

## **CYSTIC FIBROSIS**

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 11 June 2002

**Edited by D A Christie and E M Tansey**



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# INTRODUCTION

Cystic fibrosis (CF) was first described in the 1930s. The earliest account was probably that of Blackfan and Wolbach (1933) under the title of ‘Vitamin A deficiency in infants’.<sup>1</sup> Most of the 13 infants in their series were autopsied, and had the characteristic pathology in the pancreas, as well as suppurative lung disease. They included two pairs of siblings. One of the pairs of siblings had been the subject of a single published case report, ten years earlier. The authors considered that this new disease of the pancreas was the cause of the vitamin A deficiency, but concentrated their attention on the secondary avitaminosis and neglected to give it a name. As a result, in Europe credit for recognizing what we now know as CF is usually given to Guido Fanconi (1936),<sup>2</sup> who published his paper in German, and in the USA to Americans, Dorothy Andersen (1938)<sup>3</sup> or Blackfan and May (1938).<sup>4</sup>

Clearly, a genetic disorder as widespread and common as CF must have been around for a very long time before it was separately identified from the many diseases causing death in infancy in the pre-antibiotic era. An indication of this was given in the folklore of middle Europe, where grandmothers knew that the child who tasted salty when kissed was bewitched, and would soon die (Busch 1990).<sup>5</sup> But the disease is much older than that. A recent paper touching on the antiquity of CF from the geneticist’s viewpoint concluded that some of the common mutations in the CF gene may be older than the ethnogenesis process that originated present European populations (Mateu *et al.* 2002).<sup>6</sup>

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<sup>1</sup> Blackfan K D, Wolbach S B. (1933) Vitamin A deficiency in infants. *Journal of Paediatrics* **3**: 679–706.

<sup>2</sup> Fanconi G, Uehlinger E, Knaver C. (1936) Das Coeliacum bei Angeborener zystischer pankreas fibromatose und bronchiektasen. *Wien Medizinische Wochenschrift* **86**: 753–56. See biographical notes, page 94.

<sup>3</sup> Andersen D H. (1938) Cystic fibrosis of the pancreas and its relation to celiac disease. A clinical and pathologic study. *American Journal of Diseases of Children* **56**: 344–99. See biographical notes, page 91.

<sup>4</sup> Blackfan K D, May C D. (1938) Inspissation of secretion and dilation of ducts and acini. Atrophy and fibrosis of the pancreas in infants. *Paediatrics* **13**: 627–34.

<sup>5</sup> Busch R. (1990) The history of cystic fibrosis. *Acta Universitatis Carolinae Medica* **36**: 13–15. A well-known passage from German children’s songs and games from Switzerland forecasted that ‘The child will soon die whose forehead tastes salty when kissed’.

<sup>6</sup> Mateu E, Calafell F, Ramos M D, Casals T, Bertranpetit J. (2002) Can a place of origin of the main cystic fibrosis mutations be identified? *American Journal of Human Genetics* **70**: 257–64.

We cannot go so far back, but this Witness Seminar was arranged to capture the spirit of what it has been like to live through a period that spans early clinical descriptions, increasing awareness, diagnostic problems (page 11), evolving management for affected children and, increasingly, adults, medical mistakes (page 24), genetic and molecular definition (pages 59–63), and steadily improving survival and hopes for the future. The recollections of some of the more senior participants (for example pages 4–9, 16, 66) and eloquent testimony from a CF patient (pages 71–3) may serve to deepen the understanding of younger colleagues of the road we travelled before they joined the journey, and as a reminder that, ‘If we see further than our predecessors it is because we stand on their shoulders’.<sup>7</sup> And what shoulders! – Harry Shwachman, Paul di Sant’Agnese, Giulio Barbero, Martin Bodian, Dorothy Andersen, Charlotte Anderson and Winifred Young, to name but a few giants who are no longer with us. It would have been interesting to have held a similar seminar a generation or more ago, and had their input – but if we had, it would have been from a different perspective. Thankfully, those who were still available for this meeting [in the organizer’s words, some who regard themselves as ‘Johnny-come-lately’ (page 9)] were in good form: articulate and reflective. It was good to be able to compare then with now.

Since the discovery of the gene in 1989,<sup>8</sup> CF has often been quoted as an example of how genetic research has led to a better understanding of intracellular mechanisms of disease.<sup>9</sup> Although there are now more than 1000 known mutations in the relevant cystic fibrosis transmembrane regulator (*CFTR*) gene, there are already current clinical trials of targeted drugs to correct the consequences of the various types of mutation, and perhaps even an eventual possibility of gene therapy.

If the momentum of the past 65 years can be maintained, there is good reason for hope that the youngest participants will in the near future see persons with CF enjoy a life expectancy not very different from their own (page 21). They may some day recall that they were there when this little record was prepared.

**Professor John Dodge (Monmouthshire)**

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<sup>7</sup> Peter Medawar’s speech at the Nobel Banquet in Stockholm, 10 December 1960. From *Les Prix Nobel* (1960). Stockholm: The Nobel Foundation.

<sup>8</sup> Kerem B, Rommens J M, Buchanan J A, Markiewicz D, Cox T K, Chakravarti A, Buchwald M, Tsui L-C. (1989) Identification of the cystic fibrosis gene: Genetic analysis. *Science* 245: 1073–80.

<sup>9</sup> See, for example, Christie D A, Tansey E M. (eds) (2003) Genetic Testing. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 17. London: The Wellcome Trust Centre for the History of Medicine at UCL.



## ACKNOWLEDGEMENTS

We are particularly grateful to Dr James Littlewood, who assisted with the organization of the meeting, provided many of the names of individuals to be invited and helped decide on the topics to be discussed. We also thank Professor John Walker-Smith for his excellent chairing of the occasion and for his help with the planning of the meeting. We are equally grateful to Professor John Dodge for writing the introduction to these published proceedings. We thank Dr Mary Goodchild and Professor John Govan, who kindly provided the photographs, and Mr Richard Barnett for bibliographic research.

As with all our meetings, we depend a great deal on our colleagues at the Wellcome Trust to ensure their smooth running: the Audiovisual department, the Medical Photographic Library and Mrs Tracy Tillotson; Ms Julie Wood, who has supervised the design and production of this volume, our indexer, Ms Liza Furnival, our readers, Ms Lucy Moore, Mr Simon Reynolds and Mrs Lois Reynolds. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Mrs Lois Reynolds assist us in running the meetings. Finally we thank the Wellcome Trust for supporting this programme.

*Tilli Tansey*

*Daphne Christie*

*Wellcome Trust Centre for the History of Medicine at UCL*



## WITNESS SEMINARS: MEETINGS AND PUBLICATIONS<sup>1</sup>

In 1990 the Wellcome Trust created a History of Twentieth Century Medicine Group, as part of the Academic Unit of the Wellcome Institute for the History of Medicine, to bring together clinicians, scientists, historians and others interested in contemporary medical history. Among a number of other initiatives the format of Witness Seminars, used by the Institute of Contemporary British History to address issues of recent political history, was adopted, to promote interaction between these different groups, to emphasize the potential of working jointly, and to encourage the creation and deposit of archival sources for present and future use. In June 1999 the Governors of the Wellcome Trust decided that it would be appropriate for the Academic Unit to enjoy a more formal academic affiliation and turned the Unit into the Wellcome Trust Centre for the History of Medicine at University College London from 1 October 2000. The Wellcome Trust continues to fund the Witness Seminar programme via its support for the Centre.

The Witness Seminar is a particularly specialized form of oral history, where several people associated with a particular set of circumstances or events are invited to come together to discuss, debate, and agree or disagree about their memories. To date, the History of Twentieth Century Medicine Group has held over 30 such meetings, most of which have been published, as listed on pages xiii–xix.

Subjects are usually proposed by, or through, members of the Programme Committee of the Group, and once an appropriate topic has been agreed, suitable participants are identified and invited. These inevitably lead to further contacts, and more suggestions of people to invite. As the organization of the meeting progresses, a flexible outline plan for the meeting is devised, usually with assistance from the meeting's chairman, and some participants are invited to 'set the ball rolling' on particular themes, by speaking for a short period to initiate and stimulate further discussion.

Each meeting is fully recorded, the tapes are transcribed and the unedited transcript is immediately sent to every participant. Each is asked to check his or

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<sup>1</sup> The following text also appears in the 'Introduction' to recent volumes of *Wellcome Witnesses to Twentieth Century Medicine* published by the Wellcome Trust and the Wellcome Trust Centre for the History of Medicine at University College London.

her own contributions and to provide brief biographical details. The editors turn the transcript into readable text, and participants' minor corrections and comments are incorporated into that text, while biographical and bibliographical details are added as footnotes, as are more substantial comments and additional material provided by participants. The final scripts are then sent to every contributor, accompanied by forms assigning copyright to the Wellcome Trust. Copies of all additional correspondence received during the editorial process are deposited with the records of each meeting in Archives and Manuscripts, Wellcome Library, London.

As with all our meetings, we hope that even if the precise details of some of the technical sections are not clear to the nonspecialist, the sense and significance of the events are understandable. Our aim is for the volumes that emerge from these meetings to inform those with a general interest in the history of modern medicine and medical science; to provide historians with new insights, fresh material for study, and further themes for research; and to emphasize to the participants that events of the recent past, of their own working lives, are of proper and necessary concern to historians.

### Members of the Programme Committee of the History of Twentieth Century Medicine Group

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The Group's activities are overseen by the Programme Committee, which includes professional historians of medicine, practising scientists and clinicians. The Programme Committee during 2003–04 comprised:

**Dr Tilli Tansey** – Historian of Modern Medical Science, Wellcome Trust Centre at UCL, and Chair

**Sir Christopher Booth** – Wellcome Trust Centre at UCL, former Director; Clinical Research Centre, Northwick Park Hospital, London

**Dr Robert Bud** – Head of Life and Environmental Sciences, Science Museum, London

**Dr Daphne Christie** – Senior Research Assistant, Wellcome Trust Centre at UCL, and Organizing Secretary

**Professor Hal Cook** – Director, Wellcome Trust Centre at UCL

**Dr Mark Jackson** – Reader, Centre for Medical History, Exeter

**Professor Ian McDonald** – Harveian Librarian, Royal College of Physicians, London

**Dr Jon Turney** – Head of the Department of Science and Technology Studies, University College London

# HISTORY OF TWENTIETH CENTURY MEDICINE WITNESS SEMINARS, 1993–2004

- 1993     **Monoclonal antibodies**  
Organizers: Dr E M Tansey and Dr Peter Catterall
- 1994     **The early history of renal transplantation**  
Organizer: Dr Stephen Lock
- Pneumoconiosis of coal workers**  
Organizer: Dr E M Tansey
- 1995     **Self and non-self: A history of autoimmunity**  
Organizers: Sir Christopher Booth and Dr E M Tansey
- Ashes to ashes: The history of smoking and health**  
Organizers: Dr Stephen Lock and Dr E M Tansey
- Oral contraceptives**  
Organizers: Dr Lara Marks and Dr E M Tansey
- Endogenous opiates**  
Organizer: Dr E M Tansey
- 1996     **Committee on Safety of Drugs**  
Organizers: Dr Stephen Lock and Dr E M Tansey
- Making the body more transparent: The impact of nuclear  
magnetic resonance and magnetic resonance imaging**  
Organizer: Sir Christopher Booth
- 1997     **Research in General Practice**  
Organizers: Dr Ian Tait and Dr E M Tansey
- Drugs in psychiatric practice**  
Organizers: Dr David Healy and Dr E M Tansey
- The MRC Common Cold Unit**  
Organizers: Dr David Tyrrell and Dr E M Tansey
- The first heart transplant in the UK**  
Organizer: Professor Tom Treasure

- 1998 **Haemophilia: Recent history of clinical management**  
Organizers: Professor Christine Lee and Dr E M Tansey
- Obstetric ultrasound: Historical perspectives**  
Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey
- Post penicillin antibiotics**  
Organizers: Dr Robert Bud and Dr E M Tansey
- Clinical research in Britain, 1950–1980**  
Organizers: Dr David Gordon and Dr E M Tansey
- 1999 **Intestinal absorption**  
Organizers: Sir Christopher Booth and Dr E M Tansey
- The MRC Epidemiology Unit (South Wales)**  
Organizers: Dr Andy Ness and Dr E M Tansey
- Neonatal intensive care**  
Organizers: Professor Osmund Reynolds and Dr E M Tansey
- British contributions to medicine in Africa after the Second World War**  
Organizers: Dr Mary Dobson, Dr Maureen Malowany,  
Dr Gordon Cook and Dr E M Tansey
- 2000 **Childhood asthma, and beyond**  
Organizers: Dr Chris O’Callaghan and Dr Daphne Christie
- Peptic ulcer: Rise and fall**  
Organizers: Sir Christopher Booth, Professor Roy Pounder and  
Dr E M Tansey
- Maternal care**  
Organizers: Dr Irvine Loudon and Dr Daphne Christie
- 2001 **Leukaemia**  
Organizers: Professor Sir David Weatherall, Professor John Goldman,  
Sir Christopher Booth and Dr Daphne Christie
- The MRC Applied Psychology Unit**  
Organizers: Dr Geoff Bunn and Dr Daphne Christie
- Genetic testing**  
Organizers: Professor Doris Zallen and Dr Daphne Christie

- Foot and mouth disease: the 1967 outbreak and its aftermath**  
Organizers: Dr Abigail Woods, Dr Daphne Christie and Dr David Aickin
- 2002 **Environmental toxicology: The legacy of *Silent Spring***  
Organizers: Dr Robert Flanagan and Dr Daphne Christie
- Cystic fibrosis**  
Organizers: Dr James Littlewood and Dr Daphne Christie
- Innovation in pain management**  
Organizers: Professor David Clark and Dr Daphne Christie
- 2003 **Thrombolysis**  
Organizers: Mr Robert Arnott and Dr Daphne Christie
- Beyond the asylum: Anti-psychiatry and care in the community**  
Organizers: Dr Mark Jackson and Dr Daphne Christie
- The Rhesus factor and disease prevention**  
Organizers: Professor Doris Zallen and Dr Daphne Christie
- Platelets in thrombosis and other disorders**  
Organizers: Professor Gustav Born and Dr Daphne Christie
- 2004 **Short course chemotherapy for tuberculosis**  
Organizers: Dr Owen McCarthy and Dr Daphne Christie
- Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**  
Organizers: Sir Iain Chalmers and Dr Daphne Christie

## PUBLISHED MEETINGS

“...Few books are so intellectually stimulating or uplifting”.  
*Journal of the Royal Society of Medicine* (1999) **92**: 206–8,  
review of vols 1 and 2

“...This is oral history at its best...all the volumes make compulsive  
reading...they are, primarily, important historical records”.  
*British Medical Journal* (2002) **325**: 1119, review of the series

### **Technology transfer in Britain: The case of monoclonal antibodies**

#### **Self and non-self: A history of autoimmunity**

#### **Endogenous opiates**

#### **The Committee on Safety of Drugs**

In: Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds)  
(1997) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 1. London:  
The Wellcome Trust, 135pp. ISBN 1 869835 79 4

### **Making the human body transparent: The impact of NMR and MRI**

#### **Research in General Practice**

#### **Drugs in psychiatric practice**

#### **The MRC Common Cold Unit**

In: Tansey E M, Christie D A, Reynolds L A. (eds) (1998) *Wellcome Witnesses  
to Twentieth Century Medicine*. Volume 2. London: The Wellcome Trust,  
282pp. ISBN 1 869835 39 5

### **Early heart transplant surgery in the UK**

In: Tansey E M, Reynolds L A. (eds) (1999) *Wellcome Witnesses to Twentieth  
Century Medicine*. Volume 3. London: The Wellcome Trust, 72pp.  
ISBN 1 841290 07 6

### **Haemophilia: Recent history of clinical management**

In: Tansey E M, Christie D A. (eds) (1999) *Wellcome Witnesses to Twentieth Century  
Medicine*. Volume 4. London: The Wellcome Trust, 90pp. ISBN 1 841290 08 4

### **Looking at the unborn: Historical aspects of obstetric ultrasound**

In: Tansey E M, Christie D A. (eds) (2000) *Wellcome Witnesses to Twentieth Century  
Medicine*. Volume 5. London: The Wellcome Trust, 80pp. ISBN 1 841290 11 4



### **Post penicillin antibiotics: From acceptance to resistance?**

In: Tansey E M, Reynolds L A. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 6. London: The Wellcome Trust, 71pp. ISBN 1 841290 12 2

### **Clinical research in Britain, 1950–1980**

In: Reynolds L A, Tansey E M. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 7. London: The Wellcome Trust, 74pp. ISBN 1 841290 16 5

### **Intestinal absorption**

In: Christie D A, Tansey E M. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 8. London: The Wellcome Trust, 81pp. ISBN 1 841290 17 3

### **Neonatal intensive care**

In: Christie D A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 9. London: The Wellcome Trust Centre for the History of Medicine at UCL, 84pp. ISBN 0 854840 76 1

### **British contributions to medical research and education in Africa after the Second World War**

In: Reynolds L A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 10. London: The Wellcome Trust Centre for the History of Medicine at UCL, 93pp. ISBN 0 854840 77 X

### **Childhood asthma and beyond**

In: Reynolds L A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 11. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp. ISBN 0 854840 78 8

### **Maternal care**

In: Christie D A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 12. London: The Wellcome Trust Centre for the History of Medicine at UCL, 88pp. ISBN 0 854840 79 6

### **Population-based research in south Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit**

In: Ness A R, Reynolds L A, Tansey E M. (eds) (2002) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 13. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp. ISBN 0 854840 81 8

**Peptic ulcer: Rise and fall**

In: Christie D A, Tansey E M. (eds) (2002) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 14. London: The Wellcome Trust Centre for the History of Medicine at UCL, 143pp. ISBN 0 854840 84 2

**Leukaemia**

In: Christie D A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 15. London: The Wellcome Trust Centre for the History of Medicine at UCL, 86pp. ISBN 0 85484 087 7

**The MRC Applied Psychology Unit**

In: Reynolds L A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 16. London: The Wellcome Trust Centre for the History of Medicine at UCL, 94pp. ISBN 0 85484 088 5

**Genetic testing**

In: Christie D A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 17. London: The Wellcome Trust Centre for the History of Medicine at UCL, 130pp. ISBN 0 85484 094 X

**Foot and mouth disease: The 1967 outbreak and its aftermath**

In: Reynolds L A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 18. London: The Wellcome Trust Centre for the History of Medicine at UCL, 114pp. ISBN 0 85484 096 6

**Environmental toxicology: The legacy of *Silent Spring***

In: Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 19. London: The Wellcome Trust Centre for the History of Medicine at UCL, 110pp. ISBN 0 85484 091 5

**Cystic fibrosis**

In: Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 20. London: The Wellcome Trust Centre for the History of Medicine at UCL, this volume. ISBN 0 85484 086 9

**Innovation in pain management**

In: Reynolds L A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 21. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press. ISBN 0 85484 097 4

### **The Rhesus factor and disease prevention**

In: Zallen D, Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 22. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press. ISBN 0 85484 099 0

### **Platelets in thrombosis and other disorders**

In: Reynolds L A, Tansey E M. (eds) (2005) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 23. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press.

### **Short course chemotherapy for tuberculosis**

In: Christie D A, Tansey E M. (eds) (2005) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 24. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press.

Volumes 1–12 cost £5.00 plus postage, with volumes 13–20 at £10 each. Orders of four or more volumes receive a 20 per cent discount. All 20 published volumes in the series are available at the special price of £115 plus postage. To order a copy contact t.tillotson@wellcome.ac.uk or by phone: +44 (0)20 7611 8486; or fax: +44 (0)20 7611 8703.

### **Other publications**

#### **Technology transfer in Britain: The case of monoclonal antibodies**

In: Tansey E M, Catterall P P. (1993) *Contemporary Record* 9: 409–44.

#### **Monoclonal antibodies: A witness seminar on contemporary medical history**

In: Tansey E M, Catterall P P. (1994) *Medical History* 38: 322–7.

#### **Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–42)**

In: P D'Arcy Hart, edited and annotated by E M Tansey. (1998) *Social History of Medicine* 11: 459–68.

#### **Ashes to Ashes – The history of smoking and health**

In: Lock S P, Reynolds L A, Tansey E M. (eds) (1998) Amsterdam: Rodopi BV, 228pp. ISBN 90420 0396 0 (Hfl 125) (hardback). Reprinted 2003.

#### **Witnessing medical history. An interview with Dr Rosemary Biggs**

Professor Christine Lee and Dr Charles Rizza (interviewers). (1998) *Haemophilia* 4: 769–77.



## **CYSTIC FIBROSIS**

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 11 June 2002

**Edited by D A Christie and E M Tansey**

# CYSTIC FIBROSIS

## Participants

Mrs Rosie Barnes	Dr Anthony Jackson
Sir John Batten	Dr James Littlewood
Sir Christopher Booth	Dr Anita MacDonald
Dr Richard Boyd	Ms Susan Madge
Professor Alan Cuthbert	Dr Margaret Mearns
Mrs Mary Dodd	Dr Archie Norman
Professor John Dodge	Professor Sandy Raeburn
Mrs Fran Duncan-Skingle	Dr Kevin Southern
Dr Philip Farrell	Dr David Stableforth
Professor Duncan Geddes	Dr Maurice Super
Dr Mary Goodchild	Professor John Walker-Smith (Chair)
Professor John Govan	Professor Kevin Webb
Miss Tracy Humberstone	Professor John Widdicombe
Dr Peter Hunter	

**Among those attending the meeting:** Professor Ian Booth, Dr Siobhan Carr, Dr Gary Connett, Mrs Alice Farrell, Miss Diana Gaskell, Dr Lorna Layward, Dr Karen Lowton, Ms Julia Lueglinger, Dr Lesley MacVinish, Dr Henry Nicholls, Mr Peter Okereke, Miss Jennifer Pryor

**Apologies include:** Dr Robert Dinwiddie, Dr Ian Gregg, Professor Margaret Hodson, Sir Robert Johnson, Ms Sandra Kennedy, Mr Peter Levy, Mrs Alison Morton, Dr Tyrone Pitt, Professor John Price, Dr Peter Weller, Mrs Sue Wolfe

Professor John Walker-Smith: I would like to welcome you to this Witness Seminar today. I am not here in any sense as a paediatric gastroenterologist, but as a member of the History of Twentieth Century Medicine Group. I did have some experience in the management of cystic fibrosis in general at the Royal Alexandra Hospital for Children in Sydney before I came to England in 1974, and I have been interested in the treatment of the small intestinal changes occurring in children with cystic fibrosis in subsequent years.<sup>1</sup>

Although there were sporadic reports of pancreatic infantilism in the early part of the twentieth century, it was the work of Guido Fanconi in Zurich that really began the modern story of cystic fibrosis in 1928. In that year he published observations concerning a group of children that he called the 'coeliac syndrome' with symptoms that dated from early infancy;<sup>2</sup> yet the children also had bronchitis. On an anecdotal note, I remember Guido Fanconi when I was research fellow in the Kinderspital, Zurich, in 1967. He was called the 'Old Fanconi'. At that stage he was still a very tall and eminent figure, distinguished from his son, the 'Young Fanconi', who later became a professor in Zurich as well. Then Guido went on with Uehlinger and Knauer in 1936 to describe what he called 'familial pancreatic cystic fibromatosis with bronchiectasis'.<sup>3</sup>

Two years later, in 1938, the great Dorothy Andersen in New York reported on 20 infants from the Babies' Hospital, New York.<sup>4</sup> She described extensive autopsy findings: widespread pulmonary infection, and destructive and cystic changes in the lungs with fibrosis in the pancreas itself. So you could say that the era of cystic fibrosis really began then. In fact, Jim Littlewood has assembled a good deal of historical information about cystic fibrosis and people can get copies if they wish.<sup>5</sup>

We are not talking about these matters today. Today we are talking about living history. This is just the introduction. What we are really concerned with now is to hear what all of you observed and contributed yourselves, and how you felt, caring for children and adults with cystic fibrosis, from your own experience. This is living memory. Some of the questions that Tilli Tansey has asked in previous

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<sup>1</sup> Penny *et al.* (1986).

<sup>2</sup> Fanconi (1928).

<sup>3</sup> Fanconi *et al.* (1936).

<sup>4</sup> Andersen (1938).

<sup>5</sup> Littlewood J. (2002) The history of the development of cystic fibrosis care, available at [www.cysticfibrosismedicine.com](http://www.cysticfibrosismedicine.com). See also Kulczycki (1990); Mearns (1993); Busch (1991); Doershuk (2001).

Witness Seminars, such as ‘What was it like at the time?’, are very important. When you are making your remarks, we would like to get a flavour of what it was like at the time. Another question that we would like you to consider when you are speaking today is, why did things happen in the way they did? I am here, eager to learn as much as you. I think this is going to be a very exciting afternoon.

The first topic that we are going to discuss is the development of clinical knowledge of cystic fibrosis in both children and in adults. We are going to break it up into two periods. First, we are going to look at the period 1945–55. This will be followed by a discussion of the period from 1955 up to the present. So it’s a very great pleasure to have here with us today Dr Archie Norman, whom we know so well as a great contributor to cystic fibrosis. Archie, would you be kind enough to begin this Witness Seminar by talking about your own experience of the development of knowledge in the period 1945–55?

