons between~~ with~~ a single course of

[3] ~~[??This one??]~~ Murphy D J, Caukwell S, Joels L A, Wardle P. (2002) Cohort study of the neonatal outcome of twin pregnancies that were treated with prophylactic or rescue antenatal corticosteroids. *American Journal of Obstetrics and Gynecology* 187: 483–8.

steroids and multiple courses of steroids to look at the outcome ~~o~~form~~r~~ the baby. W~~And w~~hen we originally thought about this, following ~~y~~our survey of practice in 19~~2~~77, there were five trials that were designed, which would have added up to a total of 10 000 women randomized. ~~F, yes f~~ive 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 and~~, in~~ Europe, which I was going to be leading ~~fo~~rom the N~~M~~PEU. 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 th~~e~~ose trials was ours, which was the TEAMS~~teams~~ trial which was going to include 4000 women and had th~~e~~a primary outcome measured at~~acumen at~~ age two. We did undertake~~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 1,900~~over 2000 [check]~~, is still recruiting. It was due to finish several~~three~~ years ago and~~,~~ has currently recruited~~got~~ 900 women. Whether it will ever get to 1,900~~2000~~~~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. T~~While t~~he 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[1]. Then the other large trial of 2500, run by~~at~~ the M~~m~~aternal and F~~f~~etal M~~m~~edicine's Unit N~~n~~etwork, was also stopped by the Data

[1] Guinn DA, Atkinson MW, Sullivan L, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. *JAMA*. 2001;286:1581-1587.

Monitoring Committee at 500, because they found a slightly lower birthweight in the group receiving multiple courses of steroids. So it looks likely that 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~~ information to answer the question in terms of what ~~w~~we need to know which is the long term outcomes~~acumens~~. The short-term respiratory outcomes~~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 has not~~we are still not~~ necessarily taught us to improv~~ing~~ on past performance when it comes to antenatal corticosteroids.

The other thing to mention, I suppose, is that in the absence of trials evidence about~~of~~ long-term outcomes~~acumen and,~~ what people are going to rely on is observational studies of long-term outcomes~~acumen~~. The one observational study with repeated 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 to~~he~~ six years. I think, and I was discussing this with Jane during the break this afternoon, that~~. 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 used 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. C~~, but e~~learly the messages that are coming out at the moment are not that steroids are bad, but that we need to be more sophisticated in how

we use them and how that information is interpreted appears to be ~~immediate response~~ to stop using them.

So the issues for the future ~~I think~~ in terms of our current gaps are:~~;~~ the biggest one ~~I think~~ is that we cannot currently identify women who are going to deliver preterm very effectively. We can agree we are going to deliver them preterm electively, but for the vast majority of women who deliver spontaneously, we are not very good at recognizing them. And things like fetal~~people~~ fibronectin and~~;~~ cervical length on~~f~~ ultrasound 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 this~~at~~ in the future.

At what gestational age to use to steroids, 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 steroids?~~ 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 were 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 in admissions 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 offer some advantages~~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 debate is, as I said,~~ is~~ still wide open although we will see more evidence about this~~of that~~ over the coming years,

and it may hopefully answer some of ourthe questions~~, although I suspect little~~.

A big lesson which has come out of the steroids trials, not only antenatal steroids, but postnatal steroids, is that with~~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 about a study where they had done serial MRI scans in teenagers and they are suggesting that the brain does not stop developing until age 25, which seems a 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 yet 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 interventions 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. This~~at very sophistication~~ means that long-term follow up studies~~s (?) and~~ of these trial 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.

...

Brocklehurst: I think there is an issue, because I remember the Canadian study got in touch with us about the TEAMS~~our team's~~ trial, and asked~~said~~ how we~~did you~~ goet a placebo for your betamethasone, because ~~it's~~ theirs

was cloudy. We said thatudy and we went it's not o. Ours wais 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 that~~which is what wa~~ was~~s~~ available~~used~~ in this country, and in the UK you can only buy betamethasone which is a solution not a suspension.

~~[this last bit needs further amendment]~~

...

Dr Peter Brocklehurst

~~[Please provide a 2-3 sentence biography, along the lines of the sample below]~~

MBChB, FRCOG, MSc(Epidemiology) (b. 1962) trained as an obstetrician and gynaecologist and epidemiologist in London. Joined the National Perinatal Epidemiology Unit (NPEU) as a research fellow in 1994, became consultant epidemiologist at the NPEU in 1996 and was made Direcor in 2002.

~~SAMPLE biography:~~

~~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.~~

npeu
National Perinatal
Epidemiology Unit

23 August 2005

Mrs Lois Reynolds
Research Assistant to Dr Tilli Tansey
The Wellcome Trust Centre for the
History of Medicine
University College, London
210 Euston Road
London NW1 2BE

Dear Lois

corrections added 23/10/05
checked 24/10/05.

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

Many thanks for sending me the final proof of the transcript for this meeting. There are a number of typographical errors and corrections to references which I have listed below in the order in which they appear in the transcript:

- **Page 55**. Brocklehurst. First sentence:

  Delete "the" before "… press yet".