Dr Archie Norman: Thank you very much, Mr Chairman, for your introduction, but I am not quite so sure about the living memory part of it – I will have certain difficulties there. The late Tom Macnair Scott from Philadelphia, and Charles May from the Babies’ Hospital in New York, both came to this country during the Second World War as part of the war effort, and worked at Great Ormond Street Hospital, London. Charles May had written a very good paper on cystic fibrosis in 1938 at the same time that Dorothy Andersen’s much more extensive and authoritative paper really took over.<sup>6</sup> So he knew a good bit about cystic fibrosis. Incidentally, both Tom Macnair Scott and Charles May spoke at the RSM [Royal Society of Medicine] in 1943, when Charles May gave a paper on cystic fibrosis.<sup>7</sup> This paper was probably the first cystic fibrosis paper given in this country.

It’s difficult nowadays to envisage what it was like in 1945, but for those of us who had come back from the war to this country, it was an extremely exciting period. So many new advances in medicine: paediatrics itself had become accepted as a real branch of medicine, and not a junior part; there was the discovery of the antibiotics that totally changed our attitude to infectious disease, which was of particular importance, of course, regarding cystic fibrosis;<sup>8</sup> last, but

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<sup>6</sup> Blackfan and May (1938). See Andersen (1938) and page 7.

<sup>7</sup> May (1943).

<sup>8</sup> Dr Archie Norman wrote: ‘The antibiotics gave us hope of controlling, or even eradicating, the chest infection that was the cause of the mortality in cystic fibrosis.’ Note to Dr Daphne Christie, 4 November 2003.



not least, was the advent of the National Health Service in 1948. Why that was important for cystic fibrosis, was that we could prescribe drugs without worrying whether the family could afford them, a matter of immense importance in a persistent long-term disease such as cystic fibrosis. In those days everything was a bit primitive. Diagnosis of CF [cystic fibrosis] was made by the absence of proteolytic enzymes in two stool specimens, and then confirmed by the very tricky and uncomfortable business of duodenal intubation.<sup>9</sup> I had a ward sister who was particularly good at this, to the irritation of my registrars. The absence of trypsin from a specimen of duodenal juice with reduced alkaline content was accepted as confirming the diagnosis.

Treatment – again primitive. The symptomatic steatorrhoea was controlled to some extent by pancreatic tablets or powder, and by a strict low-fat diet, which may not have been the best thing, but at least reduced the number of offensive stools, and certainly reduced the amount of offensive flatus, which for schoolchildren was very upsetting and unpleasant. The low-fat diet was supposed to be supplemented by a high-protein diet, but as much as one insisted on children having a high-protein diet, it was virtually impossible. These were still the days of rationing; proteins of any sort, and particularly meat, were in short supply and very expensive, and certainly there weren't many children who received even a normal protein diet by today's standards. Chest infection, usually considered to be staphylococcal, was treated with courses of penicillin and then aureomycin, or terramycin, or whatever was coming along. Prolonged prophylactic treatment was also tried, especially in the later 1950s, notably by David Lawson at Queen Mary's Hospital, Carshalton.<sup>10</sup>

Physiotherapy I think was really pioneered in this country, rather than in the USA, with postural drainage and chest tapping. Surprisingly these very primitive measures did decrease early mortality and at least temporarily improved the outlook for the older and therefore less severely affected child. On the other hand, the amount of interest and clinical research into cystic fibrosis in this country was infinitely less than in the USA, and it is tempting to blame the effects of the war for this. Martin Bodian was appointed to Great Ormond Street as morbid anatomist in 1943. He soon began studying, in his very obsessive

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<sup>9</sup> Dr Archie Norman wrote: 'The passage of the intranasal tube was rather alarming and not very pleasant for a small child, and it had then to be steered into the duodenum. The tube tended to curl up in the stomach, and then the process had to be repeated.' Note to Dr Daphne Christie, 4 November 2003.

<sup>10</sup> Personal communication with Dr Archie Norman [late 1950–60s]. See Lawson and May (1969); Lawson and Porter (1976).

way, the histology of all the organs affected by cystic fibrosis with one single exception, which was the genital tract in males, and which was later shown to be the cause of infertility.<sup>11</sup> Cedric Carter and I joined him in 1950 to cooperate on his book *Fibrocystic Disease of the Pancreas*, which was published in 1952,<sup>12</sup> and in this book Carter established for the first time that cystic fibrosis was due to a recessive gene.<sup>13</sup> Elsewhere, Baar from Birmingham published in 1953, a thoughtful article, highly critical of some of Bodian's theories,<sup>14</sup> but it isn't widely accepted today. He and Bodian were by no means friends. There must have been more work going on in Birmingham at that time, but I haven't found anything that has been recorded.

Of those very few other developments with regard to CF that I can find in Britain at that time, Winifred Young was appointed to the Queen Elizabeth Hospital for Children, Hackney Road, London, as a research clinician in 1948, and established a cystic fibrosis clinic in 1950 which was highly successful.<sup>15</sup> At Great Ormond Street I had a fairly large number of children with cystic fibrosis, and developed a team of dieticians, physiotherapists and social workers, who saw each family every time they attended. Ruth Harris, Wilfred Payne and I published a little paper on the effect of pancreatin therapy on fat absorption and nitrogen retention.<sup>16</sup> Apart from that, not a great deal of interest was shown in cystic fibrosis in this country, and there was certainly a tendency to believe that it did not occur at all in certain regions. That is all I have to say, except that from the beginning we got the impression that the children with cystic fibrosis were exceptional in the way in which they overcame their difficulties, in their determination and in their intelligence.

Walker-Smith: Thank you for a very fine beginning. Who else would like to make any comments about this early period?

Dr Philip Farrell: I am from the University of Wisconsin Medical School. It's a pleasure to be here, with my wife Alice. She and I started out in the 1960s, she as a medical technologist performing sweat tests, while I was taking care of children with cystic fibrosis.

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<sup>11</sup> Dr Archie Norman wrote: 'Infertility was a result of fibrosis of the vas deferens in cystic fibrosis.' Note to Dr Daphne Christie, 4 November 2003.

<sup>12</sup> See Bodian (1952).

<sup>13</sup> Carter (1952): 50–64.

<sup>14</sup> Baar (1953).

<sup>15</sup> Kosky (1992). See also Chest and Heart Association (1964): 67 and 122.

<sup>16</sup> Harris *et al.* (1955).

Since you are interested in the period 1945–55, I would like to describe my experience of working with Paul di Sant’Agnese. I had the privilege of working with Paul for five years at the National Institutes of Health, and I heard him on many occasions describe his experiences of working with Dorothy Andersen, going back to 1938, after he graduated from the University of Rome Medical School and travelled to New York for his residency in paediatrics at the New York Postgraduate Hospital.

As many of you know, Dorothy Andersen was a paediatric pathologist, not a clinician.<sup>17</sup> Although Dr Andersen didn’t take care of children with cystic fibrosis, she was an astute pathologist and in her seminal publication she made the connection between ‘cystic fibrosis of the pancreas,’ the title of her article, and the occurrence of chronic suppurative lung disease.<sup>18</sup>

Dr di Sant’Agnese told me many times about the programme at the Babies’ Hospital at Columbia University in New York and why it was so successful. I would like to share some of that information with you and a few other comments from another American paediatrician, Dr Lew Barness, who was very active then in Boston, New York and at the Children’s Hospital of Philadelphia. Paul di Sant’Agnese told me that the greatest difficulty, and Dr Norman alluded to this earlier, was in actually establishing the diagnosis of cystic fibrosis. He emphasized that duodenal intubation was the key to making the diagnosis of cystic fibrosis by demonstrating pancreatic insufficiency, before his discovery of the sweat electrolyte abnormality in 1952.<sup>19</sup>

I think this Witness Seminar is timely, because we are celebrating the golden jubilee of the discovery of the sweat electrolyte defect. It was in April of 1952 that Dr di Sant’Agnese made this discovery of the high sodium concentrations in the sweat of children with cystic fibrosis.<sup>20</sup> Dorothy Andersen hired him to take care of her patients because, not being a paediatrician, but rather a pathologist, she lacked the ability to take care of the children that were referred to her for care, that is the 600 patients referred to her for care in New York.

There were four reasons why they were referred to the Babies’ Hospital and why it became such an important centre. First, of course, the seminal publication

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<sup>17</sup> See page 91.

<sup>18</sup> Andersen (1938).

<sup>19</sup> See Darling *et al.* (1953); di Sant’Agnese *et al.* (1953). See page 105.

<sup>20</sup> di Sant’Agnese (2001): 17–35; di Sant’Agnese *et al.* (1953).

I mentioned previously, and her knowledge of the pathology and the pathophysiology of cystic fibrosis. Second, the combination of her reputation and arrogance. Dorothy Andersen said that she was the only person in the world who really knew about cystic fibrosis back in the late 1930s and even in the 1940s. She was the self-proclaimed expert, and paediatricians of that era, such as Lew Barness, told me that Dorothy travelled around the east coast saying that she really was the only person who knew about cystic fibrosis. Third, parents were absolutely desperate whenever this diagnosis was suspected. Lew Barness told me that the two worst diagnoses in paediatrics at the time were cystic fibrosis and acute lymphocytic leukaemia. Both diagnoses were a 'death sentence' because in each case you knew that the disease was fatal and the paediatrician had to tell the parents that the child was likely to die within a matter of months, generally within a few months if the child with cystic fibrosis had advanced pneumonia without antibiotic therapy available to treat a staphylococcal pneumonia.<sup>21</sup> The fourth reason was that New York City was the one place in the USA that anyone could reach easily and that parents, being so desperate when a child was suspected of having cystic fibrosis, often came to New York for care. They came to Dorothy Andersen, but she didn't actually take care of the patients, but rather it was Paul di Sant'Agnese who served this vital role.

So it's very significant that Paul was the person who became essentially the right arm of Dorothy Andersen in the care of children with cystic fibrosis. He was devoted to this clinical role, but the situation was often hopeless once the diagnosis was made, particularly if there was already progressive lung disease from *Staphylococcus aureus*. Paul had some reluctance to do duodenal drainage studies, because the results, as Dr Norman just pointed out, were frightening once the laboratory tests demonstrated low levels of pancreatic enzymes – frightening in the sense that the prognosis was so grave, once the diagnosis was established. As Dr di Sant'Agnese once said and I quote: 'We watched them get progressively worse and eventually die, after making the diagnosis.'

The first break in treatment came after the Second World War when penicillin became available.<sup>22</sup> Paul di Sant'Agnese had access to penicillin from the US Army. The US Army of course was the organization in the USA with top priority in obtaining penicillin, but Paul was able to obtain it. I don't know if he did this on the black market, or how he got the penicillin, but he had enough penicillin

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<sup>21</sup> See, for example, Christie and Tansey (2003a): 25–26.

<sup>22</sup> See Wainwright (1990); Tansey and Reynolds (2000).

available to create what he called ‘miracles’ in response to antibiotic chemotherapy using aerosolized penicillin.<sup>23</sup> Paul told me that it seemed to make no difference how the penicillin was given, whether it was given by aerosol, or by parenteral therapy.<sup>24</sup> In his judgement, the *Staphylococcus aureus* was so exquisitely sensitive to penicillin that any treatment with penicillin in these children with progressive staphylococcal pneumonia could be effective. I remember vividly, Paul telling me when I was his clinical research fellow what a wonderful feeling it was, and how exciting it was to be able essentially to cause miracles through treatment with penicillin in these children who otherwise were going to die within weeks or months; patients slowly dying from the chronic pulmonary disease revived in a few days. For the first time there was an effective tool to help control the lung infection as the predominant organism in the bronchi of patients with CF. Patients who had never had an antibiotic before were very susceptible, even though by present standards ridiculously small doses were used. Penicillin was effective even by routes that were considered quite unconventional, namely aerosol inhalation, which of course we now use to treat *Pseudomonas aeruginosa* infections in children with cystic fibrosis. A key discovery was the sweat electrolyte defect. I will just take a few minutes to review the history of that.

Walker-Smith: I think we might just leave sweat electrolytes for the moment, as in the second session we are going to talk about diagnosis. What we have just heard is a fascinating account – we have been given a picture of a very grim situation, although some optimism was appearing during this period. We are now moving on to the more modern period, 1955 onwards. Jim, would you like to carry it forward?

Dr James Littlewood: Yes, I feel a bit embarrassed here, because I was, as Margaret Mearns will tell you, a rather ‘Johnny-come-lately’ to cystic fibrosis, having worked in a provincial city as a consultant paediatrician for many years before gradually more cases seemed to be coming along and I started a CF clinic in 1975. But as I notice from the general paediatricians in this country, they have always felt that they could deal with cystic fibrosis. There are even some today who believe that there is no need for specialists in cystic fibrosis.

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<sup>23</sup> di Sant’Agnese and Andersen (1946).

<sup>24</sup> Dr Philip Farrell wrote: ‘Aerosol therapy refers to self-administration of water or dissolved substances such as sodium chloride or pharmaceuticals (e.g. penicillin) by inhalation using an instrument that generates mist under pressure. Parenteral refers to intramuscular or intravenous administration of a therapeutic agent (e.g. penicillin).’ E-mail to Dr Daphne Christie, 9 November 2003.



Figure 1: A 20-month-old child (b. 1991) – patient of Dr Mary Goodchild – being tested by pilocarpine iontophoresis using the older type of sweat-test box. Photograph provided by Dr Mary Goodchild, 2003. Goodchild and Watson (1995): 187. 1995 © CRC Press. Reproduced with copyright and parents' permission.

But if we go right back to when I qualified in 1956, as a locum I was trying to get sweat off people, putting their limbs into Bunyan bags, which were used in the war for burns, and scraping these drops of sweat off to try to confirm the amazing finding of the heatwave of 1948 and the observations of di Sant'Agnese and Darling in 1952 and 1953.<sup>25</sup> It was also quite scary in those days, because people were wrapping children up to make them sweat and there was more than one fatality reported due to overheating, trying to get sweat. It was marvellous when the pilocarpine iontophoresis method became available,<sup>26</sup>

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<sup>25</sup> Darling *et al.* (1953); di Sant'Agnese *et al.* (1953).

<sup>26</sup> The analysis of sweat electrolytes is the acknowledged gold standard for the diagnosis of cystic fibrosis. The sweat glands on a localized area of skin are stimulated by the iontophoretic application of pilocarpine. The positively charged pilocarpine ions move away from the electrode and into the skin. A negative electrode is applied to the same extremity. After the sweat glands have been stimulated, the electrodes are removed, the skin cleaned, and sweat collected over the exact region where the pilocarpine was iontophoresed. Sweat electrolytes are then measured. See [www.acb.org.uk/welshaudit/sweattest.htm](http://www.acb.org.uk/welshaudit/sweattest.htm) (site accessed 30 May 2003). See also page 105.

that was really a massive advance for everybody (see Figure 1).<sup>27</sup> Also at that time, I think it is fair to say, there was some progress in the USA. In 1958 there was the classic Shwachman and Kulczycki paper, with 105 patients that included their details of clinical score.<sup>28</sup> There wasn't really a great deal going on in the clinical side in the UK that we could see from the periphery in the provinces. In the 1960s the outlook for CF was absolutely appalling. In one of Sydney Gellis's comments in the *Yearbook of Pediatrics*, (I don't think he seemed to get on with Shwachman very well, because he was always knocking him in these little comments you get in the *Yearbook*), he said, 'Despite claims to the contrary, cystic fibrosis of the pancreas continues to carry a gloomy prognosis. Present-day therapy is helpful but offers relatively little, and a realistic alteration of the course of this disorder will require a major breakthrough in discovering the aetiology.'<sup>29</sup> Well, actually, things have improved a great deal; I think he wasn't quite correct there.

But through the 1960s, what happened then? Terrible outlook, very few patients around, therefore very little call for CF centres apart from the few centres that we have heard about like GOS [Great Ormond Street] and the Queen Elizabeth Hospital [London], very little call to get patients together, because there weren't many patients. Archie, you may recall a study you did with Dr Mantle, looking at the survival from the 1940s to 1964, and 80 per cent had died by the age of five, 90 per cent had died by the age of ten, and there were no adults.<sup>30</sup> There must have been a few, because Sir John Batten started his clinic in 1965 at the Brompton, London, so there must have been some adults, somewhere, but there weren't many in the north – I can tell you that!

The Cystic Fibrosis Trust (initially the 'Cystic Fibrosis Research Trust') started in 1964.<sup>31</sup> I suppose the clinical item for discussion in the 1960s was LeRoy Matthews talking of the mist tent as a breakthrough in 1961.<sup>32</sup> This became very popular in the USA and we all got the odd mist tent for our patients and they were sweating away in these at night. In 1967 Matthews published a paper supporting

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<sup>27</sup> Goodchild and Watson (1995): 187.

<sup>28</sup> A general score of clinical severity. See Shwachman and Kulczycki (1958) and [www.rbh.nthames.nhs.uk/ChildrenCF/appendix2.htm](http://www.rbh.nthames.nhs.uk/ChildrenCF/appendix2.htm) (site accessed 29 April 2004).

<sup>29</sup> Sydney Gellis edited the *Yearbook of Pediatrics* from 1952 to 1975. See Gellis (1968): 198.

<sup>30</sup> See Mantle and Norman (1966); Norman (1967).

<sup>31</sup> See [www.cftrust.org.uk](http://www.cftrust.org.uk) (site accessed 30 May 2003).

<sup>32</sup> Matthews and Spector (1961).

the value of the mist tent<sup>33</sup> and di Sant'Agnese said that anybody with adequate experience of this disease knows that it works.<sup>34</sup> However, by the beginning of the 1970s there were a number of papers showing that mist tents didn't work at all.<sup>35</sup> But, Archie, you did a study on this and you said you had the impression that some of the patients did benefit from it.<sup>36</sup> I must say, my one patient in a mist tent did seem to do rather well in it, but who knows? Mist tents went out of fashion.

Norman: At the time I thought the principle of the mist tent was mistaken and that it was not really effective. As Jim says, I might have changed my mind over one or two cases, but I was never very convinced by the basic principle of it.

Mrs Mary Dodd: I worked for Professor Aron Holzel in Manchester in the 1960s, looking after the children there, and all of our children used to go in mist tents, and at one time there was the theory that if we put seawater in the ultrasonic nebulizers, something to do with the iodine and the seaweed would actually benefit the patients. We used to go to Treaddur Bay, off Anglesey; that was the best seawater to collect and put into the ultrasonic nebulizers.

Littlewood: Some people used to use iodides, didn't they, as a sort of mucolytic?

Dodd: I think that was the principle behind it.

Professor John Widdicombe: It seems to me the use of the mist tent so long ago was very prescient, because it's only in the last few years that people have talked about hydration of mucus as a way of treating cystic fibrosis pharmacologically, and presumably the mist tent was doing this years and years ago, simply hydrating the mucus which was not then known to be dehydrated.

Sir John Batten: I have been very fascinated, and delighted, to find that Archie Norman is here, because he has been a great friend ever since I first saw a case of cystic fibrosis with Winifred Young in her clinic. Margaret Mearns was there at the time, and from that time when I did start a clinic for older patients at the

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<sup>33</sup> Matthews *et al.* (1967).

<sup>34</sup> di Sant'Agnese (1968). Dr James Littlewood wrote: "Dr Paul di Sant'Agnese commenting on an article by Matthews *et al.* (1967) reviewed in Gellis (1968): 196-7. 'The results reported here confirm the clinical observaton of the value of mist tent therapy in the obstructive pulmonary lesion of cystic fibrosis. It is generally accepted by almost all clinicians who have had adequate experience with this disease that patients have considerable benefit from such a treatment program, but objective proof was lacking.'" Letter to Dr Daphne Christie, 28 October 2003.

<sup>35</sup> Bau *et al.* (1971); Chang *et al.* (1973); Alderson *et al.* (1974).

<sup>36</sup> Norman and Hall (1971).



Brompton in 1965, that's the first documented case we had recorded. I have never used a mist tent.

Norman: I think the basic problem with the mist tent was of getting a sufficient number of droplets of a small enough size in sufficient quantities to enter the lungs and this really couldn't be done.

Littlewood: Just to round off the 1960s, where I don't think a great deal was happening. At the end of the 1960s, [Beat] Hadorn wrote a series of very important publications on direct measurement of pancreatic function,<sup>37</sup> pointing out the characteristics of the pancreatic secretion, which was really very useful. Some of us enthusiasts obtained triple lumen tubes and spent a lot of time irradiating people in the X-ray department, doing pancreatic function tests at that stage. Warren Warwick started, I think, the very first CF database in about 1968 and I remember for many years he was at every meeting talking about his CF database,<sup>38</sup> and the importance of collecting data.

There were various descriptions of polyps, meconium ileus equivalent, reproductive failure in males, abnormal vas deferens, eye changes with chloramphenicol and xerophthalmia with vitamin A deficiency. The first description of jejunal biopsy came in the early 1960s, and many of us started this towards the end of the 1960s<sup>39</sup> – I know that was Margot Shiner – am I right? The first paediatric series was carried out by Charlotte Anderson.<sup>40</sup> [Professor Ian Booth: No, Winifred Young actually did small bowel biopsies at the Queen Elizabeth Hospital in 1958].<sup>41</sup> Unfortunately a paper from Great Ormond Street, attesting to the dangers of this in children (I think with Sir Wilfred Sheldon's name on it and Eddy Tempany) set us back in the provinces a long way because our professor wouldn't let us do any biopsies until 1968.<sup>42</sup> But I won't go into that here.

Walker-Smith: That was the story of the inappropriate use of the adult small intestinal biopsy capsule<sup>43</sup> in children. I remember when I started at the Children's Hospital in Sydney there had been three perforations of the small intestine and

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<sup>37</sup> See, for example, Hadorn *et al.* (1968).

<sup>38</sup> Warwick and Pogue (1969): 320–30.

<sup>39</sup> Shiner (1960).

<sup>40</sup> Anderson (1961).

<sup>41</sup> Young and Pringle (1971).

<sup>42</sup> Sheldon and Tempany (1966).

<sup>43</sup> Walker-Smith (1997).

one death following small bowel biopsy, due to the use of the adult capsule in children.<sup>44</sup> This was because the hole size was too large in the adult capsule. The correct size for children is a porthole diameter no greater than 2.5mm.<sup>45</sup>

Littlewood: I only started them really to save the children from adult pathologists who did biopsies with these huge capsules! Anyway, I digress. On to the 1970s. Still very gloomy, no real CF centres in the UK, not a great deal of advance, but I think there was a ray of hope from Margaret Mearns in 1972.<sup>46</sup> Far from this early demise of patients, I think you [Margaret Mearns] showed that from 1957 onwards children were doing very well up to the age of five, which was a very different experience from many places in the country that didn't have specialized clinics. Høiby in Denmark was also looking at his antibodies to *Pseudomonas*, using crossed immunoelectrophoresis, in the late 1970s.<sup>47</sup>

Mist tents were laid to rest, as I mentioned. Professor Bob Elliott, in New Zealand, an amazing man, a sort of medical inventor, had treated a child with CF with Intralipid and noticed a fall in the sweat electrolytes, and an amazing change in this child compared with other children with CF in Auckland at the time.<sup>48</sup> He was also the person who, in 1979 with Crossley, described and introduced immunoreactive trypsin neonatal screening,<sup>49</sup> which of course has become one of the standard methods of neonatal screening.

So there was quite a bit happening and in certain places the outlook was improving, but I can assure you that things were not improving in most cities in the UK. Pancreatitis was described in people with residual pancreatic function. Intussusception and the prolonged neonatal jaundice was described, the latter I think by Bernard Valman, with a good prognosis, and then inevitably at the end of the 1970s, misdiagnosis: 'Does this child really have cystic fibrosis?' by Christine Smalley, Doug Addy and Charlotte Anderson, the first of many papers showing misdiagnosis due to erroneous sweat tests<sup>50</sup> – a very, very important paper.

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<sup>44</sup> Walker-Smith (2003): 108–9.

<sup>45</sup> Partin and Schubert (1966).

<sup>46</sup> Mearns (1972).

<sup>47</sup> See Høiby (1977).

<sup>48</sup> See Elliott and Robinson (1975); Elliott (1976).

<sup>49</sup> Crossley *et al.* (1979).

<sup>50</sup> Smalley *et al.* (1978).

An amazing decade of progress took place in the 1980s. Why was that? Well, as somebody was saying earlier, there were major improvements in the giving of antibiotics, but it really was an astonishing period. One of the main influences on clinical care was the work of Phelan and Hey, which I think John Dodge was aware of before it was published in 1984,<sup>51</sup> which showed a difference in survival between England and Wales, and Victoria, Australia.

**Professor John Dodge:** I went to Australia in the early 1980s in the wake of the paper by Phelan and Hey, which compared survival in the UK with that in Victoria, and claimed that the average survival in England and Wales was about 15 years at that time, compared with over 21 years in Victoria. Unfortunately, the methodology was different, because in the UK what they did was to get all the death certificates of children or adults who had died with cystic fibrosis and calculated the mean age of death. Whereas in Victoria they did a sort of standard survival curve, which included all the living patients, and said ‘Well, this is all because you don’t look after your patients properly in the UK, you should put them all in big clinics’. So I went to Australia to see what they did, and when I came home the Cystic Fibrosis Survey was set up to see what the true picture was in the UK.<sup>52</sup> Perhaps I should comment on that later.

**Littlewood:** I think it was that finding which was instrumental in forming the British Paediatric Association Working Party on Cystic Fibrosis which you [John Dodge] chaired and which was formed in 1982,<sup>53</sup> and which concluded that people with CF should be seen in, and have access to, a cystic fibrosis centre. I think this has been central to the improvement in CF centre care, with enough patients pulled together, as had been happening at Great Ormond Street and the Queen Elizabeth Hospital, but in many other places, and through the 1980s

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<sup>51</sup> Phelan and Hey (1984).

<sup>52</sup> The UK Cystic Fibrosis Survey was an independent national register of people in the UK diagnosed as having cystic fibrosis. The first survey took place in 1985 and collected data on all CF patients in the UK alive in 1977 and patients diagnosed subsequently. Later all CF deaths since 1968 were added from data provided by the Office of Population, Censuses and Surveys (OPCS). Updates took place approximately every two years, the last being in 1995. See Anon. (1988); Dodge *et al.* (1997). See also [www.qub.ac.uk/cm/ch/people/survey.html](http://www.qub.ac.uk/cm/ch/people/survey.html) (site accessed 30 May 2003).

<sup>53</sup> A copy of the Report of the Working Party on Cystic Fibrosis set up by the British Paediatric Association (BPA) and the British Thoracic Society in 1982, printed by the BPA and endorsed by the parent organizations, the CF Research Trust and the Royal College of Physicians, was kindly provided by Professor John Dodge and will be deposited with the records of this meeting in Archives and Manuscripts, Wellcome Library, London. Recommendations were summarized by A D Jackson in 1986. See also Anon. (1988).

there were these really quite important developments. The Cystic Fibrosis Research Trust started funding clinical staff, rather than just research, and they even changed the name from the CF Research Trust to the CF Trust, because they started funding staff in clinics – CF teams, as you obviously had, Archie, at Great Ormond Street in the 1950s, but not many other people did. There were teams of experts like Anita MacDonald, the dietician, and the physiotherapists, the social workers, who became very expert in dealing with cystic fibrosis, and this is when more rapid progress occurred – these people looking at the children, seeing the problems on a daily basis and then trying to do something about it; more aggressive antibiotics, for example the classic paper in 1981 by Margaret Hodson and the people from the Brompton on the use of nebulized carbenicillin and gentamicin.<sup>54</sup> Around that time many people were worried about spraying an aminoglycoside down somebody's throat. Now, of course, they do it with impunity, and at great expense – nebulized antibiotics for the chronically infected. It was also shown in a short letter to the *Lancet*, which we wrote in 1985, that chronic infection with *Pseudomonas* was not inevitable; you could eradicate early *Pseudomonas* by giving them nebulized colistin.<sup>55</sup>

Also, there were important papers on nutrition around that time<sup>56</sup> and we didn't have dieticians involved in the 1970s, certainly where I was anyway. And in fact a lot of children with CF, when it was gone into by a dietician, were not having enough to eat. So we got the dieticians involved and also enteral feeding. I may be wrong here, but I think the first enteral feed in an adolescent with CF was by Tony Axon, an adult gastroenterologist from Leeds, who was referred a malnourished girl. He put her on nasogastric elemental feeds and she did quite well for a time but, of course, not in the long term.

Walker-Smith: I think we will just pause there and ask Sir John Batten to tell us something about the adult services that were developed. We have heard already how he was the innovator at the Brompton Hospital;<sup>57</sup> would you like to carry on and tell us what happened?

Batten: As I mentioned earlier on, we had five cases that had been reported in 1965, at a special clinic for cystic fibrosis. Just to bring you up to date, we now have 650 cases attending that clinic at the Brompton, masterminded now by Duncan Geddes

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<sup>54</sup> Hodson *et al.* (1981).

<sup>55</sup> Littlewood *et al.* (1985).

<sup>56</sup> See, for example, Gracey *et al.* (1970); Allan *et al.* (1970); Berry *et al.* (1975); Kraemer *et al.* (1978).

<sup>57</sup> See page 12.

and Margaret Hodson who, I am sorry to say, couldn't be here today. She has been a great part of our team there and apologizes for not being here.

So what can I tell you about treating adults? One is, of course, that it would be sensible if one approached the need for these special clinics, we all know that, but it's still not understood to the full in the country as a whole, that patients not in a special clinic don't do very well, and this has all been established by careful studies.<sup>58</sup> So we have our clinics, we have well-defined protocols, we have careful record-taking, and I think we have witnessed in the UK an amazing change in the use of special clinics. I don't think I want to go on for very long, because most of you know what is needed in a clinic and what is required these days for treatment.

Walker-Smith: So we do have a very clear message then from both the children's and the adult services of the development, and the need for the special clinics. These very positive outcomes you were telling us about, Jim, have in a large measure stemmed from that.

Littlewood: Yes. Just in case I forget to mention it, a massive advance in nutrition was the introduction of Pancrease (acid-resistant microspheres) in the late 1970s, first recorded in the North American CF club meetings. I remember a poster in Toronto, Canada, by Holsclaw on this,<sup>59</sup> describing Pancrease going through the stomach protected from acid by its covering and then into the duodenum and, of course, it proved to be a revolution in enzyme management, allowing the low-fat diet to be abandoned in most patients. The other thing I must mention, in case I forget, is the home intravenous (IV) treatment, which allowed for much better and more acceptable IV treatment. The totally implantable venous access devices were good for people having repeated IVs, and, on the human side, the local anaesthetic cream (EMLA cream), which allowed you to insert a needle without pain; that was an enormous advance both for the children and for people actually having to do the work.

Then came heart–lung transplantation in 1985 – a massive advance for people in the terminal stages.<sup>60</sup> Gradually publications came from Denmark, which seemed to be ignored by many, that aggressive IV antibiotic treatment significantly improves the condition and survival of the patients.<sup>61</sup> Then, rather

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<sup>58</sup> Walters *et al.* (1994).

<sup>59</sup> See Holsclaw (1978); Holsclaw and Keith (1980).

<sup>60</sup> Scott *et al.* (1988).

<sup>61</sup> See, for example, Szaff *et al.* (1983).

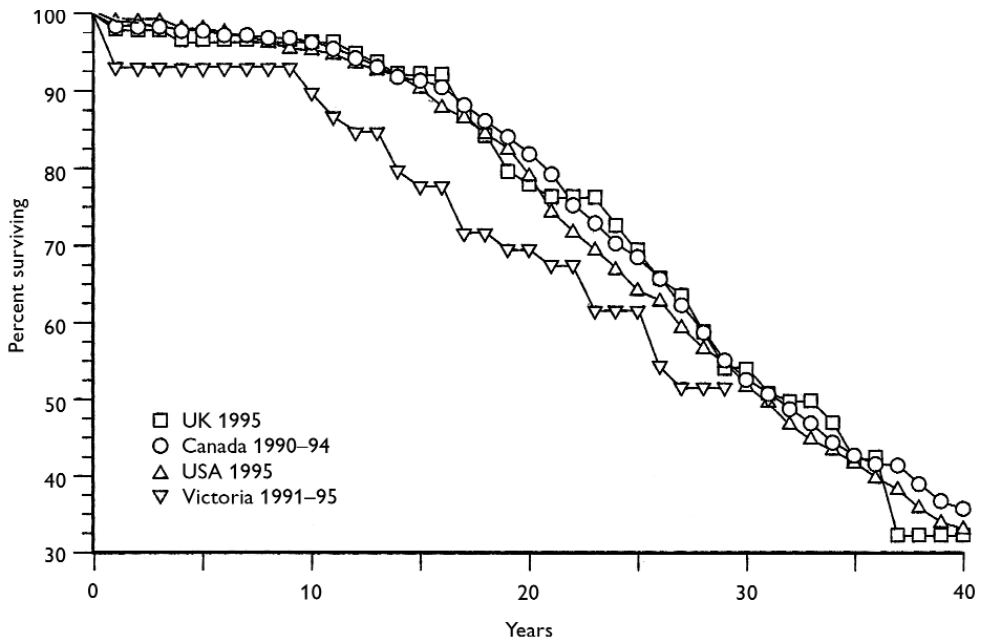


Figure 2: Current survival, males. From Hodson and Geddes (2000): 18. Reproduced by permission of Hodder Arnold.

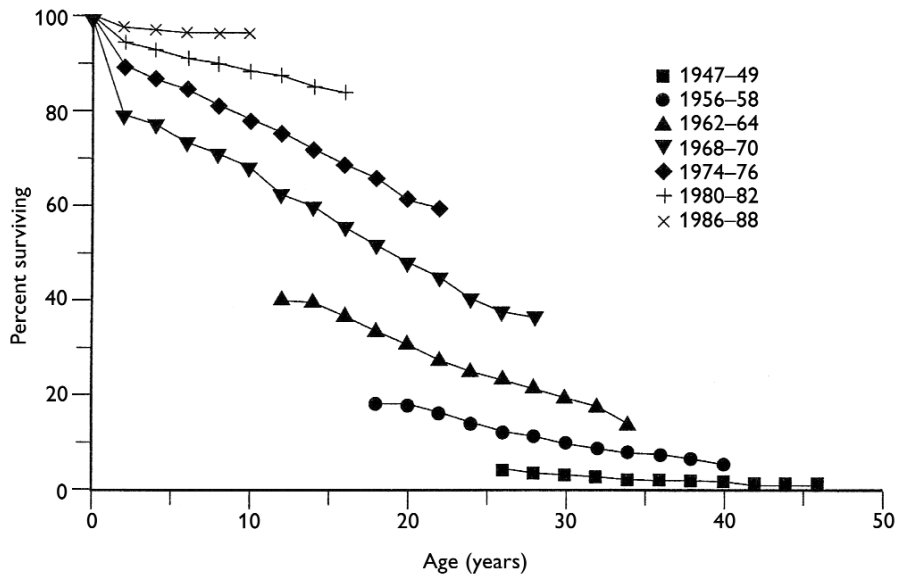


Figure 3: Selected cohort (males) and interrupted cohort (both sexes) survival for the UK. The upper four lines are the selected male cohorts, the lower three are the interrupted (both sexes) cohorts. From Hodson and Geddes (2000): 19. Reproduced by permission of Hodder Arnold.

more worryingly, came the first reports of *Burkholderia cepacia*,<sup>62</sup> a virulent organism that has totally altered the patients' social lives and their medical management.<sup>63</sup>

But I remember running a 'tertiary' referral service for CF through the 1980s in Yorkshire, and some of the patients referred were in a really terrible condition, they had never had any intravenous antibiotics and it was really very distressing. I tried to get a paper published on this in the late 1980s and it was not accepted by any journal, because the editor of one leading journal said that it was too critical of the care that these patients were receiving, and so it was never published. It's actually in the abstract book of the 1988 Australian International CF Congress.<sup>64</sup> There was another interesting paper from the USA around that time, by Wood and Piazza, comparing the care in three CF centres in the USA, showing amazing differences in survival.<sup>65</sup> The better centres saw the patients very frequently, and gave more days of intravenous antibiotics.

Walker-Smith: I think at this stage we might bring John Dodge in, concerning the changing outcomes and treatment. John, would you like to carry us forward and tell us how things began to change in terms of the outcome of children who were being treated?

Dodge: I hope most of you had a copy of two graphs from Duncan Geddes's and Margaret Hodson's book (Figures 2 and 3), and really they sum up what happened.<sup>66</sup> If you look first of all at Figure 2 you will see current survival in different countries of the world, UK, Canada, USA and Victoria, Australia, and there's not much between them. As it happens, Victoria, which started off the discussion, seems to be doing rather worse than North America and the UK, but there's not a lot between them – although they have very different health systems and very different ways of delivering healthcare.

The UK data came from the UK Cystic Fibrosis Survey set up by the British Paediatric Association and the British Thoracic Society,<sup>67</sup> and funded by the CF

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<sup>62</sup> Dr Littlewood wrote: '*Pseudomonas cepacia* has been renamed *Burkholderia cepacia*.' Note on draft transcript, 29 May 2003.

<sup>63</sup> Spencer (1995).

<sup>64</sup> See Littlewood *et al.* (1988).

<sup>65</sup> Wood and Piazza (1988).

<sup>66</sup> Figures 1.13 and 1.14, from Hodson and Geddes (2000): 18, 19, reproduced on page 18.

<sup>67</sup> See page 15 and notes 52 and 150.

Trust, and, as Jim says, he was one of the members of the working group, as was Margaret Mearns. We tried to do two things: first of all, find out what was the true survival in the UK, not just from death certification, and second to try to see if there was a difference between patients managed in large and small clinics. We didn't have any way of defining a CF centre, other than by size, and it was quite clear that those patients managed in large clinics were doing better. Now when you look at the second figure (Figure 3), which shows selective cohort data for different cohorts of patients born between 1947 and 1988. It doesn't go beyond that, because 1988 was the last group that we could properly study, because the survey came to an end in 1995 and we haven't had an update since then. But if you look at the top four lines, the oldest cohort of patients born 1962 to 1964, clearly the mortality was much higher in them than in the later cohort, children born after 1986.

But you will also see that there was a very big drop in the first year of life in the earlier cohorts, and that has almost gone. The reason for that was nothing to do with paediatricians and nothing to do with heart–lung transplant or anything else developed recently. It was all because babies no longer died with meconium ileus.<sup>68</sup> That's down to the credit of the paediatric surgeons, and it had a bigger single impact on survival than anything else that we have done before or since. In this country it was Harold Nixon at Great Ormond Street, and in the USA it was Charles Koop in Philadelphia, who showed that these children did not have to die, that surgery could save them. Archie Norman showed many years ago that survival in the Great Ormond Street meconium ileus patients, who survived the immediate post-operative period, was actually rather better than the general run of CF patients.<sup>69</sup> One of the reasons why our data in Britain for a long time were thought to be rather less good than those from the USA was that for many years the USA survival curve did not include patients with meconium ileus because they were thought to have a slightly different disease, and so they were excluded. But if you included them, you can see that a lot of them died young in the first year.

Now that that no longer happens, the other thing that is happening is that the lines are gradually straightening off. The chapter by Peter Lewis, a statistician, not a doctor, that this print was taken from, goes on to say: 'It's now beginning

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<sup>68</sup> Professor John Dodge wrote: 'Because of improved paediatric surgical techniques and joint post-surgical management with medical paediatricians, the 15–20 per cent of cystic fibrosis babies born with meconium ileus, which was previously usually fatal, were surviving and most had a subsequent course similar to that of other infants with cystic fibrosis.' Note on draft transcript, 12 November 2003.

<sup>69</sup> Norman (1967).



to look as though predictions of a 60-year survival are quite realistic.<sup>70</sup> The current survival in the UK is probably of the order of about 35 years mean, although we don't have up-to-date figures. When you think that in 1900, the average survival for all males in Britain was about 40 years, it shows you how far we have come.

Walker-Smith: So this is really a triumph, isn't it, in terms of survival? A tremendous change in the period that we are talking about.

Norman: Just one point about special clinics. Although the health service now is supposed to be very short of money, in the 1950s and 1960s various hospitals were equally short of money, and not only was there a natural conservatism, which tended to prevent our elders and betters from allowing us to establish special clinics, but the cost of them was quite considerable. It was difficult to get the nurses, dieticians and so on, time to come to any special clinic, or there weren't enough of them, anyway, to come.

Professor Sandy Raeburn: My view is from the northerly Celtic fringe, Scotland. In 1965 Professor Ellis noticed the need for somebody to look after CF patients and he appointed a young paediatrician called W Morrice McCrae, who set up the CF clinic in Edinburgh.<sup>71</sup> Later in the 1960s, I think two other things were happening that were affecting care in what were becoming more specialized clinics. First of all, there was better laboratory support for the clinics, the ability to work with the bacteriologists and choose the right antibiotics for a particular infection.

I think a second feature, too, was that the pharmaceutical industry was perhaps trying to help test its own products by offering some of them free to CF clinics.

I must make one comment, which is an adverse comment about the effect of special clinics that I discovered rather belatedly. We had a special CF clinic in Edinburgh for quite some time and the family doctor was often squeezed out. We had the multifactorial team policy, with physiotherapists, nurses, doctors, dieticians, everybody in the hospital environment, but when the patient deteriorated and perhaps was dying and wishing to remain at home during those

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<sup>70</sup> Lewis (2000).

<sup>71</sup> Professor John Dodge wrote: 'The impetus for starting special clinics came from the establishment of the Cystic Fibrosis Research Trust in 1964. The first executive director of the Trust, Ron Tucker, visited university centres throughout the UK and persuaded them to start CF clinics. Morrice McCrae in Edinburgh and myself in Belfast were in that 1965 first wave, and when I moved to Cardiff in 1971 I started another one there.' Note on draft transcript, 21 November 2003.

last few weeks, we had a GP who had scarcely met this 20-year-old individual. I think that was something that was eventually starting to be put right, perhaps as a secondary effect of intravenous therapy at home, and certainly in the 1990s, the psychosocial effect was recognized.

Professor Duncan Geddes: Just three comments about the late 1970s and early 1980s. I worked with John Batten as a senior registrar at the Brompton, and one of the things that got me into cystic fibrosis was the evidence of the benefit of specialist aggressive units. You would see these children coming in from the paediatricians, either from those like Margaret Mearns who had looked after them well, or from general paediatricians who really hadn't, and the difference was very striking in the quality of the people at the age of 16 to 18. Then you could see when they came into hospital sometimes just how much you could improve them. They would come in malnourished, badly infected, really dying and, with intensive treatment, you could actually pull people right back, and that convinced me of the importance of both a positive approach and special clinics.

It is worth remembering the impact of nihilism on the patients and their families before that time, many of whom had been told, 'Your child will die at the age of five, oops, all right, by the age of ten. Still alive – well, wait until 15', and we would then inherit them with this feeling of nihilism and negativity running all the way through that child's life. The second main point was the enormous difference in dietary management as we went from low-fat diets, from dietary restriction in people who were undernourished, to Pancrease and high-fat diets, and suddenly people's weight took off, and instead of inheriting very malnourished sort of sexually immature 18 year olds from the paediatricians you began to get these rugby first-row forwards coming through.

The third point is the sort of epidemiological cohort trap that a number of adult physicians fell into. I certainly did on starting a clinic, because I inherited patients just about the time that the median survival was reaching the age of 18, so patients came to me and then they died within three years. We thought that it was something that we were doing wrong, but as we stuck with it a little longer, we realized that they died at 24 or 26 and it wasn't our fault entirely after that. The benefits of centralized care became evident at that time but it took about ten years before all the debates finally stopped and it was accepted by everybody.<sup>72</sup>

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<sup>72</sup> Professor Duncan Geddes wrote: 'Centre care was promoted by the finding of better survival in Australia where centre care was more common and eventually recommended by the British Paediatric Association and the Royal College of Physicians.' Note on draft transcript, 3 October 2003. See Phelan and Hey (1984).

Dr Maurice Super: I first encountered cystic fibrosis in Windhoek in South West Africa [Namibia], as it was called at the time, in 1967. I inherited a patient who had been looked after by the paediatrician who had left there two years before, and his care had been neglected and I admitted him to hospital. He looked much as what Duncan Geddes mentioned a moment ago, almost at death's door. On active antibiotics, pancreatic enzymes and physiotherapy, he gained 4 kg in ten days in hospital. This particular boy was then for many years one of the less ill patients on our cystic fibrosis clinic, because, although I was on the edge of the medical world, I read a lot and I realized the importance of setting up a clinic. But unfortunately at the age of 16 he attempted to take his own life. Why? Because he and his parents had been told that he would not survive beyond the age of 12. He finally did die at the age of 24. The other thing is that if you work in a place where more or less if you say cystic fibrosis is your interest, that's it, and you do what you like in a way. I read Elliott's work on Intralipid<sup>73</sup> and we had a monthly meeting of the parents and of the CF clinic staff, and while we were having this general meeting, the children sat on the paediatric ward and they were all given Intralipid for an hour, intravenously.

Just very anecdotally, which I think we have been encouraged to do, an Australian locum who came up to look after my patients once when I was on holiday, was struck by how healthy the children were and how little *Pseudomonas* there was. I don't ascribe that to the Intralipid, I ascribe that probably to the very dry atmospheric environment of South West Africa.

Littlewood: I was just going to say the Intralipid stories resulted in the first controlled trial of nutrition by Chase and colleagues in 1979,<sup>74</sup> where it was not shown to be of any significant benefit.

Farrell: I don't think the point has been emphasized yet, but it is very important. We now know about the variation in severity and the milder forms of cystic fibrosis. I believe that one of the major lessons of the last decade or so is that this disease is so protean in its manifestations and has such a variable prognosis, that one has to be cautious about not over-treating and taking on unnecessary risks, and so I wanted to comment briefly about the risks. There have been numerous

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<sup>73</sup> Elliot (1976).

<sup>74</sup> Chase *et al.* (1979).

iatrogenic problems with this disease, related both to diagnosis and treatment. The purpose of this seminar and the purpose of studying history is to learn the truth; and the truth is that we have done many things with CF patients that have been harmful to them. Sweat-test bags caused deaths. Jim mentioned one death; there were many deaths that just weren't reported.

Mist-tent therapy was a source of *P. aeruginosa*; there is no question about that adverse effect of a commonly used 'treatment'. Mist tents also caused increased airways obstruction. There are papers that report decreases in airflow after mist-tent exposure.<sup>75</sup> The psychosocial harms of mist tents are absolutely incalculable. I remember well that I stopped recommending mist tents to my patients in about 1973, because one was getting married and she wondered if they should take the mist tent along on their honeymoon. I said to this young couple, 'It's time to stop the mist tent'. The research on mist tents causing 'a decline in ventilatory function'<sup>76</sup> had just been published, and I had cultured *P. aeruginosa* from mist tents. Frankly, it was time to stop using this misguided strategy.

Other iatrogenic adverse effects are attributable to antibiotics, such as tetracycline staining, and fragility of teeth and bones.<sup>77</sup> Harry Shwachman told me once that physicians had no choice at one time and that the benefit outweighed the risk, but as his patients aged he told me how much he hated to see them come back with teeth that were ruined by the treatment he gave when they were younger. Gentamicin is another problem. Soon after we started to use that first aminoglycoside antibiotic, the problem of deafness and nephrotoxicity was recognized,<sup>78</sup> and we over-treated patients and, frankly, they paid a price. Finally, oral prophylactic antibiotics are unquestionably one of the factors in increasing the risk for *P. aeruginosa*. I think it's one of the reasons we began to see *P. aeruginosa* emerge. You rarely find it reported in the literature on cystic fibrosis prior to the advent of broad-spectrum antibiotic therapy.<sup>79</sup>

Pancreatic microspheres are another source of harm as well as benefit. I agree with Jim [Littlewood], they were miraculous, but the more recently introduced high-strength pancreatic enzymes can cause severe colonic strictures, and now we

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<sup>75</sup> See, for example, Bau *et al.* (1971); Chang *et al.* (1973); Alderson *et al.* (1974).

<sup>76</sup> Motoyama *et al.* (1972).

<sup>77</sup> See, for example, Mello (1967).

<sup>78</sup> Shwachman (1983).

<sup>79</sup> See, for example, Feigelson and Pecau (1967); Kilbourn (1970); Doggett *et al.* (1971); See also Tansey and Reynolds (2000).

are paying a price for that also. Cystic fibrosis camps were developed to improve psychosocial opportunities for these children. However, they turned out to be extraordinarily damaging as a source of cross-infection or person-to-person transmission of *B. cepacia* and, I believe, *P. aeruginosa*. And you can go down the list. I know of children who deteriorated while receiving Intralipid when severely ill, so I think we have to take the responsibility for the harm that we have caused as well as the good that we have achieved.

Walker-Smith: That's a pretty grim story, outlining all the bad things the doctors did.

Littlewood: We were talking about fat and Duncan was saying how important it was that they got enough to eat with a decent enzyme. A man who influenced me a lot, although I never met him, was [Doug] Crozier from Toronto and his 1974 paper, 'Cystic fibrosis: A not so fatal disease'.<sup>80</sup> I read it if I am feeling depressed. He insisted that you did a thorough assessment of every aspect of the patient and then repeatedly tried to get everything back to normal. Am I right in thinking that he was the man that really gave up low-fat diets, pumped people on 60, 70, 80 Cotazym capsules a day and – what's the word he said – it's ridiculous to reduce fat in children who are so skinny?

Farrell: It was the Toronto CF centre more than any other cystic fibrosis centre that promoted the shift from low-fat diet to normal or high-fat intake with higher doses of pancreatic enzymes. This change is attributable to the leadership of Doug Crozier.

Littlewood: In his clinic it preceded the new enzymes, didn't it?