- **Page 56**. At the top of the page, in the sentence starting "having tried to do one of the large trials …" the phrase "…I think one of the issues ***with*** clinicians …" replace "with" for "for" to read "….I think one of the issues ***for*** clinicians …"

- **Page 88**. In the middle of this page there is a reference which refers to a survey conducted by myself and others which can be referenced. The reference for this is referred to later in the manuscript, (number 167), but the reference is incomplete and should read:

  Brocklehurst P, Gates S, McKenzie-McHarg K, Alfirevic Z, Chamberlain G. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. Br J Obstet Gynaecol 1999; 106(9):977-9.

- **Page 93**. You asked whether the references under 164 were correct and I can confirm that they are.

- **Page 94**. The section of the text which is marked in square brackets should read "…have a remarked reduction in the incidence of death and respiratory distress syndrome, while dexamethasone has …". In the subsequent sentence, could I suggest amending this to read "although one of the things they report is that the number of trials …"

National Perinatal Epidemiology Unit
University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF
T +44 (0)1865 289700 F +44 (0)1865 289701 www.npeu.ox.ac.uk

- **Page 95**. I can confirm that reference 166 is correct. However, reference 167 is not complete in the list of references (see point above referring to Page 88).

- **Page 96**. Reference 168 asks for details of the five trials that were planned. Unfortunately, I can find no reference to these trials in any of the literature. They are not included in our website and the transcript of this meeting may be the only place where they are explicitly referred to in such detail.

  First sentence of the second paragraph on Page 96. Please replace the word "dose" with the word "course", so that the end of that sentence reads

  "… will ever get an answer to the single course or multiple course of steroids debate."

  Towards the bottom of that page. The sentence starting "The US trial aimed to recruit 1,000 …" should have the word "but" inserted after "1,000".

- **Page 97**. At the top of this page the sentence starting "So it looks likely that we may end up …" should have the word "the" removed before "…a single course, instead of the 10,000 women."

  At the end of that paragraph the word "evaluating" should be inserted before "antenatal steroids".

  You asked whether reference 171 was the correct reference. This is not the correct reference. The correct reference should read:

  French NP, Hagan R, Evans SF, Mullan A, Newnham JP. Repeated antenatal corticosteroids: effects on cerebral palsy and childhood behavior. Am J Obstet Gynecol. 2004;190:588-95

- **Page 98**, second paragraph, fourth sentence starting "They randomised nearly 1,000 women to receive steroids or not and showed a …" the word "significantly" should be "significant". Later in that same sentence "given" should be deleted and the word "receiving" included.

  Reference 172 is an abstract and the reference for this is:

  Stutchfield PR, Zbaeda M, Furneaux L, Satelle J, Banfield P, Bickerton NJ, Cameron D, Whitaker R, Russell I. Antenatal steroid therapy for elective caesarean section at term. Arch Dis Child (Supplement) 2004;89:P14

  ? check.

- **Page 99**, third paragraph, penultimate sentence should start "Not ***just*** that there is no benefit…"

  Final sentence. Instead of "of funding" in the square brackets, include the phrase "data protection and confidentiality issues"

  At the bottom of that page, where you have included in square brackets, "who ?? from ??" please insert "the investigators from".

  Similarly later in that same sentence the word "how" is more accurate than the word "where".

- In the **references**, the only comment I have is one referred to earlier about our survey of practice, which you have listed under Brocklehurst, P.

Please let me know if any of the above does not make sense!

With best wishes

Yours sincerely

Peter Brocklehurst
Director

Professor Martin Buxton
Department of Health Economics
Brunel University
Uxbridge
Middlesex UB8 3PH

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

19th March 2004

Dear Professor Buxton

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

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

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

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

Continued/... Page 2

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

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

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

Yours sincerely

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

encs.

Wendy Kutner

From: Dr Daphne Christie [d.christie@ucl.ac.uk]
Sent: 30 March 2004 12:04
To: Wendy
Subject: FW: The Wellcome Trust's History of Twentieth Century Medicine Group

please add details to grid and attendance list, and acknowledge. Thanks,
Daphne

-----Original Message-----
From: Nicky Dunne [mailto:Nicky.Dunne@brunel.ac.uk]
Sent: 30 March 2004 11:47
To: d.christie
Subject: The Wellcome Trust's History of Twentieth Century Medicine Group

Dear Dr Christie

Professor Buxton would like to accept your kind invitation to attend the Witness Seminar on 'Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth' on Tuesday 15th June, and looks forward to receiving further details in due course.

Kind regards.

Nicky

** PLEASE NOTE NEW TELEPHONE NUMBER **

Nicky Dunne
PA to Professor Martin Buxton
Health Economics Research Group
Brunel University
Uxbridge
Middlesex UB8 3PH, UK

Tel: +44 (0)1895 265443
Fax: +44 (0)1895 203330
Email: nicky.dunne@brunel.ac.uk

Wendy Kutner

To: Nicky.Dunne@brunel.ac.uk
Cc: Daphne Christie
Subject: Witness Seminar: Prenatal corticosteroids - 15th June 2004 - 2pm/6pm

Dear Nicky, thank you for your e-mail confirming Professor Buxton's attendance at the above meeting. We are delighted he is able to attend. We will be in touch again prior to the meeting. Yours sincerely, Wendy Kutner

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

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

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

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

UCL

Professor Martin Buxton
Department of Health Economics
Brunel University
Uxbridge
Middlesex UB8 3PH

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 Professor Buxton

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

Dr Daphne Christie
Senior Research Assistant to Dr Tilli Tansey

enc.

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