Farrell: It did, but remember there's one other factor in Toronto and this is a factor I mentioned before. The enormous number of patients referred there meant that they were receiving patients with relatively mild mutations and pancreatic sufficiency, as we found out later, so patients that were not so severely ill, and that's one reason the statistics look good.

Littlewood: Patients who needed to get there [to the Toronto Centre], rather than dying locally.

Dr Anita MacDonald: Can I just make a comment on the introduction in changing low-fat diets to high-fat diets, which occurred very much in the early 1980s?<sup>81</sup> My background is as a dietician; I started working in Leeds in 1980. I

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<sup>80</sup> Crozier (1974).

<sup>81</sup> MacDonald (1996).

think there has always been a general assumption among physicians that if you tell a patient to do something they will always do as they are told. What actually happened in Leeds, when we started the systematic assessment of dietary intakes, was that many of the patients were already on a normal-fat intake. They had abandoned the fat restriction. Pancrease wasn't used until the 1980s.<sup>82</sup> What we saw clearly was that the patients who were cheating and actually eating a high-fat diet were doing far better, in terms of growth, than the patients who were keeping to the original low-fat diet. So it actually bore out the very early work that had been done by Crozier and Chung.<sup>83</sup> This was before the new enzymes became available.

Walker-Smith: It shows you how important dieticians are in the care of these children.

Professor Kevin Webb: I think I would like to turn round Dr Farrell's comments slightly. There are a few withered, ageing adult-CF physicians in this room, and I think the only reason we exist actually, is because of the superb care of the paediatricians who sent their patients to us, for which I blame them in a positive way really, because I don't think we would exist if it wasn't for them. It was the twentieth anniversary this year of our CF unit and I have never forgotten when I emigrated to north Manchester, which was a sort of Third-World district where they fire guns at each other, Mary [Dodd], who had looked after the children, said, 'When are we are going to look after the adults?' and I looked around and said, 'Where are they?' And they were all in the children's hospital still. They were shipped over in a cartload because the paediatric hospital had had enough of them at the age of 16, and we took over this really grumpy bunch of 16–20 year olds at that time.

Going back to Duncan's words, and really CF centre care isn't anything clever, actually, it's the delivery of finite, multidisciplinary care. There were two of us who started off and now there are 40 of us, and that's really why, apart from the paediatricians, the mean survival over the last 20 years in fact has gone from about 22 to 34. It's nothing clever, the advances came beforehand, it's really the finite multidisciplinary care of physiotherapists, doctors, social workers and dieticians, who put it all into the patients.

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<sup>82</sup> Dr Anita MacDonald wrote: 'Pancrease is an enteric-coated microsphere enzyme preparation. They were more effective at absorbing fat than 'older' enzymes. They became available in the early 1980s.' Note on draft transcript, 17 October 2003.

<sup>83</sup> Chung *et al.* (1951); Crozier (1974).

Raeburn: Two quick anecdotes from Morrice McCrae, which illustrate the difficulty of transfer from paediatric to adult care. Morrice said that he knew it was time to transfer them to an adult physician, when first of all they grew much too tall for the toilets in his paediatric wards and, second, when they asked him directly for contraceptive advice.

Walker-Smith: It does touch on a more general problem in Britain, which is the failure of adolescent medicine to really take off in the way that it has in the USA. In many chronic diseases of children such as Crohn's disease, care of the adolescent is a very difficult matter. In such circumstances it is now accepted that the paediatrician and the adult physician should meet together at the handover clinic, where adolescent patients are actually handed over personally.

Raeburn: I think Jim could say more about this, but in the Scottish system I was a physician and a geneticist. Therefore I played a part in the transfer to adult care, but clearly as a geneticist I didn't have active use of beds, so a link-up developed in which I was a cog between the paediatricians and then the adult chest physicians in north Edinburgh.

Walker-Smith: Can I ask a more general question? Was it the custom to have the paediatrician and physician meet over the patient? Did they actually have a hand-over clinic anywhere in the country?

Raeburn: What tended to happen was that some of us came to the paediatric clinics for several months and met people there, but despite that, transfer was very difficult.

Littlewood: I think many people used to run a transition clinic for a year or two, and it was staffed by a paediatrician, an adult physician and staff from both units, so that over two or three years they would get to know the members, and then the move there would be a gradual transition, when they wanted to go in, they would be shown the adult unit, and then could go in if they wanted. If they didn't want to change, they could stay on until 16 or 17, if they wanted to move very quickly, they could go quite quickly. I think most units now have it organized, but it has been a point of discussion for a long, long time, with, I think, a lot of unnecessary difficulties. But remembering the problems we had in the early days and the adult ward I tried to transfer patients to, I know the difficulties can be considerable.

Sir Christopher Booth: I would like to know something about the relationship between paediatric and adult medicine. My experience of this came through coeliac disease and Winifred Young at the Queen Elizabeth Hospital for

Children [London], who sent me patients from 1960 onwards, and we developed a joint arrangement. I think that developed in respect of coeliac disease all over the country.

My question about cystic fibrosis is, at what stage did this happen? What sort of date did these things begin to happen? Was the development of cystic fibrosis influenced by other conditions, for example, people with genetic diseases living on into adult life? Where did the pressure come from? Was it the paediatricians or did it come from adult physicians?

Dodge: The outcome of our first survey was that we produced a document that recommended that specialist CF clinics should be set up when there were about 50 patients,<sup>84</sup> and I think we recommended that that should apply to adult clinics, as well as to children's clinics. In those days there were fewer adults than children, today there are probably more adults with cystic fibrosis in Britain than children. That means that if you want to have a viable clinic, with all the different specialities represented – the physios, the nurses, the dieticians and so on – you do need a core number of patients of the order of 50, to make it financially and professionally viable.

I think it has become easier to transfer patients now, because, of course, one group that nobody has really mentioned has been the cystic fibrosis nurses. I think they often act as midwives in taking the child into the adult clinic in a way that perhaps doctors no longer need to, because we can leave it to our expert nurses to arrange the hand-over. Obviously, we send over the notes and everything else, but we don't need a physical hand-over from doctor to doctor.

Dr David Stableforth: I just wanted to return to the subject of transfer from childhood to adult clinics. When I first went to Birmingham in 1977, having been trained in John Batten's unit at the Brompton Hospital, London, Birmingham had a very large childhood clinic, but as far as I knew on arrival there, and having an interest in looking after these patients, there were few adults. They were scattered around the region, and there was a Professor Anderson in the paediatric clinic at Birmingham.<sup>85</sup> At that time she was resistant to all approaches that she should hand over her patients. [Booth: It wasn't just cystic fibrosis.] I can remember an interview, going to see her in 1977 to

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<sup>84</sup> Working Party on Cystic Fibrosis (1982) *Report to the British Paediatric Association, Royal College of Physicians of London, British Thoracic Society*. See note 53 and Jackson (1986). See also Anon. (1988); Jackson (1996).

<sup>85</sup> See biographical notes, page 91.



persuade her that I could look after adult patients, and just a very small number of new patients were referred to me after that meeting. There was this large growling dog under her desk, I think there to intimidate me!

Anyway, following that meeting, about five patients followed over the next five years from her, and it wasn't until my colleague, Dr Peter Weller, arrived in Birmingham that there was an agreeable relationship between the paediatricians and the adult physicians. Following his arrival in the early 1980s we developed a transition clinic of the type that Jim Littlewood has talked about. Peter Weller and myself, and members of the multidisciplinary team, all sitting down in the consultation room – a rather intimidating group I feel in retrospect – and the adolescents and adults would come in and sit down, and the child would be handed over in that way, perhaps not at the first visit, but at subsequent ones. That's now all been streamlined and the transition clinic is now looked upon as very important for the smooth transfer of care from the childhood to the adult cystic fibrosis clinic.

Walker-Smith: Those remarks about Charlotte Anderson are extremely interesting. Incidentally, Charlotte Anderson died on 15 April of this year [2002], in Melbourne. Dr Goodchild is from Charlotte Anderson's unit.<sup>86</sup>

Dr Mary Goodchild: Following on a little bit from the remarks just now: I also remember this dog, a poodle I think and not too large, but it definitely growled. But to be serious for a moment and straying slightly into the role of the CF Trust which is the next item on the agenda, there was a very nice survey and investigation of the actual mechanics of transferring from a paediatric to an adult clinic done very thoroughly by a lady whose name I forget at the moment [Jean Pownceby], commissioned by the CF Trust.<sup>87</sup> She went around many of the clinics in England and for all I know in Scotland as well, and worked out a number of factors that were necessary for a smooth transfer from paediatric to adult clinics. One thing that was very clear, from the patients' point of view, was that the last people they wanted in the clinic when they attended as patients were their parents.

Walker-Smith: I can echo that in chronic inflammatory bowel disease, the children really wanted to talk to the doctor on their own.

Ms Susan Madge: Talking about transition and the comment that was just made, often the problem with the transition seemed to be the parents. I used to work

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<sup>86</sup> See Walker-Smith (2002). See also biographical notes on page 91.

<sup>87</sup> Pownceby (1996).

at Great Ormond Street, and transition started when we found that we had children surviving and they weren't dying, and I think that's what prompted us into it, the expectation of a longer life ahead for them. One or two survived and they were just moved by letter almost, to the Brompton, but as the population of survivors grew, then transition became more of a serious subject, and the children then became very eager to move, but the parents seemed to be the ones to hold back, and to put the brakes on. Eventually everyone moves, because it's a children's hospital and everyone has to be out of there, and having guidelines helped us. It was often the parents that were reluctant to lose that trust that they had had for 16 or 17 years, and the faith they had had in the people caring for their children, and it was often that which seemed to be the problem.

Walker-Smith: I visited Harry Shwachman in 1966 at the Boston Children's Hospital. There, they had pregnant girls cared for in the Children's Hospital. Harry was very reluctant for the young people to go over to the adult hospital.

Dr Peter Hunter: Could you explain exactly what was different about pancreatic microspheres in getting effective pancreatic enzyme action into the right part of the gut? It's been a problem throughout most of the twentieth century. What was special about this device, and when and where was it discovered?

Littlewood: Pancrease and Creon are the trade names for the two new acid-resistant pancreatic preparations. The thing that was very special about Pancrease, and later Creon, was that they were not destroyed by stomach acid, so the actual enzyme was not released until the surrounding environment became alkaline in the duodenum or even a bit further down. Whereas before, as di Magno showed in the 1970s,<sup>88</sup> the vast amount of exogenous enzyme powder is destroyed in the stomach, leaving only a tiny little bit of it. Pancrease sounded like a gimmick initially. I can never forget seeing the poster in Toronto, but by Jove it was miraculous! I can well remember a girl of about 15 weeping when she had been put on to Pancrease, and saying that her whole life, as I think Archie was suggesting, was dominated by her terrible bowels, and she said, 'Now I can live a normal life'. It was absolutely awesome, the effect in some patients. I pushed it hard because it was a very, very important area.

Hunter: Let's come to a much more serious point – a point about 'why did things happen the way they did?', and 'why did things happen at the time they

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<sup>88</sup> di Magno *et al.* (1977).

did?’ I would like to look at this from the point of view of the history of drug discovery and specifically the discovery of streptomycin by Selman Waksman.<sup>89</sup>

The second point is that he opened up that new area of microbiology; he discovered actinomycetes and defined them. Then we come to an extremely important point; that is the question of how he was financed. In 1940 he had tried and succeeded in obtaining from *Actinomyces antibioticus*, the antibiotic actinomycin A, and this was highly toxic. The next thing that happened was that he was given a very significant amount of money. Basically discoveries tended to happen because a private source of money, a charitable source, financed a person and then a drug company did the same thing.

**Booth:** Can I just stick to the question of special clinics? One of the problems for those looking after patients in such clinics, dealing with patients with genetic disease, is a danger that a man and a woman may fall in love with each other, following their time at the clinic. My question therefore is, has anybody here any experience of that happening in his or her clinic and, if so, what was the outcome in terms of children?

**Webb:** I don’t know quite how to answer that. Our patients fall in love with each other all the time. I am in charge of sexual morals on the ward and ask the advice from the sisters, because of the cohabiting that goes on. And that is absolutely serious. We have had patients leave their spouses to associate with others, and some of them actually do have very strong relationships and live with each other. Part of the problem obviously is with the inevitable sequelae if the patients don’t get a transplant, there are no offspring from two CF patients, because the men are sterile, so that’s quite fortunate, and male sterility is the only thing one can think of that is fortunate. But the cohabitation of two CF patients can and does cause a lot of grief.

**Stableforth:** I just wanted to recall a very special grief which was historically rather important to our clinic at Birmingham Heartlands – East Birmingham Hospital as it was then – when a couple fell in love. A young man with cystic fibrosis in 1990, or 1991, had acquired *B. cepacia* infection, possibly from contact with someone who had been to a Canadian cystic fibrosis camp, and he met and fell in love with and was shortly to marry a girl who also had cystic fibrosis, and she grew *Staphylococcus aureus* only in her sputum. Within two months of the start of that relationship, this girl had acquired *Pseudomonas*

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<sup>89</sup> See biographical notes on page 99. See also Waksman and Curtis (1916); Waksman (1954); Tansey and Reynolds (2000).

*cepacia*, as it was then called. The young man died within six or eight months of their meeting, following a lung transplant operation and three months later the young woman died. This terrible event alerted us to the facts of this dreadful infection by which so many clinics in the UK have been so scarred over the years. This is a problem which we are only now getting to grips with through segregation and other infection-control measures.

**Geddes:** Just to extend that a bit. The love between patients is one problem, but love between patients and members of staff is another, and that too can be quite a difficult thing to handle, with medical or nursing staff leaving their spouses because they have become so intimately involved with the patient. It's something that's very seldom talked about, but I have seen enough of it, and I bet a lot of other people have too.

**Webb:** Yes, I have seen that. I have to echo what Duncan says, the CF patients have an enormous charisma, we have had at least four very strong relationships between male CF patients and the nurses who look after them, and a couple of them are getting married. There are obviously the inevitable consequences that apply to that as well. I always find it rather odd, and always have found it rather odd, that if a doctor was in such a situation he would be struck off [the Medical Register], but it doesn't apply to the nursing staff.

**Walker-Smith:** May I ask Margaret Mearns what her views are about transition clinics – children-to-adult clinics?

**Mearns:** I was very fortunate because I could go to the Brompton when the patients were due to be transferred and I could attend the clinic with them, and I think I went most weeks to the Brompton, even if there weren't any new patients. I could either sit in on the consultations or I could see them at the side and then discuss their progress over the previous weeks with the consultant in charge of their care.

**Walker-Smith:** So you actually introduced the children to the physician? [Yes.]

**Farrell:** I want to comment on the role of the CF patients in pressuring physicians and nurses to transfer them to an adult-care setting. This was our experience. Many patients who required repeated hospitalization for intravenous antibiotic therapy, as they became older than 18 years, absolutely insisted on transfer to another care setting. They wanted to come to our cystic fibrosis centre for care, but they no longer wanted to come to the Children's Hospital or to the children's clinic, and so some of them just insisted that we transfer them. These admissions for intravenous antibiotic therapy, these tune-ups in the hospital that

would last a week-and-a-half or two weeks, allowed us really to train the adult pulmonologists to care for these patients. Then, subsequently the patients would be seen in a specialized clinic at the medicine department, that is chest medicine clinics. I think the patients themselves played a pivotal role as well as the nurses, as Dr Dodge mentioned.

Walker-Smith: You didn't develop adolescent clinics?

Farrell: We didn't develop adolescent clinics, and we didn't think it was really necessary because in our centre we were accustomed to taking care of both children and adolescents.

Mrs Fran Duncan-Skingle: It was in 1980, when I started as clinical nurse specialist at the Royal Brompton, that Sir John Batten, Professor Margaret Hodson as she is now, and Dr Mearns were running joint clinics for transition from paediatric to adult care. It's taken a long time to initiate transition clinics, and we are still talking about it 20 years later. But it is happening in most centres now.

Super: When Kevin Webb first came to Manchester, I had thought that it would be a good thing if we did a couple of transition clinics, but Kevin said, 'No', and Gary Hambleton and I accepted that, but we also spoke to the children from the age of about 12 onwards, telling them that at the age of 16 they would be moving, and it was seen as a positive milestone in their lives. Our CF nurse and Kevin's social worker used to be the transition links between the particular patients and Kevin was absolutely right, none of those people have ever come back to us, or asked to come back to us, they found it a great thing to have moved.

Littlewood: I must say I think I agree with Fran [Duncan-Skingle]. It seems a pity that we are discussing transition clinics after 20 years. Just to put a spanner in the works, if you go to Denmark and speak to Christian Koch and his nurses, and the lovely staff there, and ask, 'What about the adults?' They say, 'Well, they are attending this clinic'. And I say, 'What about the transition?' They say, 'We have known them since they were small, and we go on looking after them'. Of course they have different clinic days, different wards, different everything, but the same people. So I said I used to find it difficult about birth control, as a paediatrician, and he said, 'Oh, the nurses talk to them about it'. And I thought 'It seems to run very well'. I wouldn't approve of it, but I just thought I would mention it.

But in Leeds we had problems initially, but fortunately had a doctor working in paediatrics [Steven Conway], who moved to infectious diseases, and

subsequently became a consultant in infectious diseases. We started moving the adults with CF in his direction, and now he has developed one of the biggest adult centres in the country, but he started treating both children and adults, and he's still doing both as lead clinician of the Leeds Regional CF Clinic.

Dr Tilli Tansey: May I ask a question about something that has been raised by a couple of speakers? CF camps. Is this a North American phenomenon, and are they also in Britain? How were they started? Could somebody tell us more about CF camps, please?

Dodge: They were started in North America. But the CF Trust prevailed upon some of us to start camps in this country. There was a Scottish camp, I think, Sandy? [Raeburn: Yes.] And we certainly ran one in south Wales for a number of years and Scottish kids used to come to our camp and ours used to go up to Scotland, and we had them from Ireland and from Wales and England, and I am sure they all infected each other, but they had a jolly good time, and we had volunteers, physios, nurses, doctors and, of course, Ron Tucker. Nobody has mentioned Ron Tucker yet, but I am sure he will be mentioned later. Ron was the driving force behind a lot of these things.

I think, with hindsight, camps were a bad thing. At the time they seemed awfully good. They were certainly good for morale, and the thing that astonished me was that when the professionals were totally exhausted by about midnight, and had just sort of slumped into sleep wherever they happened to be, the kids were still racketing around until the early hours of the morning. I don't know where they got their energy.

Raeburn: Two very quick comments. One comment just to finish the earlier theme, which is that clearly there was a psychological issue in the medical and professional staff themselves about the transfer to adult care. We have got to learn from that, as Philip says, it wasn't just the psychology of the patient nor the psychology of the parents, it was the psychology of the doctors and nurses. We need to consider that, too.

We ran two or three very successful CF camps that were very much watersport-based in Scotland in the middle 1980s. We realized that infection was a possible problem, and we did pre-camp testing and we did post-camp testing. Within the short duration of those camps (one week), we weren't able to show that there had been cross-infection. I am quite sure, as John [Dodge] says, that learning afterwards there was a problem demonstrated that we just could not test, with enough precision.

Goodchild: I thoroughly agree that the camps were on the whole very enjoyable, but we had a very unfortunate experience in Cardiff where I was working most recently: one girl went over to Canada and brought back with her a genotype of *Pseudomonas cepacia*, which John Govan would know about, a particular strain of *Pseudomonas cepacia* (or *B. cepacia* as it became known later on), which became the lead for six further cases of *Pseudomonas cepacia* of the same type in patients who became infected at the Paediatric Clinic at the University Hospital of Wales.<sup>90</sup> So this was very unfortunate and the original strain almost certainly emanated from that camp in Canada.

Walker-Smith: That's very interesting indeed. Now I think we need to change over to the role of the Cystic Fibrosis Trust, and it's a pleasure to have Dr Tony Jackson here, who is going to tell us about that.

Dr Anthony Jackson: Thank you, Chairman. I was Chairman of the Trust's Research and Medical Advisory Committee from 1984 to 1994. John mentioned Ron Tucker. Actually what happened was that Ron Tucker invited me to lunch. As you know there's no such thing as a free lunch, and I ended up as the successor to Archie Norman as Chairman. What I remember most of my ten years in the research committee was, first, the gradual development of the attitude that the Trust should be supporting clinical development, specialist centres and so on, by funding clinical fellows and nurses and how, at first, the scientific members of the committee rebelled against this, saying that this was not proper research, and we certainly should not provide staff for the NHS.

We managed, I think in the end, to accept the role of the Trust and we did really make very strong efforts to get a centre in every region. I remember going round some of the more distant parts of the country with my colleague, Martin Scott, who was the scientific adviser, and seeing some of the arrangements. For example – well, I had better not say where – somewhere in the northern part of the country, there would be four or five different hospitals, with four or five different adult physicians treating one or two patients each. The paediatricians were not much better, except they had three or four patients each. But, I think, as a result of providing money for those who followed the theme of developing a regional centre, we gradually spread the number of centres throughout the regions.

The other thing I remember most is the constant discussion we had about the type of laboratory research we should be doing. Of course we had many, many

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<sup>90</sup> Ryley *et al.* (1995).

discussions about how gene research was going (and we indeed put a great deal of money into research in that line), particularly its merits or demerits, and it was rather disappointing for the Trust that the gene was not discovered in our research laboratories, but in North America.

The other thing we did was to start on heart–lung transplants. I have got in front of me here the notes of an *ad hoc* meeting that was held on 1 August 1984 and most of the people on this nominal roll are here today: John Batten, John Dodge, Duncan Geddes, John Widdicombe and myself. The only other person not here is the surgeon John Wallwork. This was a meeting at which we had to decide whether or not heart–lung transplant was a possible or feasible approach in cystic fibrosis and whether or not the Trust should support it. In fact as time went by the developments, as you know, were that heart–lung transplant was certainly fully developed and became a useful component of treatment. In fact there was one time I remember when we made a grant of £500 000 to the Brompton Hospital for the development of heart–lung transplantation.

The other thing that we were concentrating on at the end was the matter of John Dodge and his UK CF survey,<sup>91</sup> which the Trust supported, and we used to have regular meetings. I think we used to meet at Heathrow, John, didn't we? [Dodge: Yes.] Because John came from Belfast, and the statistician came from Cardiff. At any rate, the Trust got involved in that and supported it, and was, I think, instrumental in gradually merging the statistical activities regarding cystic fibrosis with the Scottish database, and I think this has now become the UK National Database.<sup>92</sup> Those are some of the things I remember that we did in our research advisory committee.

**Walker-Smith:** It's interesting that in the early part of your remarks, you describe a historical reluctance for specialization to develop. This is quite an important theme that is coming through today.

**Booth:** Two fundamental questions I would like to ask: one is where does the money come from, and secondly did you have lay people on your research committee? Did you have patients on it?

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<sup>91</sup> Dr Jackson wrote: 'This report described the size, distribution and status of the CF population in the UK.' Note on draft transcript, 9 May 2003. See Dodge *et al.* (1993).

<sup>92</sup> Professor John Dodge wrote: 'The UK CF survey was terminated in 1996 when funding was withdrawn by the Cystic Fibrosis Trust. The Trust hope that the national CF database, which grew out of the Scottish database, will be able to fulfil the same epidemiological role as the survey.' Note on draft transcript, 21 November 2003.



Jackson: We did not have patients on the Committee, but there was the pressure for doing clinical research, as opposed to basic research. In those days we didn't have lay people, and perhaps Rosie could answer the question about money.

Mrs Rosie Barnes: The money comes from a variety of sources. There is always a hardcore of money each year raised by the families of those coping with cystic fibrosis, their schools, their Brownie packs and community initiatives, often supported by families. That tends to bring in up to £2 million a year and has been fairly recession proof.

Over and above that, we have turned to charitable trusts, corporate sponsorship, legacies, the National Lottery – there's nobody we don't ask – and most people eventually give us something, because we won't go away until we have got it. But there is a backbone of patient support and very often the big donations we get from companies will come about as a result of somebody on the inside, perhaps with a child with cystic fibrosis, asking their company to bear us in mind when making their charitable decisions for the year.

Walker-Smith: And you have lay people now?

Barnes: We now have an adult with cystic fibrosis on our Research and Medical Advisory Committee, and we would have another one were it not for the problem of cross-infection. We now also have a parent of a child with cystic fibrosis on the committee.

Walker-Smith: We do have a patient with cystic fibrosis here today.

Ms Tracy Humberstone: To be honest, I am keeping quiet because I do not wish to deter anybody in the room from saying anything that may be of interest to me or to others present, or to restrict them. I am making notes, but I would rather speak later. I have a number of points: e.g. 'tetracycline' staining. I do have severe tetracycline staining to my teeth and if anybody wishes to see the damage, please feel free.<sup>93</sup> There are many concerns, i.e. the nihilism, age barriers, and so forth, but I am sitting here absorbing the contributions.

Barnes: There are one or two things that perhaps I could follow on with, which have been mentioned today, from the Cystic Fibrosis Trust perspective. First, we offer clinical support grants to 27 paediatric CF centres throughout the UK, but only 17 adult centres, and so, although we are talking about the number of adults versus the number of children, and the arrangement of the transition, one

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<sup>93</sup> See page 24 and Mello (1967).

of the problems we have faced in parts of the country was there was nowhere for them to transit to. It's worked better and moved faster in some areas than in others and obviously there's still a shortfall there, which we need to address.

I think it's also important to say that although we talk about as many or more adults than children now, that only seems to hold strictly true if you make the dividing line at 16 years old, and by the time you get to 18 or 21, you are looking at relatively few adults compared with those younger than that age. Approximately 6000 of the 7500 CF patients in the country are 21 or under.

I would like to make a comment from a study done by the Cystic Fibrosis Trust on transitional arrangements and parents.<sup>94</sup> Both adults with cystic fibrosis and their parents, not interviewed in pairs, or the same parents of particular children, both admitted to a sort of conspiracy against their medical teams, with adults with cystic fibrosis pretending to be far more independent in terms of managing their CF than they in fact are. They go off and manage all sorts of other aspects of their lives very independently, but they tend to leave their CF a bit at home, and it's very often the parents that come to Cystic Fibrosis Trust branch meetings, put out medication for their adult child to take and continue to do their adult child's physiotherapy, even though the adult clinic may have taught them to do it independently.

But there's been this great pressure for those becoming adult with cystic fibrosis to become completely independent in a way that I think has been rather false, in that if you got a new condition at the age of 17 or 18, you wouldn't be expected to manage it all on your own, as has sometimes perhaps been the case with cystic fibrosis. One or two of the things that have been mentioned today, are areas where the Cystic Fibrosis Trust has made changes over recent years. We started, as the early talks we had today indicate, very much as a support group for the parents of children with a life-threatening disease, and we have had to learn to change, to be responsive to adults with the condition as well, and that's something we are taking on board. We try to fill the gaps in what the state just won't or can't do, so apart from the database which we fund, we have funded quite a lot of complex work and facilities in the area of microbiology that just might not have happened had the Cystic Fibrosis Trust not facilitated it. I think the fact that we have facilitated guidelines in recent years has been a great tool for both the clinical teams and indeed patients to lobby with, to get better care in their areas, and we are now pioneering an advocacy project where we employ

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<sup>94</sup> See Pownceby (1996).

12 adults with cystic fibrosis to be the user representatives for their particular region, which I am hoping is going to be a great success.

But I would just like to conclude with an anecdotal story of today, which shows there's still no room for complacency. I got a phone call yesterday from the father of a girl aged 13, who, he told me, was not expected to survive, she was in hospital and her medical team had told him to prepare for the worst. I asked which hospital she was in and it was clearly a local district hospital, and I said what do her CF centre team say? He said that she has never been to a CF centre. So although we are making great strides, we do have to make sure that the 'St Elsewheres', as Jim and I often describe them, somehow get brought into the equation.

Walker-Smith: One would have thought that this reluctance to accept the need for paediatric specialities would have been dealt with ages ago. In fact it is a general problem still, and it's rather shocking that we still have this occurring in this country.

Norman: I would like to say something about the formation of the Trust, if Mrs Barnes isn't going to do so later. In the late 1950s, I think, John Panchaud (who was a Swiss businessman) came to me. I was looking after his daughter who had cystic fibrosis, and he said that he wanted to form a parents' association. Now in those days, parents' associations were not looked on with great favour by many doctors, partly because of the activities of the Spastics Association.<sup>95</sup> However, I thought this was a good idea, and I supported him in it. He then spoke to David Lawson, whom he knew from Carshalton, and he agreed, too. John Panchaud went ahead and formed this, with the support of Joe Levy, a very successful businessman, who was a business colleague.<sup>96</sup>

Joe Levy put in an immense amount of time and money in supporting the Trust. He was one of the most generous of men, and that is really how the Trust got going. As far as the research committee is concerned, I and David Lawson and Winifred Young got together and we then appointed David as Chairman of the Research Committee of the Trust, but we were agreed that at that time it should be a research trust in order that the maximum amount of money could go to

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<sup>95</sup> Information about SCOPE (formerly the Spastics Association) can be found at [www.scope.org.uk/50/timeline.shtml](http://www.scope.org.uk/50/timeline.shtml) (site accessed 20 February 2004).

<sup>96</sup> Dr Archie Norman wrote: 'The Cystic Fibrosis Research Trust (CFRT) was formed in 1964 with the remit of research into the causes and cure of the disease known as cystic fibrosis, and for the care, treatment, education and advancement...[sic] of persons suffering from cystic fibrosis in any form.' Note to Dr Daphne Christie, 4 November 2003.

research. We had no idea then, of course, how much Joe and his colleagues would supply, and how much the Trust itself would raise later.

**Dr Richard Boyd:** I was on the RAMAC [Research and Medical Advisory Committee] for a number of years and took pleasure in being a scientist trying to find out at what point the clinical application of research findings was picked up by the NHS in the way that Tony mentioned. But I think there's a larger general issue here: how does a very effective charity behave so that it does not pick up the slack, the proper province on the one side of the National Health Service and on the other side the MRC [Medical Research Council] and, dare I say it, even the Wellcome Trust? I would like to hear a little bit more about the Chairmen's views. We have got three eminent Chairmen covering the Trust for the last 35 years. It would be interesting to know if they felt they were ever picking up the brief that properly belonged to other people.

**Jackson:** Yes, we knew we were, and we were criticized by some paediatricians at any rate in saying that we were providing, for example, a research fellow who did the work of a registrar as well, and we were expecting that this would be taken over by the NHS in due course, but we were criticized because it was made clear that the NHS was not going to take these people over and once you had started the specialized clinic that these people allowed, it became very difficult not to continue with this. Certainly we were anxious about the amount of money we were putting into the NHS, but the benefit to the patients was such that we felt the [CF] Trust was doing a good job for the patients by doing so. Certainly the intention was largely to stimulate the activity of a centre and then to back out and let the centre make its own way. Many of them did. But I still remember it as being a difficult time for us, and certainly the amount of money we put into laboratory research and scientific research, as opposed to clinical research and the support of the NHS, didn't seriously fall, because the amount of money being collected gradually rose.

**Walker-Smith:** This is quite a common theme, isn't it? I know both in cancer research in children and also research concerning Crohn's disease, that substantial sums are given by private charities to maintain the health service. One might argue that the health service has a real debt to such bodies.

**Madge:** I think it was important that the CF Trust funded these early posts. I was funded originally by the CF Trust, but the NHS didn't recognize the posts we were taking on, they were unexplored, no one knew what they were about, and the NHS wasn't going to start funding them, so the CF Trust was needed to show and to prove the worth of these posts. Most of the specialist ones have been taken over by the NHS – not all, the Trust still funds some – but they would never

have got going if we had had to wait for the NHS to start funding them. I tried for years to get the funding out of the hospital. Before the Trust took it up we were trying to go to drug companies for sponsorship. So I think the CF Trust was important and unique in recognizing the innovation of new posts and funding them so that the NHS would then take them up.

**Barnes:** If I could just clarify the outcome, following on from what Su Madge has said. Over 92 per cent of the posts that the Cystic Fibrosis Trust has funded within the NHS have been taken over by the NHS, we haven't then withdrawn the money, we have allowed it to be used to extend the teams even further, so we do feel that we have got very good value for it. It's pegged at around £800 000 a year. We don't allow it to go beyond that. We don't allow it to run away with itself, but I think we work on the principle that in terms of families coping with CF we are trying to offer and ensure the best for today, and even better for tomorrow. We feel that with all the research funding in the world, unless we can be sure that families are getting the best, we won't be honouring our part of the obligation to them in the here and now.

**Walker-Smith:** So it's pump-priming you are doing really, isn't it? It is very important.

**Littlewood:** Richard Boyd, I think you were actually asking about the MRC, the other side of research, rather than clinical care. I always found that very difficult to grasp. The Cystic Fibrosis Trust receives research applications from scientists who are often receiving grants from the MRC, Wellcome and other sources. It's always very difficult to know exactly what proportion of that piece of research you are funding. I don't know. Did you find that, Tony [Jackson]?

**Stableforth:** Can I just first of all speak as a recipient over many years of numerous grants from the Cystic Fibrosis Trust and say that without any question my own hospital trust, or district as it was then, would not have allowed the development of cystic fibrosis and the multidisciplinary team that has gone with it, without pump-priming from the Trust, and in almost each and every case the posts that they enabled to be created have been taken over by the hospital trust. We are all enormously grateful for the Trust for that.

**Littlewood:** I would support that entirely.

**Goodchild:** May I extend that very slightly and say that in my view and, I think, in the view of many people, the work done by the CF research fellows was so good and so committed that it actually played a major part in raising the standard of CF care throughout the country; for this I think that we have to thank the Cystic Fibrosis Trust.

**Stableforth:** I just want to make a point that has not been alluded to by Rosie Barnes or others speaking about the Cystic Fibrosis Trust, which is the help that they are now extending to the centres that want to build their own buildings to house the patients and the multidisciplinary team. We know that there are a number of centres throughout the country that they have helped a great deal and we can say for our own emerging centre that they have contributed very significantly and I know that there are other centres that probably wouldn't exist, but for this support. So that's just another aspect of their patronage and support that I would like to point out.

**Raeburn:** My comment is to say that the Cystic Fibrosis Research Trust, as it then was, often cross-subsidized quite a lot of other things. Thus, much genetic research money went to St Mary's [Hospital, London]; that team may not have found the CF gene, but it certainly did a lot of the background genetic work, and CFRT [Cystic Fibrosis Research Trust] support led them to find the Duchenne muscular dystrophy gene.<sup>97</sup> The CF grant didn't benefit people with cystic fibrosis directly, but I think we have to accept that this cross-subsidization is going to happen.

Another comment: Ron Tucker. We need to realize that much developed through the friendship of Joe Levy and Ron Tucker. Ron was a man who had set up an immense network of friends; he realized that the strength of the Cystic Fibrosis Research Trust was due to its links with and networks throughout the country. If people didn't know about cystic fibrosis out in the back of beyond, Inverness or places like that, then CF centres weren't going to work. I used to abbreviate some of my slides CFRT and a little old lady in Scotland thought that it really stood for CF Ron Tucker!

I think somebody ought to try to capture the image of this man whose personality was large, his body was large. I don't know about the other people he used to see, but I was terrified when Ron phoned me up, because I knew he was going to give me work to do, and I knew it was probably going to be a talk somewhere. I knew, too, that in the hours after my talk I was going to have what I said dissected by Ron, phrase by phrase, just to get right what was the politically correct and patient-correct comment to make. I do hope that in your history you are going to somehow try to capture some of Ron's charisma and the music hall act that worked so well for the Trust.

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<sup>97</sup> See, for example, Christie and Tansey (2003b): 10, 33, 34.

Professor John Govan: Just a quick comment on Ron Tucker. I remember travelling with Ron. Very often we were asked to do talks round branch meetings, and I remember one occasion on the third night he said, 'That was a different talk from the one you gave last night.' And I said, 'Yes Ron, but your introduction was also different'. And I remember another night at a meeting in Perthshire, 'There's not a lot in the audience, John, tonight. But just wait until the bus arrives with the folk from the Dunkeld branch.'

Walker-Smith: And now the focus is towards research. There were considerable advances during the period that we are looking at. I would like to ask Professor John Widdicombe to introduce the general notion of basic research into cystic fibrosis. This is a rather general topic, but he is very well placed to introduce it.

Widdicombe: It's a pleasure to be here, although I think I may be here under false pretences for two reasons: first, I have done no research at all on cystic fibrosis, but the person who has done a lot of important research on CF is my son, who works in the University of California, Davis, Sacramento, so you may be confusing me with him, in which case I am very flattered.<sup>98</sup> The second point is that I was on the CF Research Trust a long time ago, in the 1970s and early 1980s, and what struck me then was that they were greatly supporting clinical research, and we have learnt a lot about that and it was very commendable and productive, but they also supported a lot of basic research. That was also a great stimulant to basic scientists working on mucus and mucous membranes in the UK, and it stopped many of us going off to the USA. We stayed put. I think that was a very valuable task that the Trust carried out.

As a basic scientist on the Trust, I sometimes felt that I was a lay member compared with the clinical members, but I learnt a lot from listening to them. In the 1980s, as you have heard already, there was a tremendous expansion of treatment of patients with CF and prolongation of their lives, and at the same time there was a great expansion of research on the basic mechanisms of CF. However, probably the two aspects of study didn't relate very much to each other because, although the basic understanding of mucosal physiology expanded enormously, it couldn't very easily be applied to the disease. This application only came about in the late 1990s, in the last few years, but the foundations were laid in the 1980s. Before that, it was recognized that CF was a disease of mucus, both in its original name, mucoviscidosis, and the fact that patients were coughing up these large amounts of very unpleasant high-viscosity mucus.

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<sup>98</sup> For details about his son, Dr Jonathan Widdicombe, see page 100.

But there were two problems in studying the disease in patients. One was that almost inevitably the mucus was from infected and inflamed lungs, and the infection and the inflammation changed its properties far more than the actual disease itself. The more recent studies on CF mucus, which have been on unadulterated mucus, suggest that the actual chemical composition of the mucus is not very different in CF patients compared with normals. There may be some differences, but they are minor ones, and the main difference occurs when the mucus gets infected.

The other problem about studying mucus, which applied not only in the 1980s but continues through to today, is that nobody has yet discovered a way of measuring mucus flow or output. You can collect mucus in a sputum cup, but that is extremely inaccurate and not very scientific. Airway mucus must be about the only body fluid for which no one has yet thought of a way of measuring its flow rate. That seems to me to be a tremendous gap, not just in CF but in other conditions such as chronic bronchitis, where one needs to have a good quantitative method to study it. So if you look at the analyses of mucus in the early 1980s and even before, in the 1970s and 1960s, the values are all over the place, including the viscosity measurements, the ion contents, whether or not there are lots of lipids present and so on. All the publications then, of which there are probably a dozen or more, show enormous variation and don't really make sense.<sup>99</sup>

Then in the 1980s, the position began to change. The formative paper was published by Kilburn in 1968<sup>100</sup> and most people working on mucus quote that. He didn't make any measurements, but he deduced that deep in the airways you have a tremendous production of mucus, probably several litres per day, but by the time it gets up to the trachea has been reduced to a very small amount. It's not been very accurately measured,<sup>101</sup> but we know it's a small amount, so something must be happening between the small airways and the trachea to absorb the bulk of this liquid coming up the airways. This was the paper that stimulated research and interest into how the epithelium transports water and sodium and chloride.

I am going on to say a bit more about that in a moment but, in passing, one of the big mysteries about mucus and airway fluid absorption is that although we now know how mucus can be dried out, how liquid can be taken up in the

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<sup>99</sup> King (1981); Chernick and Barbero (1989).

<sup>100</sup> Kilburn (1968).

<sup>101</sup> Yeates *et al.* (1975).



airways, nobody has yet discovered what happens to the mucus glycoproteins; you have an enormous bulk coming up from the small airways, and if they were to get to the trachea, then the trachea would be filled with a very adhesive glue, so there must be a different transport mechanism for glycoproteins that has yet to be sorted out.

But in the 1980s two things happened. One was there were many studies on the physiology of mucus secretion; various models were prepared which showed how it was controlled by nerves, by inflammatory mediators and by chemicals, and the chemical composition of the mucus, and I was happy to be involved in some of that research.<sup>102</sup> It gave us a tremendous background or understanding of the secretion of mucus. But even more striking, and I think more relevant to this group, is the development of studies on ion transport systems through the airway epithelium and their relevance to CF. This came about, partly as always, through methodology; people began to set up epithelial preparations in Ussing chambers and measured ion transport and water transport.<sup>103</sup> Now you can't easily do that for CF, because you need quite a big specimen of airway mucosa. There have been some studies taking airway specimens from CF patients who were having transplants, and these you can set up in Ussing chambers, but obviously the scope is very limited.<sup>104</sup> But the second major advance was the use of extracted epithelial and glandular cells to allow growth into confluent cell sheets, and to study their properties, and that can be done from CF patients.<sup>105</sup> Oddly enough you can take them from somebody who has died of CF even up to 24 hours before, and if you nourish the cells properly they will grow into an intact sheet and you can study the way that CF epithelium behaves. So that was a tremendous advance that came along in the late 1980s.

The studies on epithelial transport have been conducted all around the world, and there are dozens of names. The main groups include that of Boucher and Knowles, and their colleagues in North Carolina, whose work I am sure you all

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<sup>102</sup> Widdicombe (1982); Kyle *et al.* (1987, 1988); Boucher *et al.* (2000): 1291–1324; Knowles and Boucher (2002). For a historical perspective, see Quinton (1999).

<sup>103</sup> Welsh (1987). Experiments originally used frog skin, and later CF epithelium, mounted in a 'Ussing chamber', where each surface was bathed in a separate fluid. Chemical manipulation and analysis of the medium on each side allowed information about the transport processes across the skin. See, for example, Ussing and Zerahn (1951); Ussing (1954); Ussing (1989): 337–62.

<sup>104</sup> See, for example, Alton *et al.* (1992).

<sup>105</sup> Widdicombe *et al.* (1985).

know.<sup>106</sup> I would like to think that the younger Widdicombe contributed quite a lot to the study as well, but I mustn't blow the family trumpet.<sup>107</sup> It has led to a comprehensive picture of what takes place in the CF epithelium compared with normal; there are various ideas as to how this may apply, but essentially the concept is that the chloride output into the lumen is decreased, because the cystic fibrosis transmembrane regulator (CFTR) receptor is either blocked or absent, probably blocked, so the chloride can't be secreted. The sodium is taken up more readily from the lumen into the tissues, and the reason for this is not quite clear; it's quite possible that the CFTR inhibits sodium uptake so that if you get rid of CFTR then sodium uptake is increased. But the net effect is perfectly clear, you have less chloride and less sodium in the airway lumen, and as a result you get less water, because water follows the salts. So the airway mucus is decreased in concentration and the mucus is dehydrated. This is thought to be the underlying basic mechanism that causes the mucus changes in CF.

There are a lot of controversies and gaps in this description still. Boucher has been suggesting recently that there are two possible mechanisms, one where the mucus and the liquid in the airways are kept isotonic, and the other where it's hypotonic, and there's a lot of argument about this.<sup>108</sup> But the fact that the ion pumps can change the behaviour and the adhesiveness of the mucus seems to be well established, and to be a fundamental mechanism to explain why CF airways behave abnormally.

Professor Alan Cuthbert: I would like to make two comments about what John Widdicombe has just said, one in relation to organs like the airways that produce a lot of mucus, and a second comment about another organ that produces no mucus at all, but is also affected in CF, namely the sweat gland. To start with the airways, I think if you look at where the product of the CF gene is found in the airways, it's found in the superficial epithelial cells of the large airways, but the major contribution, or the main concentration of CFTR, the protein which is coded for by the CF gene, is found in the cells at the bottom of the mucus glands. There is quite a lot of evidence that these glands secrete bicarbonate, and if that bicarbonate can reach the surface of the airway epithelia, being slightly alkaline, it reduces the mucus viscosity.

So what I am really saying is not only may mucus viscosity be increased in CF, as John [Widdicombe] was describing, but that while clearance is very much

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<sup>106</sup> See, for example, Knowles *et al.* (1983); Boucher *et al.* (2000); Knowles and Boucher (2002).

<sup>107</sup> Yamara *et al.* (1991); Jiang *et al.* (1993).

<sup>108</sup> Boucher (1999).

impaired by the withdrawal of water, viscosity may also be increased because of a lack of a suitable pH. With regard to what's going on in the large airways, I think there are quite a lot of people who would support the postulate that the major function of CFTR in the airways themselves is to downregulate ENaC, epithelial sodium channels. There is a three- to four-fold increase in sodium absorption in CF airways compared with normal, this is also an enormous contributory factor to the concentration of all those substances which are not only making it difficult for the CF patient, but making access of drugs given via aerosols or when considering giving gene therapy by an airway route, this is a barrier to getting into those positions.

But I wanted to say something else about the sweat gland and to pose a philosophical question. The question is 'Would we have been better off never having had the sweat test?' Thirty years ago physiologists knew how salt secretion in the sweat gland was controlled. Salt was secreted into the proximal coil of the sweat gland as an isotonic fluid and, as it moved into the reabsorptive coil, it was reabsorbed leaving you with relatively hypotonic fluid on the surface, which we call perspiration or sweat. It was also known that that process was driven by the active reabsorption of sodium, chloride followed passively, and because that part of the sweat gland is not permeable to water, the water ended up on the surface of the skin. So it was a sodium-led process.

Now when it was found, by di Sant'Agnesse and others, that the salt content of the sweat was high in CF<sup>109</sup> and since the process of salt absorption in the reabsorptive duct was sodium-led, this led to the postulate that there was a defect in the absorption of sodium which was responsible for CF. About 30 years ago I looked at the CF field, wondering whether I should move into it, and decided not to because it was in a right mess, the reason being people were collecting saliva, urine and sweat from CF patients and looking for things within these fluids that inhibited salt absorption. I think one of the greatest discoveries, particularly seen in hindsight, was that of Paul Quinton who, in 1983, published a paper where he used the perfused human sweat gland and found that if you perfused it with a solution without any chloride, you produced basically a sweat gland with all the properties of a CF sweat gland.<sup>110</sup> That was the first indication that it wasn't really the cation, although the cation was actively transported, it was the failure of the anion to be able to move with the cation that was the cause of CF. And as many of you know, Paul Quinton, who is now about 60, is himself a

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<sup>109</sup> Darling *et al.* (1953).

<sup>110</sup> Quinton (1983).

CF patient, and if you visit him or his lab and you look at the inside of his forearms, they are covered with little scars where he's donated so many skin biopsies for all his experiments over the years, that he is permanently marked by these. But it was he who pointed to the fact that the protein coded for by the CF gene was maybe something to do with chloride and, of course, we know now that the CF gene does indeed code for an epithelial chloride channel.<sup>111</sup> I think that was a very early formative influence on how basic research has gone since that time.

Widdicombe: I can give you another reason why the secretion of sweat is not a good analogy of secretion of airway liquid or mucus, and that is that, as you explained, in sweat you normally end up with a hypotonic excretion because of the absorption of sodium and chloride following it. Whereas most of the evidence on the tonicity of airway secretions suggests that they are either isotonic or slightly hypotonic because the airway epithelium is so permeable to water that it flows through readily to follow the sodium and chloride concentrations, the sweat glands are quite different.

I am sure you are right about the submucosal glands being the most important site of the abnormal secretion of the airways in cystic fibrosis. This leads me to a comment that I was going to make later, and that is the use of a mouse model. The mouse is a model beloved by geneticists for very good reasons. It's rather like the guinea-pig for pharmacologists; pharmacologists love the guinea-pig because every time you ask it a question it says 'yes', and you publish a paper. It's the most compliant of species for pharmacology and, of course, the mouse is the same for genetics.

But the problem with using the mouse for CF studies is that it has virtually no submucosal glands.<sup>112</sup> It also has almost no goblet or serous cells in the epithelium if it's healthy; if it's airways get diseased and inflamed, you get some mucus cells appearing in the bronchi. The number of CFTR receptors in the mouse is far smaller than in most other mammalian species, which is understandable if they haven't got much mucus secretion tissues. So the mouse is fine for genetics, but if you move on to study the physiology of mucus secretion, I think it is probably a very poor model.

Walker-Smith: I think that leads us logically on to another aspect of research, which is more focused, namely microbiology. Professor John Govan is going to introduce the topic.

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<sup>111</sup> Riordan *et al.* (1989).

<sup>112</sup> Pack *et al.* (1980).

Govan: What is microbiology? I actually started off as an organic chemist. The reason I say that is that when I went to work in a lab my boss was obsessed with the idea of what a chemist does and kept asking questions like, 'Is this stuff stable at 4° C, John, can I fridge it?' It's the same with microbiology. Not always as straightforward as it seems. Consider the germ that causes cholera. Things are fairly straightforward. Most microbiologists will tell you that the *Vibrio cholerae* is attracted to mucin lining the human gut, indeed the bug swims towards it, penetrates the mucosal blanket and then delivers its toxin. Well, *P. aeruginosa* is also attracted to mucin lining the gut and airways – that's the way we get rid of it. The mucin is moved up the airways and taken away by mucociliary clearance. So why do we have problems in cystic fibrosis? It's a complex story, and I hope I am not breaking the rules by giving you a handout with illustrations (includes Figures 4–8 below).

This is a difficult job. I remember listening to Margaret Mearns many years ago, saying that there are people who use slides, and there are people who have something to say, so the natural thing is not to use slides, and I have never forgotten that. Duncan Geddes, whom I respect very much and always try to follow, says that there are lots of grey areas in microbiology. So these are black and white but I have the colour versions as well. It was just to try to give you some pictorial thoughts as we go through the microbiology. The theme is that there are many aspects to it.

We have heard of the original work of Paul di Sant'Agnese and I thought we should start off by looking at the very strange spectrum of pathogens in CF. To a microbiologist this is very unusual. The first illustration is the table by di Sant'Agnese in 1945 describing the aerosolized use of penicillin (Figure 4).<sup>113</sup> At that time there were 14 post mortems, no less than 12 due to *Staphylococcus aureus*. For people who say that *Haemophilus* and *Pseudomonas* were not around at that time, if you look carefully, *Haemophilus influenzae* non-capsulate type B is there, and for people who say microbiologists keep changing names, because we can't pronounce them or we can't remember them, note *Bacillus pyocyaneus* is there in the third patient from the bottom. *B. pyocyaneus* was the original name for *P. aeruginosa*, so name changing isn't something that only happens now.

This was the pre-antibiotic era and there's absolutely no doubt that antibiotics have made a major impression. However, the use of antibiotics in cystic fibrosis is an art and has been described by Stutman and Marks as a science unto itself.<sup>114</sup>

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<sup>113</sup> di Sant'Agnese and Andersen (1946).

<sup>114</sup> Stutman and Marks (1987).

Case no.	Age (months)	Lung		Other organs
		Predominating organism	Also present	
S2	4	Haemolytic <i>Staph. aureus</i>	A few <i>Pneumococci</i> , type 14	Trachea: <i>Staph.</i> only
S3	2½	<i>Pneumococcus</i> , type 25	Many haemolytic <i>Staph. aureus</i> ; a few nonhaemolytic <i>Staph. albus</i>	
S8	15	Haemolytic <i>Staph. aureus</i> (m+c+)	Moderate number <i>Haemophilus influenzae</i> (not B)	
S10	4	Haemolytic <i>Staph. aureus</i> (m+c+)		
S15	4	Haemolytic <i>Staph. aureus</i> (m+c+)	Haemolytic <i>Strep.</i> a few	
S16	15	Haemolytic <i>Staph. aureus</i> (m+c+)	Haemolytic <i>Strep.</i>	Bronchus: <i>Staph.</i> and <i>Strep.</i>
S18	11	Haemolytic <i>Staph. aureus</i> (m+c+)		
S19	15	Haemolytic <i>Staph. aureus</i> (m+c+)		
S20	2	Haemolytic <i>Staph. aureus</i> (m+c+)		Ear: <i>Staph. aureus</i> (m+c+); a few <i>B. coli</i>
S23	12	No culture. Microscopic examination: clumps of Gram-positive cocci, morphologically <i>staphylococci</i>		
S25	32	Haemolytic <i>Staph. aureus</i> (m+c+)	<i>B. pyocyaneus</i>	
S30	9	Haemolytic <i>Staph. aureus</i> (m+c-)	A few <i>Strep. viridaos</i> , <i>B. coli</i>	
S33	1	No growth		
S37 (12)	40	Haemolytic <i>Staph. aureus</i> (m+c+)		Trachea: <i>Staph. aureus</i> (m+c+); a few diphtheroids

**M+ C+ = Mannitol fermenting and coagulase positive**

Figure 4: Post-mortem cultures – cystic fibrosis of the pancreas. January 1939 to June 1945. Table provided by Professor John Govan, 2002. Adapted from di Sant’Agnese and Andersen (1946): 21. 1946 © American Medical Association. All rights reserved. Reproduced with permission.

Why is that? Well, when Alexander Fleming discovered antibiotics, even he didn’t look at the therapeutic value. He was more interested in cultivating his beloved *Haemophilus*. I am sure that today he would be asked about the intellectual property rights and the patent. Many clinicians and many microbiologists think of antibiotic sensitivity as the zone of antibiotic attacking organisms, growing in a totally artificial environment in the lab. Historically, the antibiotic ciprofloxacin was the first antipseudomonal agent available in oral

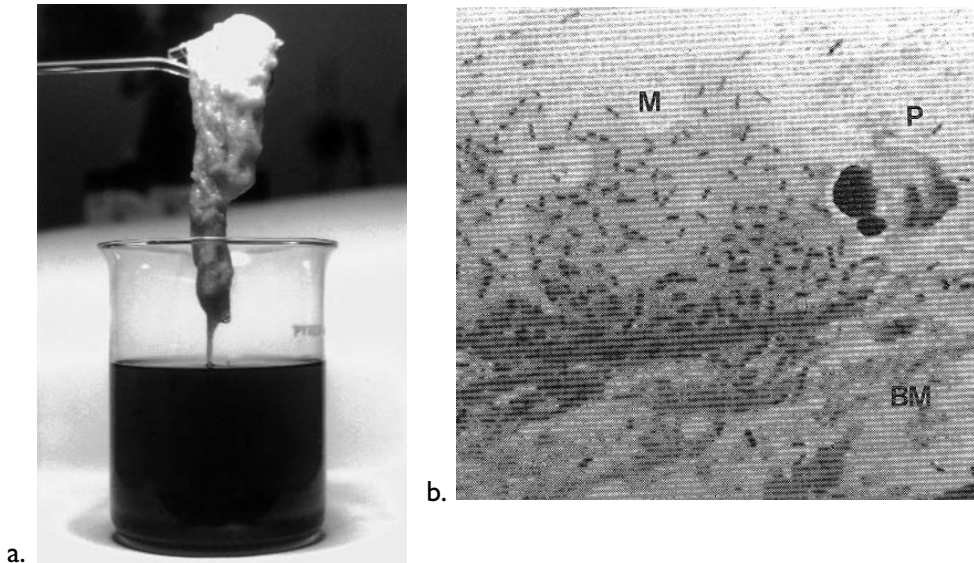


Figure 5: (a) The Doggett legacy – mucoid alginate-producing *Pseudomonas* in cystic fibrosis. Govan and Harris (1986). 1986 © Blackwell. Reproduced with permission. (b) Gram-stained sputum from a patient with cystic fibrosis harbouring mucoid *P. aeruginosa*. The bacteria can be seen in a gelatinous microcolony (M), which is attached to the bronchial mucosa (BM) and is significantly larger than the adjacent phagocyte (P). Govan and Glass (1990): 22. 1990 © Longman Group UK Ltd. Reproduced with permission. Photographs provided by Professor John Govan, 2002.

formulation. I don't know if Sandy Raeburn was there but certainly Morrice McCrae was, and I was taken by Bayer to Leverkusen, Germany,<sup>115</sup> in the early 1980s and asked, 'What do you think of an oral anti-*Pseudomonas* agent?' and I thought, 'Wonderful – CF kids can go to summer camps and have jobs'. Of course, at that time we had little cross-infection and we didn't realize that the hazards of summer camps would come back with a vengeance later on.

The point I want to make is that although antibiotics do have lots of benefits in cystic fibrosis, they have to be looked at in a very different way to that in which antibiotics are used elsewhere. I am thinking particularly of urinary tract infections. In contrast to the high concentrations achievable in the bladder the levels we can achieve even with the very best anti-*Pseudomonas* antibiotics today are only barely reaching the killing levels. What do we mean by sensitive and resistance? How can we use antibiotics best? Clinical trials are enormously expensive. This is another very, very grey area.

<sup>115</sup> Bayer Pharmaceuticals.

The next illustration (Figure 5) that I want to remind you of, since this is historical, is about the work of a man who does not get the kudos he deserves. Bob Doggett was a larger-than-life Texan, who, in the early 1960s, pointed to a number of important aspects of CF microbiology. We often talk of Americans rediscovering the wheel. However, Doggett made many observations, which are still true today. For example, the important link between not only *Pseudomonas* but mucoid alginate-producing *Pseudomonas* in CF, and the fact that these organisms are highly unstable in the laboratory, very difficult to maintain, and yet are very stable in the CF lung, indicating the role of selective pressure.

Well, why is the CF spectrum of pathogens so strange? Why is *Pseudomonas* so dominant? The clue is the photograph on the left (Figure 5a). We heard Mary Dodd talking earlier about the use of seaweeds and iodine. This material you see being lifted up by the glass rod is alginate – the polysaccharide from mucoid *Pseudomonas*. It's a major constituent of seaweed, giving it its flexibility and strength to stick to stones and avoid being flushed away by the waves. Alginate is also in Flora margarine, it's in ice cream, it's in fruit and flavoured milk drinks, and it's also the E40 additive to Carlsberg lager. So, in CF, we have a very unusual polysaccharide and a pathogen, which having got into the mucosal barrier are not moved away. *Pseudomonas* alginate is also a beautiful gelling agent. Far better than seaweed alginate. It gels exquisitely in the presence of calcium. So, with the raised calcium concentration in the CF lung, the alginate from the organism, the DNA from the neutrophils and the mucosal blanket, you have a highly protective bacterial biofilm.

In the 1970s we introduced the term 'frustrated phagocytosis' to describe the protective effects of the biofilm. One thing that you do not want in the lung is a phagocytic neutrophil coming to the site of infection with its armoury and being frustrated. So we have a chronic infection and a very difficult kind of infection. I think the dominance of *Pseudomonas* in CF is because very few other bacterial pathogens can put these bits and pieces together to colonize the lung.

What is the lesson from this? Enormous amounts of work have been done on alginate genetics. This is how I came into CF as an MRC Travelling Research Fellow in Australia. The major impact of genetic studies is the justification for going in with early aggressive antipseudomonal therapy to prevent the emergence of mucoid mutants. This is probably one of the major therapeutic advances of the 1980s, thanks to Jim Littlewood, and Niels Høiby and his group in Denmark.<sup>116</sup> By the 1990s, we were aware that there were many individual strains of these

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<sup>116</sup> See, for example, Høiby (2002).



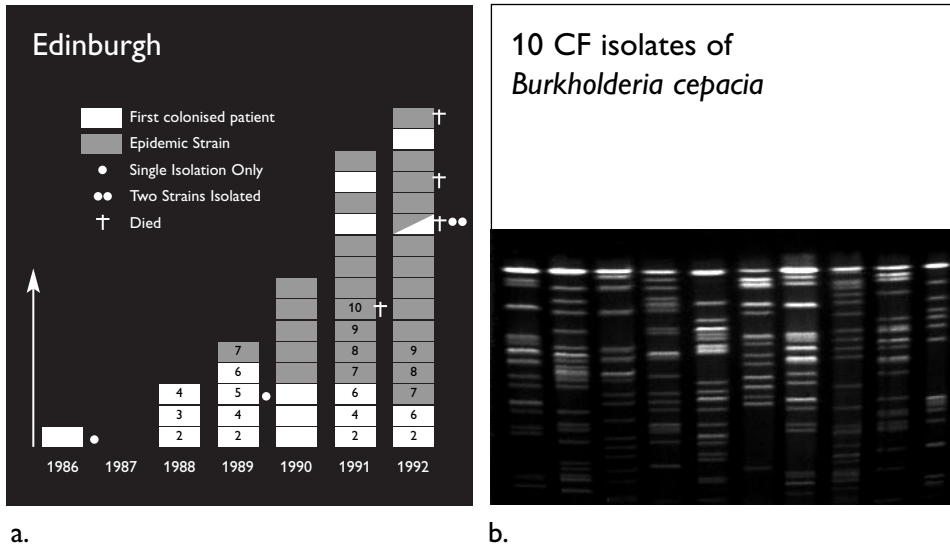


Figure 6: Epidemic spread, cross-infection control and genomic fingerprinting. Unpublished photograph provided by Professor John Govan, 2002.

microbial pathogens. However, cross-infection was not really a problem. People with CF would get their own *Pseudomonas*, keep it for life and, although camps were being encouraged and people were mixing, unlike in haematology wards and in burn wards, cross-infection was not a problem. Why not?

Perhaps *Pseudomonas* was becoming such a parasite in the lung that it was losing its ability to spread. That all changed in the late 1980s and 1990s, when we were faced with a new CF pathogen from the soil. Although many people are aware nowadays of previously sensitive, pathogenic organisms becoming resistant – for example, methicillin-resistant *Staphylococcus aureus* [MRSA]<sup>117</sup> – I want to warn you about another development, and that is naturally resistant organisms from

<sup>117</sup> Methicillin-resistant *Staphylococcus aureus* (MRSA) is a so-called 'superbug' commonly found as part of the normal skin flora. Both MRSA and *S. aureus* can occasionally enter the body through cuts, surgical incisions or indwelling catheters. Although *S. aureus* was originally sensitive to penicillin and other first-generation antibiotics, overuse of broad-spectrum antibiotics has selected for a strain of the bacteria which produces  $\beta$ -lactamase, an enzyme that degrades penicillin-type antibiotics. In the last decade MRSA has been recognized by the international medical community as a threat, particularly to immunosuppressed patients in large hospitals. See [www.netdoctor.co.uk/diseases/facts/mrsa.htm](http://www.netdoctor.co.uk/diseases/facts/mrsa.htm) (site accessed 30 May 2003).

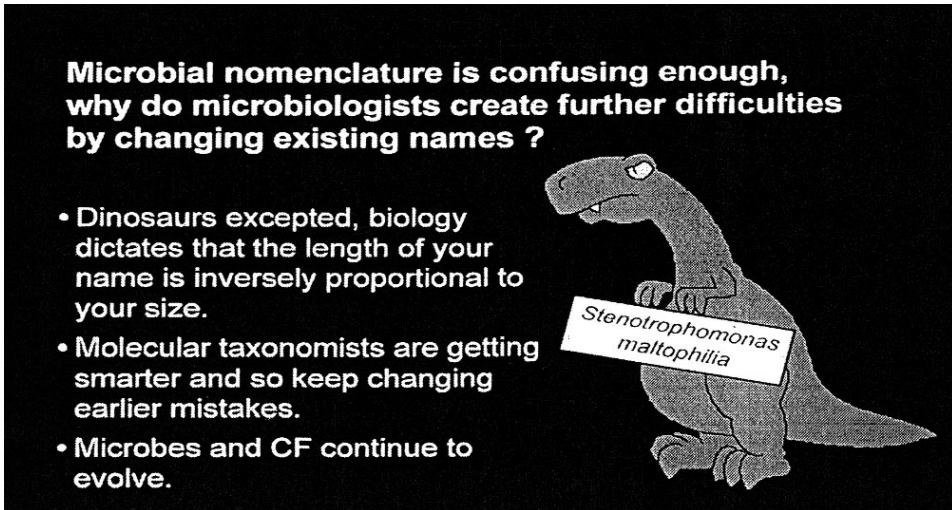


Figure 7: Emerging cystic fibrosis pathogens – Thoracic Park. Unpublished photograph provided by Professor John Govan, 2002.

the soil acquiring virulence. The paradigm of this development is the organism that we know as *B. cepacia*. In the 1990s, we had evidence that it was spreading in Edinburgh and Manchester, and between other centres (see Figure 6a). Such spread had enormous implications for cross-infection control and multicentre collaboration. We also had important developments in genomic fingerprinting of bacterial pathogens. Somebody mentioned earlier about patients falling in love. I remember when we were looking at the Edinburgh epidemic, noting evidence for cross-infection outside the clinic through social contacts. What were patients getting up to socially? In this histogram, patient 7 was described as a flirtatious Scotsman. What does that conjure up in terms of social contacts at summer camps?

I want to just introduce the idea of interdisciplinary bridging. Is there life after *Pseudomonas*? Is there life after *Burkholderia*? The organisms that I think we are going to see in cystic fibrosis now and in the future are really quite challenging. Think of the genome size of *Burkholderia* to scale. It's three to four times bigger than *Haemophilus influenzae*, twice as big as *E. coli* (*Escherichia coli*) – an enormous genome. This organism is not just resistant, but can actually use the the antibiotic, penicillin, as its sole nutrient. This isn't just resistance, this is

thumbing its nose to clinicians and microbiologists. And why do we need interdisciplinary bridges? This is a wonderfully adaptable organism. It's so metabolically active, it can break down the noxious herbicide, Agent Orange. You can use it to decontaminate soil in the preparation of golf courses, you can use *Burkholderia* to decontaminate water reservoirs. There's a lot of interest in using its antifungal properties to protect crops against fungal diseases. It's better than the best herbicides available. It's also a wonderful soil fertilizer, reducing the need for nitrogen fertilization by 20 per cent.

So we have a problem. How do you tell the good bacteria from the bad ones? This is a major challenge to microbiologists and clinicians today in CF. The more we know about organisms, the more we can try to tailor infection control to the organism's behaviour and what the patient will accept. *B. cepacia* is a good example of the increasing problem of name changes and pronunciation. You can't think of microbiology now without thinking of these 'Thoracic Parkers', as Stuart Elborn calls *Stenotrophomonas maltophilia* (Figure 7). These are natural organisms of the environment, what they do have in common is that they are all multidrug resistant. We have isolated them with more frequency now in CF. I think because of more aggressive therapy. It doesn't mean to say they are all clinically relevant.

We are never going to be able to avoid the challenge altogether of multidrug-resistant bacteria. That is evident from the most recent survey in the UK, which showed that there are more resistant strains among the CF population than there are in the *Pseudomonas* population outside CF. Fortunately, when Paul di Sant'Agnese was using penicillin in CF, acquired resistance was not in the microbiological repertoire. I can't mention Paul di Sant'Agnese without sharing an experience that occurred early in my career.

I remember as a young microbiologist at a CF meeting in Brighton in 1984, standing by my poster and being aware that the great man was around. I went behind a counter to get a drink of water. The door opened and this man came in looking like something out of the Mafia, long dark coat and a hat, 'Are the lunches being served?' he asked. I looked at him and said, 'Well, I don't know, Dr di Sant'Agnese,' because I recognized him from a photograph. I saw these British Airways lunch packs under the counter, gave one to Dr di Sant'Agnese, and one to his friend. I then walked back to my poster. The American at the poster next to me said, 'You've done it now, John, you are in deep trouble'. I said, 'What's wrong?'. He said, 'Protocol! The Royal Party are about to come round and this pair of men are sitting having their lunch and you gave it to them.'

Walker-Smith: It is very interesting historically that the presence of bacterial organisms in the soil at the end of the nineteenth century was widely believed to be important for human disease. Investigators were measuring soil temperature.<sup>118</sup> Sir George Newman, Medical Officer of Health in Finsbury, London, used actually to go out into parts of London to measure soil temperature. He observed that when the soil temperature rose there was an increased risk of infantile diarrhoea and mortality.<sup>119</sup> So it is a fascinating concept, organisms from the soil.

Govan: I think what the *Burkholderia* story has done is force us to make bridges with the soil microbiologists. We now have an international working party, which the CF Trust supports.<sup>120</sup> The International *B. cepacia* Working Group started with six of us; now 60 people are involved with input from soil microbiologists who hope to learn from us, and vice versa. I think we have got a lot to learn from the way organisms behave in the soil and the way plants protect themselves. It's a big topic.

Littlewood: Could I just ask about these plants and soil? The *Lancet* this week has got rather a disturbing paper on quite a few isolations of *B. cepacia* from soil specimens.<sup>121</sup> Is that something new? I know you get it from soil, but it looked to be a lot.

Govan: It is surprisingly difficult to prove that CF individuals acquire bacterial pathogens like *Burkholderia* from the soil. However, genomic fingerprinting shows that in some cases isolates from the soil and from patients are clonal. The other evidence is that we also had a large outbreak of sheep infection with the same *Burkholderia* that are causing problems in CF. I am concerned, but there are some rogue strains that are adapting to the human population.

Walker-Smith: That paper suggests that the human pathogenic strains are not necessarily distinct from environmental strains, which is remarkable.

Govan: I agree. The US Environmental Protection Agency had a meeting in 1999 to discuss the human hazards of *Burkholderia* biopesticides. Recent

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<sup>118</sup> Mill (1894).

<sup>119</sup> Newman (1906).

<sup>120</sup> The International *Burkholderia cepacia* Working Group. See [www.go.to/cepacia](http://www.go.to/cepacia) (site accessed 25 September 2003).

<sup>121</sup> Lipuma *et al.* (2002).

proposed legislation suggests that licensing of new biopesticides will be difficult.<sup>122</sup>

Littlewood: It does explain sporadic instances though, doesn't this?

Govan: Yes. It means that no matter how far you take segregation down the line you will always expect sporadic cases from the environment. But the *Burkholderia* in the environment may not all be harmful.

Raeburn: If you look at the microbiology of CF over the last 60 years, it's gone through the *Staphylococcus* stage, the *Haemophilus* stage, and so on, and John [Govan] has brought us up to date. There was a lot of uncertainty in the late 1960s, early 1970s, about what were really the important organisms that might be destroying lung tissue. I think it's worth mentioning David Lawson again, whom Archie Norman mentioned;<sup>123</sup> working with David was a laboratory scientist, Barry Saggars, who was doing measurements of precipitins, *Haemophilus influenzae*, *Staph* and later on *Pseudomonas* (although it was Niels Høiby who took that on). What their data seemed to show was that first there was *Haemophilus* in very small quantities, then *Staph*, and later on the *Pseudomonas*. The story of cystic fibrosis has also the story of clinical immunology interwoven with it, because how did you know that the particular bacteria you were finding in the sputum were likely to be pathogens? I recall great, furious arguments and discussions with, among others, David Lawson, as we tried to work out what was the best treatment.

Dodge: Going back to John Govan's first illustration (Figure 4), I was interested in the age at which the autopsies were carried out, because the age is in months, and the only one who had *Pseudomonas* (or *B. pyocyanea* as it was called) was 32 months old. They weren't living long enough to acquire *Pseudomonas*, they were dying from their first infection, which was *Staphylococcus aureus* in those days, and I think that's a measure of what we have seen in terms of shifting microbiology.

Govan: I think we should expect the microbiology to evolve, because the CF population is not the same and the immunology is not the same. The one constant

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<sup>122</sup> Professor John Govan wrote: 'This proposed rule [US Environmental Protection Agency. (2002)] would require persons who intend to manufacture, import or process *Burkholderia cepacia* for a significant new use to notify the Environmental Protection Agency at least 90 days before commencing the process. This would provide the EPA with the opportunity to evaluate potential human hazards in advance.' Note on draft transcript, 20 July 2003. See [www.pestlaw.com/x/law/SCR11.html](http://www.pestlaw.com/x/law/SCR11.html) for the full text of this resolution (site accessed 26 June 2003).

<sup>123</sup> See page 5.

factor in this is the expectation that microbiologists will provide black-and-white answers. In the biopesticide argument, both sides started off friendly. Then we got labelled as so-called 'medical microbiologists'. They said *Burkholderia* biopesticides do not fulfil Koch's postulates and so are harmless.<sup>124</sup> In reality it is difficult to show that any pathogen in CF fulfils these historical postulates. When I came back from Australia in 1975, and I went to my first CF meeting, they said *Staph. aureus* is the pathogen, and *Pseudomonas* is a marker of CF lung disease. I just about gave up. Then *B. cepacia* arrived and again this was considered to be just a marker. It wasn't really a pathogen. The problem is that these organisms are parasites in the CF lung. As Sandy said, it's the immune response that's really doing the damage. The bacteria are just surviving and provoking a damaging immune response. They are not toxigenic pathogens like the cholera ones.

Farrell: In the spirit of the question you posed about what was it like at the time, and why things happened in the way that they did, I want to emphasize a point about *P. aeruginosa* and its pathogenicity. I started in this field in the late 1960s, and at that time there was a raging debate about whether or not *P. aeruginosa* was a respiratory pathogen.<sup>125</sup> I remember when I joined Paul di Sant'Agnes in 1972 that he did not believe it was a pathogen until we began to treat his patients with gentamicin, and a dramatic response to this aminoglycoside, a relatively new antibiotic then, convinced him. So I really do think what happened with regard to the importance of *P. aeruginosa* came about because of the observations of clinicians about the dramatic response to antibiotic therapy, just like the penicillin response to *Staph. aureus*, that is history repeating itself.<sup>126</sup>

Littlewood: I think it's also Høiby's work on crossed immunoelectrophoresis and antibodies, correlating it with the clinical condition, wasn't it in 1977?<sup>127</sup>

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<sup>124</sup> In 1883 the German microbiologist Robert Koch (1843–1910) set out four postulates that allowed a specific pathogen to be linked to a specific disease: 1. The specific micro-organism should be shown to be present in all cases of animals suffering from a specific disease but should not be found in healthy animals. 2. The specific micro-organism should be isolated from the diseased animal and grown in pure culture on artificial laboratory media. 3. The freshly isolated micro-organism, when inoculated into a healthy laboratory animal, should cause the same disease seen in the original animal. 4. The micro-organism should be reisolated in pure culture from the experimental infection. Koch was awarded the 1905 Nobel Prize for Physiology or Medicine for his work on tuberculosis and the aetiology of disease. His postulates are still widely seen as the basis of bacterial pathology. See Sutter (1996): 581–92.

<sup>125</sup> Doggett *et al.* (1966).

<sup>126</sup> See Tansey and Reynolds (2000): 5, 31, 37.

<sup>127</sup> Høiby (1977).

Super: I wanted to give credit to our microbiologist, Fraser Williams, in Manchester, who at the end of the 1970s or in the early 1980s was already reporting his *Pseudomonas* as rough, smooth or mucoid.<sup>128</sup> There is no doubt about the increased pathogenicity of the mucoid variety and lots and lots of places have been catching up with what he was doing in helping us with our patients for years.

Walker-Smith: We had better move on now and come to Dr Maurice Super to talk on the huge subject, the search for the gene. Would you like to give us some comments about that, introducing the subject for us?

Super: Unlike haemoglobin, the gene product of cystic fibrosis was unknown. Therefore indirect methods were needed to find it, the so-called reverse genetics. Eiberg in Denmark in 1986 studied the polymorphic enzyme paraoxonase,<sup>129</sup> which occurs in two normal forms in almost equal proportions. He found that affected siblings shared the same form 90 per cent of the time and they might have inherited either form from their parents. The odds were about 10 000:1 that paraoxonase and the cystic fibrosis gene were linked. No one knew the chromosome localization of paraoxonase. John Edwards from Oxford presented a negative gene map at the Human Genome Conference in 1984.<sup>130</sup> In other words, a summary of publications of similar experiments to those that Eiberg had done, but which had been negative. Lap-Chi Tsui in Toronto used this negative map and he concentrated on the least-studied regions, and in a very short time, in fact later the same year, in 1985, he had already localized the cystic fibrosis gene to the long arm of chromosome 7.<sup>131</sup> The marker that he discovered was further away from CF than paraoxonase, but there had been other recently discovered lengths of DNA known to be on the long arm of chromosome 7.

One notable one was called the *Met* oncogene and there was another one from Professor Bob Williamson's lab at St Mary's Hospital Medical School, London, which was called *pJ3.11* and these were found to be sitting almost on top of the cystic fibrosis gene.<sup>132</sup> It was in the nature of Bob Williamson to share this information very quickly with clinicians throughout the UK. We, for instance,

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<sup>128</sup> Unpublished work.

<sup>129</sup> Eiberg *et al.* (1985); Schmiegelow *et al.* (1986).

<sup>130</sup> See Edwards (1987).

<sup>131</sup> Tsui *et al.* (1985).

<sup>132</sup> Farrall *et al.* (1986).

had been more or less expecting this discovery to be made, and had been storing samples from our patients with cystic fibrosis and their parents for about two years when the discovery was made. Immediately very accurate prenatal diagnosis became possible and also carrier detection in the siblings of the person with cystic fibrosis.

The search for the CF gene itself was now on in earnest. Unfortunately, the St Mary's team were held up by a false dawn. So between 1986 and 1989, there was a publication on a gene called *CS<sub>7</sub>*, with Estivill as the main author,<sup>133</sup> he was working with Bob Williamson at the same time. They thought that they had discovered the cystic fibrosis gene, except as I said this was a false dawn. Francis Collins from the USA realized that Lap-Chi Tsui was a name to follow and he set up a collaboration with Lap-Chi Tsui and also their brilliant biochemist, John Riordan, and he introduced a technique called gene jumping, rather than gene walking. Gene jumping is a catchy title, but in actual fact it meant you threw a type of DNA lasso along the gene and you skipped over a certain part but it could stick to a part in a place of relevance.<sup>134</sup> And by doing that they discovered an open reading frame rich in GC [guanine and cytosine] bases, which looked very much like a gene. Not only that, they also discovered that this particular open reading frame expressed itself all the way down through species, down as far as the chicken.

So in other words it sounded as if this had the characteristics of a gene. There were classic publications in *Science* in September 1989 where the structure of the cystic fibrosis gene was elucidated by Lap-Chi Tsui, John Riordan and Francis Collins,<sup>135</sup> showing the structure of the gene and also showing the major mutation, delta F508. John Riordan, a brilliant chemist, did expression studies, and I think the reason why we were beaten to the discovery of the CF gene was the fact that they were more advanced in their studies of expression of what they found. It is sad fact that we were sent a probe from Bob Williamson's lab to test against our panel of cystic fibrosis patients and we found, 'Yes, yes, it's very good, it's just as good as *KM19* and *XVC2*,' which had been discovered, and that were extremely close to the CF gene. It is sad that the particular probe that we had been sent by Michelle Ramsey from Bob Williamson's lab was in the cystic

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<sup>133</sup> Estivill *et al.* (1987).

<sup>134</sup> Rommens *et al.* (1989).

<sup>135</sup> See, for example, Tsui *et al.* (1989a).



fibrosis gene, but no one realized that they had actually discovered the cystic fibrosis gene, because unfortunately their expression studies were not as powerfully developed. John Riordan, in one of the classic papers, published a hydropathy plot looking at the amino acids, and showing which ones were hydrophobic and which ones were hydrophilic. This allowed him to propose a model for CFTR, with two trans-membrane domains, two nucleotide binding folds and a large R domain, sometimes called the 'Riordan domain'.<sup>136</sup>

This model from 1989 has stood the test of time and has helped us towards a basic understanding of pathophysiology and hopefully to the development of new treatments based on the knowledge of the structure of the CF gene, and also gene replacement treatment. So these things are on the go, although unfortunately they are in their infancy and have not been successful yet. Delta F508 in the Canadian and American population was found in about 67 per cent of CF genes.<sup>137</sup> This knowledge shot round the world and within days we were able to test our populations in many, many places. We found that in Britain the delta F508 is 75 per cent, in the Manchester area it was 81 per cent, and in some parts of Scotland it's 84 per cent.<sup>138</sup> There were other publications from Europe that showed a cline, in other words a genetic incline plane showing that delta F frequency rose the further north and west you moved in Europe. So at the time Denmark – and I think it still does – holds pride of place with 88 per cent of delta F508.

Further mutations of the CF gene were discovered quickly and Lap-Chi Tsui formed an international consortium of laboratories and centres to share their information, done very successfully indeed by e-mail. Currently, more than 1000 cystic fibrosis mutations have been described, although fortunately only 20 of them reached any significant proportion. I have looked in the programme to see where this is going to be dealt with and I don't think it is, so if I could be permitted a little bit of genotype–phenotype conversation: obviously the next big thing was how this would correlate with the clinical picture in our patients.

The original publication spoke about those who are homozygous for delta F508, which was about 45 per cent of their population, who were pancreatic insufficient, and those who were heterozygous, either with delta F and another mutation or with two different mutations, who were either pancreatic sufficient

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<sup>136</sup> Riordan *et al.* (1989).

<sup>137</sup> Kerem *et al.* (1989).

<sup>138</sup> Hendrickx *et al.* (1991).

or pancreatic insufficient. They used the terms ‘severe’ and ‘mild’ mutations. There is some truth that when there is pancreatic sufficiency the disease may be milder in certain respects, but I think adult physicians are rather offended now by the term ‘mild’, because the lung disease need not necessarily be mild at all. Nevertheless, a lot of the patients who had delta F and another mutation had very late diagnoses, so the diagnosis was more subtle. Obviously, if there is pancreatic sufficiency one might not think of the diagnosis of CF that quickly.

Other than pancreatic sufficiency and insufficiency, knowing the actual mutation was a poor guide as to what would actually happen in your patient, with one or two small exceptions. For instance there’s a Celtic gene called *G551D*, which has a negative correlation with meconium ileus. This was realized by Brandon Wainwright from Australia, who also worked in Bob Williamson’s lab at one stage. He engineered a *G551D* cystic fibrosis mouse that did not die of intestinal disease as most other cystic fibrosis mice did.<sup>139</sup> In other respects genotype–phenotype correlation generally was poor. We thought that *G542X* had a positive correlation with meconium ileus – which was also so in Toronto – it’s the second commonest mutation in Spain and there’s no correlation between *G542X* and meconium ileus in Spain. So there’s a lot that we don’t understand completely.

The last thing that I would say, is that knowing the actual genotype does not allow you to say that the patient is going to be mildly affected, or that the patient is going to be severely affected. Is there another gene, or are there other genes, affecting the way that the cystic fibrosis gene works? In a collaboration study looking at siblings born with meconium ileus and especially for siblings where one was born with meconium ileus and the other was not, Lap-Chi Tsui and his research workers looked for markers first in the cystic fibrosis mouse, in certain mice that did not die of intestinal disease, and quickly found a gene on chromosome 7 in the mouse, which seemed to be able to predict which ones were going to survive.<sup>140</sup> Chromosome 7 in the mouse turns out to be analogous to chromosome 19 in the human, and they have extended that study to humans with meconium ileus and have found indeed that you can predict from a gene on chromosome 19 as to the likelihood of meconium ileus recurring in the family. The actual gene on 19 hasn’t been discovered, and sadly no other gene

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<sup>139</sup> Delaney *et al.* (1996).

<sup>140</sup> Tsui *et al.* (1989b).

has yet been discovered that might tell us about who's going to get mild and who's going to get severe lung disease.

Walker-Smith: Thank you very much, and that's a very eloquent account of a very complex area and we are very grateful for that. Who would like to make any comments?

Geddes: I would like to comment on Bob Williamson and the great gene race, and the disappointment that was expressed before at the CF Trust at not being the winners of the race. It's probably not a fair way of looking at it, because the contributions, which that money made to Bob's lab, fertilized all the other work as well, so the contribution was large. Also I wanted to point out the three other major contributions that Bob made: he elevated the scientific level of RAMAC by insisting on high scientific standards and getting away from a sort of more anecdotal approach that had happened before, and then he attracted in a whole lot of top scientists in a very generous way. As soon as anything happened, he went out and talent-spotted and got people into the CF world, people like Alan Cuthbert and Chris Higgins, who thought they went into the CF world out of scientific interest, but actually Bob attracted them in telling them how important it was, and he made a big contribution in that way. His third contribution was that he was a fantastic enthusiast and used to attend branch meetings – he probably raised at least as much money as he spent – and his contribution was very large in the 1980s to the whole CF effort, for these reasons.

Booth: May I strongly support those comments.

Farrell: I think it would be important for everyone to know what initially motivated Lap-Chi Tsui to do this research. This was because of Bob Williamson and the conference that was sponsored in part by the CF Trust in Brighton in 1984. Lap-Chi told me last year or the year before at the European CF Conference that he had gone to the previous conference at Padre Island, Texas, sponsored by the National Institutes of Health and the US CF Foundation, and he decided that the state of fundamental research in CF was disappointing – a 'mess,' as he described it to me. He came to Brighton and he found that the same situation was evident, except for the paper presented by Bob Williamson, which convinced him that the only way to figure this disease out, to get through this 'mess' of confusing information, was with a molecular genetics approach. So it was that conference in Brighton sponsored by the CF Trust, that he regards as being pivotal.

Walker-Smith: It shows how worthwhile a scientific meeting can be.

Raeburn: One other thing about Bob Williamson is that he actively went out and spoke to the branches of the CF Trust and explained in a very, very understandable way what they were doing, and won the support of patients, parents, and the other lay people.

Norman: As a side issue, if you like, Cedric Carter came to me in about 1974 and said he had just heard a lecture from a very bright young man called Bob Williamson. I was collecting speakers for a course on advanced medicine, and wanted somebody on genetics. We got Bob Williamson to come. Immediately afterwards we, Cedric and I, said to him, 'What about getting interested in cystic fibrosis?' 'Oh, I haven't heard of that, and anyway I'm too tied up with renal problems at the present.' But he came back to us, and with the help, as usual, of Joe Levy and the Trust, we enticed him to start a small department within his laboratory [at St Mary's Hospital, Paddington, London], for which the Trust increased the funds four or five years later, so he was able to have a totally cystic fibrosis laboratory.

Dodge: I just want to make one comment, which is that we should not forget that cystic fibrosis isn't only about genes and their modification. There was a paper this year in *American Journal of Respiratory Disease and Critical Care Medicine*, which said that the single biggest factor in determining the severity of cystic fibrosis for anyone with a given genetic make-up was their socioeconomic circumstances.<sup>141</sup> I think that's one of the factors that has contributed to the increasing lifespan since the 1940s, when as Archie said, before we even had the [National] Health Service, that improving socioeconomic conditions have, I am sure, made quite a big contribution to the survival of patients.

Goodchild: You ask about diagnosis and the work at Birmingham. For me that was from 1969 until 1974. I have taken 'diagnosis' in this context to mean *confirmatory investigations*, following appropriate features by clinical history, which would vary according to the age of the child, and characteristics on clinical examination, including chest X-ray, cough swab or sputum culture for the so-called 'typical organisms' – that is, for *S. aureus*, *H. influenzae* and *E. coli* in the younger child, with *P. aeruginosa*, often of the mucoid type, in the older child.

In those days, some 15 to 20 years before the recognition of the CF chromosome in 1985 and the gene in 1989, confirmatory investigations consisted primarily of sweat tests, at least two in number, carried out by pilocarpine iontophoresis, usually on the forearm but sometimes on the back (in small babies), with the

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<sup>141</sup> Schechter *et al.* (2001).

absorptive paper left in place for at least one hour.<sup>142</sup> Prior to this, stool microscopy on three occasions, under a regime of known and adequate fat intake, was likely to have shown excessive numbers of fat globules and very low values for chymotrypsin, or none at all. For patients with positive results by sweat test and stool examination, this was usually considered sufficient for the diagnosis of CF. I remember Geoff Brown working out a methodology for detecting stool chymotrypsin in the laboratories at Birmingham.<sup>143</sup>

In the later years of these children, at any age from two or three years, an attempt was often made to distinguish the pancreatic sufficient from the insufficient (and we suspected even then, on clinical grounds, that it was likely that there were at least two different types of CF). This distinction between the pancreatic sufficient and insufficient was made by examination of a three- or five-day faecal collection for fat content (although usually without markers), ideally under conditions of known dietary intake, looking for fat absorption that was below 50 per cent. In this area, I think perhaps the laboratories were a little more cooperative in the late 1960s and early 1970s than they are now!

To return to the sweat test for a minute, values were positive if they were greater than 60 mEq/l, for both sodium and chloride, with doubts raised and further tests if sweat weights were less than 100mg, if electrolyte values for sodium and chloride were between between 50 and 60 mEq/l, or if these measurements differed from each other by more than 30 mEq/l. In babies of less than one year, values greater than 40 mEq/l were regarded as suspicious.

Equivocal results, for sweat tests in particular, required duodenal intubation for pancreatic function tests, which was a considerable ordeal for the patient, not to mention the attendants, taking several hours. Stomach and duodenum were intubated separately but there was no provision at that time for the infusion of a non-absorbable marker solution, via a third tube, situated approximately at the Ampulla of Vater; this was a modification introduced later, in order to obtain a more accurate measurement of fluid volume, produced during continuous intravenous infusion with cholecystokin/secretin, in that order.<sup>144</sup> Hormonal stimulation was by sequential shots of intravenous pancreozymin and secretin in that order. For the majority of CF patients, duodenal fluid was scanty in volume, sticky in nature, with a pH of less than 7; enzymes and bicarbonate were present

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<sup>142</sup> Gibson and Cooke (1959).

<sup>143</sup> Brown *et al.* (1988).

<sup>144</sup> Kopelman *et al.* (1988).

in negligible quantities, or undetected. In some 10–15 per cent of CF patients (no doubt those who would be properly termed pancreatic sufficient in later years, with the appropriate genotype) enzyme concentration was normal, but bicarbonate concentration was very low and the juice was still mucus-like.

Walker-Smith: It's interesting how difficult it became to get a faecal fat done. When I came to the Queen Elizabeth Hospital for Children, Hackney Road, London, in the 1970s I found faecal fat estimations were no longer being done. They would have been at the Children's Hospital in Sydney. I remember I actually crossed swords with Barbara Clayton about that. She refused to estimate faecal fats, except in the most exceptional circumstances. I suppose it's understandable for laboratory workers not wanting to work with faeces in the labs. Who would like to make any further comments about diagnosis? Dr Farrell, I cut you off a little bit earlier when you were talking about diagnosis in the early days.

Farrell: I think we all know the story, but I should like to comment on it just because of the nature of this Witness Seminar. It was back in August of 1948 that Paul di Sant'Agnese was taking care of Dorothy Andersen's patients while she was here in England on vacation. At the time this large number of patients was being followed at Babies' Hospital, Columbia University, New York, during a very intense heatwave, Paul observed that many of the children admitted for heat prostration, most of whom died, had 'cystic fibrosis of the pancreas' as it was called at that time. He made the very astute observation that there must be something about this disease that was leading to the depletion of serum electrolytes.

He then collaborated with Bob Darling. In April 1952 two children with cystic fibrosis who were actually teenagers, and two children who were matched controls, were placed in a constant temperature room, and sweat was collected for measurement of electrolytes, principally sodium at the time. The difference was so great between the two with cystic fibrosis and the two others, that, as he said to me many times, Paul never needed a statistician to analyse the data; and, in fact he never needed a statistician to analyse any of the data he obtained from measuring sweat electrolyte concentrations because the difference is so striking. Paul also pointed out that there were three major dividends of this investment in research. First, another heatwave came just a few months later, in June 1952, but this time they were prepared and they brought the patients in to give them additional salt to prevent death. Second, this improved method of diagnosis with the sweat test led to the identification of patients that had chronic lung disease, but pancreatic sufficiency; in other words they had negative duodenal intubation studies and this was very revealing. Finally and ultimately, Paul's clinical research

observations discovered the basic defect in cystic fibrosis, that is the ion channel or chloride channel defect, which of course is the most significant long-term implication. I think it's remarkable that the question arose in Paul's mind about electrolytes. What would we do if there wasn't a sweat test? Would we be better off without knowing about sweat electrolyte concentrations? It seems incredible in retrospect that someone would have the interest to determine sweat electrolytes back in 1952.

Cuthbert: Perhaps I didn't quite make it clear why I suggested we might have been better off without the sweat test, and that was that it led to the domination of thinking that sodium was the important ion – as you said yourself, the concentrations of sodium were measured. I just wonder if we would have got to the chloride channel effect, maybe ten or so years earlier, if the sweat tests hadn't existed. That was my point about whether we would now be better off. It's not a question we can answer.

Norman: I just wonder whether we should ask Jim Littlewood or John Dodge to mention the value or not of neonatal screening.<sup>145</sup>

Littlewood: I think it's fair to say that people who have been involved with cystic fibrosis on the ground see no problem about neonatal screening being valuable, and the various studies have all failed to show a great deal until recently. We will come to Phil's in a moment, because the treatment, particularly the Wales–West Midlands study, which the CF Trust funded, was given for many patients at local district hospitals, they didn't have a high standard of treatment. So I think the general feeling now is that screening with centre treatment is great; if you don't have centre treatment, screening is not so valuable.

But battling away over the years, I am sure you know because you [Archie Norman] rang me one night asking me why we weren't screening. I don't know whether you remember that, but you asked, 'Why?' You had read something in the newspaper about that. You said, 'What are you doing at the Trust, you should be getting this screening going?' Anyway, we achieved national neonatal CF screening only after about a six-year battle and after Rosie Barnes had involved politicians. I think the final little thing that tipped over the national screening committee to advise the Minister to recommend neonatal screening was the study from Wisconsin, the very long study, which showed undoubted nutritional benefit out of, I think, 13 years, wasn't it really?<sup>146</sup>

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<sup>145</sup> For a history of neonatal intensive care in the UK, see Christie and Tansey (2001). See also note 148.

<sup>146</sup> Farrell *et al.* (2001).

Most of the clinicians are now absolutely convinced that neonatal screening is right. It would be absolutely horrendous to go back to no screening. [Walker-Smith: It's really an argument for special centres again, so this is one of the great themes, the absolute vital need for care in special centres.] That's also being looked at in Scotland where they want to make sure the services match up to standard before screening is introduced.

That is going to be one of the subjects of a meeting that Kevin Southern over there is organizing in July, the actual nitty-gritty procedure following a positive result, who tells them the parents, what do you do? Who looks after the patients? Who gives the initial advice and talks to the parents? Is it somebody who has seen numerous cases before, a nurse that's done it many times before, or is it this team at a district general hospital, who have seen this once in a blue moon? It's very, very difficult, because although saying that the battle has been won about centres, it has not been won in this country. There are still hospitals who do not see the need and it was as late as 1990 when a senior academic in this country said, 'I don't know why Jim Littlewood makes all this fuss, any paediatrician worth his salt (appropriate word) can look after cystic fibrosis'.

Walker-Smith: You find that across the board in Britain. But what about Kevin Southern – would he like to make a comment?

Littlewood: We are right behind it, all the clinicians in the country are right behind it. The Trust circulated them. Unanimous, every paediatrician dealing with CF was right behind them, very strongly, or strongly believe in it. The Government were bombarded with these surveys.

Dr Kevin Southern: I completely agree with Jim about the centre care, but for children who live 100 miles away from a centre, I think the key is that there is contact with a centre, and I think a local paediatrician can provide a very good service in our experience, if they work as part of the bigger team. We do undertake good shared care with many centres throughout the north-west.<sup>147</sup>

Littlewood: Kevin, can I just say, without wishing to be rude, there is no scientific evaluation of shared care? I just throw that in to be really cantankerous. Although I agree with what you said.

Walker-Smith: You mean as opposed to general practice care, you mean shared care versus general practice care?

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<sup>147</sup> See, for example, Simmonds *et al.* (1998); Littlewood (2000).



**Littlewood:** There is confusion there – I am glad you raised that point. We are talking about CF centre–local hospital, similar to obstetrics, with a GP in hospital. We are not talking about shared care with the GP.

**Goodchild:** I agree about the benefits to be obtained from newborn screening having suffered over the years through the Wales–West Midlands screening survey, which seemed to go on for ever, but which was ultimately successful in achieving its objective of obtaining newborn CF screening (for Wales initially). However, I am sitting next to Maurice Super, and I should like to say that one of the benefits of newborn screening is the opportunity for cascade screening,<sup>148</sup> which is one of the most efficient ways of recognizing the CF carrier, not only within the known family, but also within the community. I think that's very important.

**Barnes:** We are delighted that newborn screening is going to be introduced into the UK and we are very, very pleased that the Wisconsin study did tip the scales in terms of the decision being made. We did a huge amount of work over many years and one thing that we did was a study of the parents of children who were born between 1994 and 1998 with cystic fibrosis, which we presented to the then Minister for Health, Yvette Cooper, and I think it was helpful that she was pregnant at the time, because it focused her mind a bit.

The one story from that survey which really stuck in our minds, is that of a mother who had lost her child to cystic fibrosis at the age of 22 months or thereabouts, only received the diagnosis at the time of death, and was well advanced in a second pregnancy when this diagnosis was made. As it was so late in the pregnancy, where she would have automatically terminated the pregnancy, having had the experience she had had of many months of a very, very sick baby, she was referred to a CF centre who gave her a lot of reassurance and encouraged her to proceed with the pregnancy. At the time of our survey, her second baby was the same age as the first baby when it died, and she made the point that the disease in the second baby was virtually nonexistent, to all intents and purposes, compared with the disease in the first baby, who had been under-treated, and we highlighted that case to emphasize the point. I think there were those kinds of instances that came through time and time again, which, on top of the statistically significant evidence from Wisconsin, really did make people take note.

**Dodge:** I would just like to make a comment on the historical context of both the Wales–West Midlands screening study and also on centre care. As far as the

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<sup>148</sup> Super *et al.* (1994). See also Elliott (1991); Super (1992).

Wales–West Midlands study was concerned, we alternated and screened all the babies born in Wales one week and the West Midlands the second week, alternate weeks, so that half the population was unscreened. We wanted to put the patients picked up through screening into the regional clinics, and although the CF Trust eventually funded the study, the original application was to the MRC, and Peter Weller and I went to the MRC to discuss this project with them, and they said, ‘Oh, that’s no good, because how will you know whether it’s the early diagnosis through screening or the centre care, if your patients who are screened do better?’ There wasn’t really an answer to that. So that was imposed on us at that stage.

The second thing was the context of that time. Jim will remember that original report of the British Paediatric Association Working Party, showing that patients in centres did better than those who were looked after in ones and twos in general hospital clinics around the country, was initially rejected by the British Paediatric Association.<sup>149</sup> They refused to accept our recommendations until we toned them down. I had the experience of meeting the BPA council and trying to talk the report through, and being told by my colleagues, ‘You’re taking all our interesting patients away from us’. I said ‘Well, this isn’t about paediatricians’ job satisfaction, this is about where the CF patients will get the best care’. But it was a pretty hostile atmosphere and we had quite a problem getting it through, and you, Chairman, were one of the people who helped, because if you remember it was also discussed at the Royal College of Physicians’ Gastroenterology Committee, accepted and endorsed, and I should say also by the British Thoracic Society.<sup>150</sup> That’s a historical background to some of these things, and I am sorry to hear that attitudes have still not changed, at least in some places.

Walker-Smith: I now would like to be very provocative in a general way. I think paediatric specialists in gastroenterology as well as paediatric specialists in other organ-based disciplines have lost out by the creation of the new Royal College of Paediatrics and Child Health. These paediatric specialities sat more easily in the Royal College of Physicians, where we were plugged in to fellow specialists, in the case of paediatric gastroenterology into the gastroenterology group. It was self-evident in the Royal College of Physicians that speciality care was essential. Within the Paediatric College, sadly in the UK in the year 2002, I think there is not always such an awareness of the importance of a speciality within paediatrics.

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<sup>149</sup> Report of UK Cystic Fibrosis Survey 1985 to British Paediatric Association, Royal College of Physicians of London, British Thoracic Society. Unpublished, but main findings summarized in Anon. (1988).

<sup>150</sup> See [www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk) (site accessed 30 May 2003).

**Super:** Just a brief comment, having helped to run peripatetic clinics and to support what Kevin Southern was saying, and that is because of this really powerful feeling among paediatricians that they wish to look after their patients with cystic fibrosis, one has to work with them. I think the big advance has been that in each district hospital at least they are now selecting one colleague to look after all the patients with cystic fibrosis and to run the shared care with the big clinic.

**Littlewood:** I still feel that shared care has not been scientifically evaluated and I am concerned that as the treatment regimes become more clearly delineated by documents coming out, perhaps from the CF Trust, and the children being in much better health, there is an increasing reluctance to evaluate shared care and it's all right paying lip service to shared care, but there are problems when you get down to the nitty-gritty, the everyday management and the lack of CF teams, particularly relating to medical staff leave and home IV treatment.

**Super:** It does not need to be lip service. It can be done properly and the CF Trust can take a lead in making sure that it is done properly. There is a really powerful feeling among the paediatricians who don't want to send all their patients with cystic fibrosis to a big centre, and one has to learn, to find a way to work with that.

**Littlewood:** I have been trying that for 20 years, Maurice, running a shared-care service. Some are excellent, and I know that you have ones in your region that are excellent, but there are still many who do not believe that they need a CF centre. I can name three cities in Yorkshire.

**Webb:** It's just a curious paradox, as an adult CF physician, we don't share our patients with anyone at all. The reason is simplistic actually, it's because the paediatricians refer them directly to our centre, there are actually no other respiratory physicians on the whole who are skilled in CF care. If you turn it round again, it's a curious paradox. We have so many patients in our centres now as adults, we don't know what to do with the increasing numbers, and so we are going to lose quality at the expense of quantity. We actually want more centres, but aren't quite sure how to achieve it. So the circles change, but we don't share our patients with anyone.

**Humberstone:** Looking at the centres, I am in a situation where my centre is approximately 100 miles away from me, and my local hospital has said, 'Really, looking at the treatment you need, even for everyday care, we are unable to

provide that' – so where do I go? I don't actually want to go into hospital because of the risk of cross-infection, so I think we have also got to look at something which hasn't really been mentioned yet: treatment in the community, in your own home. This is day-to-day care. We have got to look at community care. When I speak to the community people, they say, 'Chest physio is not in the paperwork' and they appear uncertain and insecure. It's not in the paperwork because – yes – cystics weren't living long enough at the time the papers were drawn up. But cystics are, and are going to be, living longer and we have got to take away the age barrier which would change the view of people treating cystics. I get very annoyed. Nihilism came out earlier this afternoon about age, and it is a constant problem.

Somebody asked me at lunch two months ago (and it's the first time it hit me), when they asked a younger colleague (who is not CF), 'What's your ambition?' The colleague turned round and said 'My ambition is...' She then asked me what my ambition was, and I thought to myself that I really had no ambition because I was supposed to have died when I was 16, and then it was 18, and so it has gone on – even now at the age of 38. If a cystic isn't strong enough to say, 'Well, there's a first time for everything,' it is extremely difficult to live through. There is a first time for everything, good and bad, and I get very annoyed when people fail to think that how they treat the patient now can affect the patient in the future.

The other day I was at Guy's, where the 'doctors of the future' were present. It was a training evening where they have to diagnose what disease the patient has. One student doctor examined me, and was asked what her diagnosis was. In passing she said, 'Well, I ruled out cystic fibrosis because she's too old.' I sat there and thought, 'This is the young doctor of today, and she's going out on to the wards and she is going to encounter CF in adults.' From a patient's point of view, there are a number of sensitive issues. We have also got to reach out to the teaching hospitals and start with the basics, with the doctors who will take care of you. Somebody asked me once, 'Well, can't you tell the doctors?' If you are in hospital and that doctor is looking after you for two weeks or more, especially the young doctors, they do not take advice, and patients really do not want to upset them. I try to say, 'I want to help you. I have CF and I have lived with CF for 38 years, so please listen to me,' and so on. While we have centres, we have got to get to local hospitals and to all medics as it's a constant problem. We have to get out to the local hospitals, to GPs and care staff. What do I do?

I have recently had two years' bad health because I have had no support for my physio needs. I think that if they had kept the physio going I would be OK.

Now, I know that I am referring to my own experience, but there must be other cystic fibrosis patients out there too in a similar position. Now, they say parents tend to do the physio. My father is aged 70 and still he says, 'Tracy, do you need physio?' He lost an elder daughter to CF, he has had two hip replacements, arthritis of the knees, four discs worn in his spine, and this is the person offering to do my physio! We have got to get out there and look at the community. CFs are living longer, so let's get out there and give them care. I do not want my parents involved in my care. I can (and do) live on my own but I need support from community physios when I need it. I would like my parents to go to their graves knowing that I am cared for.

When I am seriously ill and I think there's a problem beyond the knowledge of the community people, then I go to my centre. But, to be honest, to put yourself into local hospitals is pointless, life-threatening and very frustrating.

So there are a number of things to be done. Change the view of people – cystics are living longer. When people give averages and facts about the treatment of the condition, it's a new condition and the facts are fairly new when it comes down to papers and statements, so it is better saying, 'We have only been collecting the information over so many years, so we can only tell you this is based on *recent* research.' It is such a dead-end job for carers and patients when, at 38, that's it. I know through reading international newsletters that people do live longer. I can tell you all now that medical care is not always as good for older patients. In fact, you tend to feel that doctors are thinking, 'Well, she's only going to live to whatever age, so what's the point?' I've noted quite a few things from others' contributions.

Walker-Smith: I think you have made an eloquent testimony about community care being particularly important. Then, of course, I think there is a responsibility of specialists in a centre to achieve the community care that is right for you. Also, the other observation of why young doctors should be encouraged to listen to patients with experience. That's rather a criticism of young doctors if they don't listen to the patients. We must train young doctors to be more receptive perhaps.

Littlewood: I have enjoyed very much hearing all these comments, and Tracy Humberstone's. I think, quite honestly, it is a hopeless task to train everybody who is going to deal with cystic fibrosis throughout any small hospital in any part of this country. Every difficult serious disease now is dealt with, should be dealt with, by teams of experts who see hundreds of patients, and what I have heard today has strengthened my view that CF centre care, really rigid, not

perhaps all attendances, but not just lip service, should be available for everybody in this country. Amateurism should be finished now in managing these diseases.

Walker-Smith: Now we have two last comments before we conclude today and you are first, David.

Stableforth: I would like to speak up strongly for shared-care medicine for cystic fibrosis in adult patients. I have heard a lot of opposition to it here today. I work in a big region, 40–50 miles in diameter. You cannot expect patients to travel that sort of distance on a daily basis, for their day-to-day treatment needs. Exclusive care by major centres is absolutely fine, but in the West Midlands we have a small network of people who are experts but who look after small numbers of patients. Some physicians in the West Midlands find that shared care between paediatric and adult centres works well where there are interested and enthusiastic specialists.

I think that we should encourage the development of shared-care schemes, because there are going to be more cystic fibrosis patients and more people in the dilemma of the young lady patient who spoke previously. I think the way forward is going to be to develop this.

Raeburn: Unlike Jim, I didn't think that what Tracy said was making the case for centre care. I think what she was doing was making a case for professionals listening to the patient, and developing a programme of care with them, wherever they live, so that the best of the local resources and the best of the centres can be applied to that individual's healthcare.

Southern: Obviously centres that specialize in cystic fibrosis care have got to lead the way. I have really enjoyed today, like Jim, and what's come through to me has been the enormous enthusiasm and warmth that you all have. I was born in 1964, so hardly qualify to be here. Rather than focusing on the specialist centre versus shared care, which I believe can be done well and properly, with enthusiasm, I would like to finish on the point that maybe something that we have learnt over the last 50 years is that we need to listen to the patients more. I get the slight impression from what some people have said that it's been an experimental 50 years, and that maybe at times the patients haven't been listened to. I hope that patients have greater input into the partnership that we are hoping to forge over the next 50 years.

Duncan-Skingle: I would first like to reassure Tracy that there are many patients in their 40s, 50s, 60s, and our oldest is 72, so hopefully she will have a long and productive life. I think all of us have an uphill struggle as healthcare

professionals, trying to fulfil what patients perceive as their needs and rights. We must listen to patients, that's the way we have always learned, and is the reason why a lot of things have developed in the way they have today. I think community care is an excellent idea, and that home care from specialist centres could be developed further. In the future, nurse-led clinics for the patients could be the way forward, especially for the less seriously affected patients that are reaching adult life. It is a challenge for us all, in the future.

**Madge:** I was just going to remind people about the home-care service that's currently spreading throughout the country from the top of Scotland, right down into the south-west, where specialist centres are providing a home-care service for the day-to-day needs of their patients, and encouraging community nurses who are not necessarily CF experts, but they are getting training to look after their CF patients for their home care, rather than having to travel to centres quite so regularly.

**Humberstone:** The one point I was trying to make earlier – yes, I do agree with the need for centres but there has to be a package put together – knowledge, education, coming through from patient to GP to local hospitals to the CF centres, and there has to be communication between all four. There has to be something set up so that you have the transition from birth onwards, because the GP is not educated in CF so, straightaway, the person who is your closest and first point of call does not know. I am speaking from my experience and from what I have heard over the years.

So yes, I agree that the centres should be there but I have to say that from a patient's point of view, (and I have always kept myself well), I have isolated myself from centres; I absolutely hate going to the centre and will only go there if I have to. It's nearly always me phoning up to say, 'I need IVs', but I will not go there for routine checks for fear of cross-infection. And I have a good centre that isolates cases.

Until the knowledge is greater than my centre, I would not go to the Brompton because there are too many cystic fibrosis patients there. So, have smaller centres that are experienced and more local to people in my opinion, and I think that is the way forward, working with the community team to keep you in your own home and also to break that barrier, because having had a partner who turned round and said, 'Tracy, I am sorry, I am forever seeing you as a sick person'. Why? Because he did my physiotherapy every night – that has to be considered too. The way forward is also looking at adult problems to prepare for the younger generation. If you do not lift the age barrier, the problems will not go away.

Walker-Smith: I am sure that one fundamental problem you [Tracy] raise is the problem of communication within the National Health Service. There is often inadequate communication between the consultants in the hospital centres and the periphery (i.e. the community and GPs).

Humberstone: The communications problem has been there for years and it has not improved, except in the centres. One thing I would like to say is 'thank you' to all those dedicated people who have worked on CF over the years and particularly through the years when CFs were not surviving long. So I thank everyone in this room that has worked on CF and ask them please to continue.

Walker-Smith: We are all extraordinarily grateful to all of you witnesses here today, who have made such a memorable contribution. The only thing I can say at the end: so much has been done, yet there's so much to be done. Thank you all very much.

Tansey: On behalf of the History of Twentieth Century Medicine Group, I would like to thank you all very much for participating in this afternoon's Witness Seminar, and also to thank John for his excellent chairing of this meeting.



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## Biographical notes

**Professor Dorothy Andersen** (1901–63) graduated in medicine from Johns Hopkins Medical School, Bethesda, in 1926. In 1935 she joined the Babies' Hospital, New York, as an Assistant Attending Physician and worked there until her death. From 1952 she became Chief Pathologist and in 1958 she was made Professor of Pathology. In addition to cystic fibrosis her other research interests included cardiac malformations and glycogen storage in infants.

**Professor Charlotte Anderson** FRACP FRCP (1915–2002) set up Australia's first cystic fibrosis clinic in 1953 and in 1958 established a reliable method of sweat collection. She became Professor of Paediatrics at the University of Birmingham and Director of the Institute of Child Health in 1968. See Gracey (2002).

**Professor Anthony Axon** FRCP (b. 1941) has been Consultant Physician and Gastroenterologist at Leeds General Infirmary since 1975, and Honorary Professor of Gastroenterology at the University of Leeds since 1995.

**Mrs Rosie Barnes** (b. 1946) has been Chief Executive of the Cystic Fibrosis Trust since 1996, having been Director of the health research charity, WellBeing, for four years. She has also served for nine years on the Gene Therapy Advisory Committee and was SDP Member of Parliament for Greenwich between 1987 and 1992.

**Dr Lewis Barness** (b. 1934) was Professor and Chair of the Department of Pediatrics at the University of South Florida in Tampa (1972–88), and was Visiting Professor at the University of Wisconsin, Madison, from 1987–92. He received the John Howland Award in 1993 and a Lifetime Achievement Award in Medical Education from the American Academy of Pediatrics in 1995.

**Sir John Batten** KCVO FRCP (b. 1924) was Physician to the Queen from 1974 to 1989, and President of the Cystic Fibrosis Trust from 1986 to 2003.

**Dr Martin Bodian** (1910–63) qualified in medicine in 1934 from the University of Vienna and in 1946 was elected morbid anatomist at the Hospital for Sick Children, Great Ormond Street, London. See Anon (1963).

**Sir Christopher Booth**

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

**Dr Richard Boyd**

(b. 1945) has been Medical Tutor at Brasenose College, Oxford, since 1980 and works in the Department of Human Anatomy and Genetics where he carries out research on membrane transport in epithelia. He trained in Dennis Parsons' laboratory from 1971 to 1975.

**Professor Cedric Carter**

FRCP (1917–84) was Director of the MRC Genetics Unit from 1964 to 1982. He founded the UK Clinical Genetics Society in 1972 and, with John Fraser Roberts, established the first genetic counselling clinic in Britain at the Hospital for Sick Children, Great Ormond Street, London, in 1957. See Wolstenholme (1989).

**Professor Francis Collins**

(b. 1950) has been Director of the National Human Genome Research Institute, Bethesda, Maryland, since 1993. He was Assistant Professor of Internal Medicine and Human Genetics, Ann Arbor, Michigan, from 1984 to 1988, and Chief of the Division of Medical Genetics in the Department of Internal Medicine and Human Genetics, Ann Arbor, from 1988 to 1991.

**Dr Steven Conway**

FRCP FRCPCH is a consultant in paediatrics and infectious diseases at Seacroft Hospital, Leeds, with a special interest in paediatric infection, immunizations and respiratory medicine.

**Dr Douglas Crozier**

was Director of the Cystic Fibrosis Clinic at the Hospital for Sick Children, Toronto, in the 1960s.

**Professor Alan Cuthbert**

FRS FMedSci (b. 1932) was Shield Professor of Pharmacology in the University of Cambridge from 1979 to 1999 and Master of Fitzwilliam College, Cambridge, from 1990 to 1999. He was Editor of the *British Journal of Pharmacology* from 1974 to 1982 and Foreign Secretary of the British Pharmacological Society from 1997 to 2001. Currently he is President of EPHAR (Federation of European Pharmacological



Societies) and works in the Department of Medicine at Cambridge University.

**Professor Paul Emilio Artom di Sant’Agnese**

(b. 1914) was paediatrician in the Presbyterian Hospital, New York, USA (1944–59) and was Chief of the Pediatric Metabolism Branch, National Institute of Arthritis, Metabolic and Digestive Diseases, National Institutes of Health, Bethesda, USA, from 1959.

**Mrs Mary Dodd**

FCSP (b. 1944) worked at the Manchester Regional Paediatric Unit in the 1960s. She started the Manchester Adult Cystic Fibrosis Centre with Professor Kevin Webb in 1982, and since then has worked there as a consultant physiotherapist.

**Professor John Dodge**

CBE FRCP FRCPE FRCPI FRCPCH DCH (b. 1933) has been Emeritus Professor of Child Health in the Queen’s University, Belfast, since his retirement in 1997, and is currently Honorary Professor of Child Health at the University of Wales at Swansea. He set up regional cystic fibrosis clinics in Northern Ireland (1965) and in Cardiff, Wales (1971). He was Chairman of the Scientific and Medical Advisory Committees of the International Cystic Fibrosis

(Mucoviscidosis) Association from 1992 to 1996, and has chaired numerous working parties on CF for the World Health Organization.

**Mrs Frances Duncan-Skingle**

(b. 1939) was the first CF Clinical Nurse Specialist at the Royal Brompton Hospital, London, in 1980, until her retirement in October 2002. She initiated the National CF Specialist Nurses’ Group in 1988 and CF Home Care Services in 1990. Her interests include raising the clinical standards of education to nurses and clinical services to CF patients.

**Professor Stuart Elborn**

FRCP has been Consultant Physician in Respiratory Medicine at Belfast City Hospital and Honorary Senior Lecturer at Queen’s University, Belfast, and is Visiting Professor of Health Sciences at the University of Ulster.

**Professor Robert Elliott**

FRACP (b. 1934) was Professor in the Department of Pediatrics, School of Medicine, Auckland University, New Zealand. He was awarded the Companion of the New Zealand Order of Merit in 1999 and is considered to be one of the world leaders in diabetes and autoimmune-related research.

**Professor Guido Fanconi** (1892–1979) graduated from the University of Zurich in 1918. From 1929 he was Director of the Kinderspital, Zurich, and Professor of Paediatrics at the University of Zurich. In addition to his description of cystic fibrosis Fanconi pioneered the use of intravenous fluids as a treatment for dehydration, studied calcium metabolism in rickets and took a keen interest in child health in the developing world. In 1947 he was elected President of the International Paediatric Association. See Anon. (1979); Zellweger (1980).

**Dr Philip Farrell** (b. 1943) has been the Alfred Dorrance Daniels Professor of Diseases of Children, Dean of the Medical School and Vice-Chancellor for Medical Affairs at the University of Wisconsin–Madison. After completing his MD and PhD (biochemistry) in 1970, he trained under Dr Paul di Sant’Agnese at the National Institutes of Health, in the 1960s. He moved to the University of Wisconsin–Madison in 1977 as Director of the CF Center and has since studied the epidemiology of cystic fibrosis as part of a 20-year investigation of the benefits, risks, and costs of early diagnosis through DNA-based neonatal screening.

**Sir Alexander Fleming** Kt FRS FRCS FRCP (1881–1955) was Professor of Bacteriology at St Mary’s Hospital Medical School, London, from 1928 to 1948, and later Emeritus Professor of Bacteriology at the University of London. He shared the 1945 Nobel Prize for Physiology or Medicine for his work on the discovery of penicillin. See Matthews (1988).

**Professor Duncan Geddes** FRCP (b. 1942) has been Professor of Respiratory Medicine, Imperial College School of Medicine since 1996, and Consultant Physician and joint Director (with Professor Margaret Hodson) of the Adult CF Service at the Royal Brompton Hospital, London, since 1978. His research interests include CF gene therapy, on which he worked initially with Professor Bob Williamson and subsequently with Professor Eric Alton.

**Professor Sydney Gellis** (1914–2002) established the first paediatrics department and first birth defects centre at Tufts University School of Medicine, Boston, USA (1965–91), later Professor Emeritus of Pediatrics and Chief of Pediatrics. His research focused on growth hormones, seizure control, birth defects, hepatitis, autism and newborn jaundice. See [www.medicine.tufts.edu.oit.news021218.htm](http://www.medicine.tufts.edu.oit.news021218.htm) (site accessed 6 June 2003).

**Dr Mary Goodchild** (b. 1937) was Associate Specialist in Cystic Fibrosis in the Cystic Fibrosis Unit, Department of Child Health, University Hospital of Wales, Cardiff, from 1984 to 1997. She was HP to Dr Winifred Young at the Queen Elizabeth Hospital for Children, London, in 1963; Research Fellow to Professor Harry Shwachman at the Children's Hospital Medical Center, Boston, MA (1965–66); and CF Fellow to Professor Charlotte Anderson at the Children's Hospital, Birmingham, (1970–75). Her clinical and research interests include CF liver disease and bile acid metabolism (the subject for her 1980 Birmingham MD); genetics; allergic bronchopulmonary aspergillosis; *Burkholderia cepacia*; and newborn screening.

**Professor John Govan** DSc (b. 1942) is Professor of Microbial Pathogenicity at the University of Edinburgh Medical School. Since 1975, his research has focused on the microbiology of cystic fibrosis lung disease. He has been a member of the Cystic Fibrosis Trust's Research and Medical Advisory Committee since 1989.

**Professor Christopher Higgins** FRSE FMedSci (b. 1955) has been Director of the MRC Clinical Sciences Centre, and Professor and

Head of Division at Imperial College School of Medicine, London, from 1998.

**Dr Margaret Hodson** FRCP FRSM is Reader in Respiratory Medicine at the Cardiothoracic Institute, University of London, and Honorary Consultant to the Royal Marsden Hospital, London.

**Professor Niels Høiby** is Professor and Chairman of the Department of Clinical Microbiology and the Danish Cystic Fibrosis Centre at the University of Copenhagen.

**Miss Tracy Humberstone** (b. 1964) and her elder sister Tina Eder (1957–80) were born with cystic fibrosis. Care from birth has enabled Tracy to maintain reasonable health. Since 1989 she has worked for management consultants in health, administrating various medical projects.

**Dr Peter Hunter** (b. 1938) qualified from Middlesex Hospital, London, in 1963, and was Consultant Physician at the Royal Shrewsbury Hospital, specializing in endocrinology, from 1974 to 1993. From 1994 to 1997 he read Pharmacology at King's College London, as preparation for research on the history of drug discovery in the modern era.

**Dr Anthony Jackson**  
FRCP FRCPCH (b. 1918) was a consultant paediatrician at the London Hospital and worked in a specialist cystic fibrosis clinic with Winifred Young at the Queen Elizabeth Hospital for Children, East London, in the 1960s. He was Chairman of the Research and Medical Advisory Committee of the Cystic Fibrosis Trust from 1984 to 1994.

**Professor Charles Everett Koop**  
FAMA (b. 1916) was Surgeon in Chief at the Children's Hospital of Philadelphia from 1948 to 1981, and Professor of Paediatrics at the University of Pennsylvania Medical School from 1959 to 1985. He was Surgeon-General of the USA from 1981 to 1989. Between 1959 and 1985 he edited the *Journal of Paediatric Surgery*.

**Mr Joseph (Joe) Levy**  
was Chairman of the Cystic Fibrosis Trust from 1964 to 1984. See [www.cfww.org/pub/6JLevy-final.pdf](http://www.cfww.org/pub/6JLevy-final.pdf) (site accessed 24 February 2004).

**Dr James Littlewood**  
OBE FRCP FRCPE FRCPCH DCH (b. 1932) was a consultant paediatrician at St James's University Hospital in Leeds from 1968 until his retirement in 1997. In 1975 he introduced neonatal CF screening and started a CF clinic in Leeds –

one of the first in the UK to be recognized and funded by a Regional Health Authority as providing a tertiary referral service for children with CF in 1983. Since 1995 he has been Chairman of the UK CF Trust's Research and Medical Advisory Committee and in 2003 became Chairman of the UK CF Trust.

**Dr Anita MacDonald**  
(b. 1956) qualified from Leeds Polytechnic with a BSc in Dietetics in 1979. She worked as a paediatric dietician from 1980 to 1987 at St James's Hospital, Leeds, working with CF children. Between 1987 and 2003 she was Head Paediatric Dietician at Birmingham Children's Hospital, continuing to work with CF children until 2001.

**Ms Su Madge**  
RGN RSCN is nurse consultant at the Royal Brompton Hospital, London. She was at Great Ormond Street Hospital for Children, London, from 1984 to 2002 and was instrumental in setting up the CF Multidisciplinary Team there. She also initiated the International Nurse Specialist Group – Cystic Fibrosis and is currently Chairperson.

**Dr Margaret Mearns**  
qualified in 1951 at King's College School of Medicine in London. She

later worked at the Queen Elizabeth Hospital in Hackney where Winifred Young ran a clinic for children with cystic fibrosis. On her retirement Dr Mearns was asked to take over the clinic. She retired from medical practice in 1989.

**Sir George Newman**  
GBE KCB FRSE FRCP  
(1870–1948) was Chief Medical Officer to the Ministry of Health from 1919 to 1935 and to the Board of Education from 1907 to 1935. See Brown (1955).

**Dr Archie Norman**  
MBE FRCP FRCPI (b. 1912) was Physician to the Hospital for Sick Children, Great Ormond Street, London, from 1950, and Paediatrician to Queen Charlotte's Maternity Hospital, London, from 1952 until his retirement in 1977. From 1976 to 1984 he was Chairman of the Medical Advisory Committee of the Cystic Fibrosis Research Trust.

**Dr Wilfred Payne**  
FRCP (1894–1978) was a research biochemist at Queen Charlotte's Hospital, London, from 1959 to 1962 and Chemical Pathologist to Great Ormond Street Hospital, London, from 1926 to 1959. He helped develop techniques including flame photometry and chromatography and chylomicron

counting, and did pioneering work on calcium and phosphorus metabolism. He received the Dawson Williams Prize in 1959 and the James Spence Medal in 1971. See Cathie (1984).

**Professor Paul Quinton**  
is Professor of Biomedical Sciences at the University of California Riverside, USA. He also holds the Nancy MacCracken Chair in Pediatric Pulmonary Medicine in the Department of Pediatrics, University of California at San Diego Medical School.

**Professor Sandy Raeburn**  
FRCPE FRCPI (b. 1941) is currently Professor of Genetics in the College of Medicine and Health Sciences, Sultan Qaboos University, Sultanate of Oman. From 1973 to 1990 he was Senior Lecturer in Human Genetics at Edinburgh University and from 1990 to 2003, Professor of Clinical Genetics at Nottingham University. He was also Chairman of the South-East Scotland branch of the Cystic Fibrosis Research Trust from 1981 to 1986 and from then until 1990, Chairman of the Scottish Council of the Trust. From 1993 to 1997 he chaired the Family and Adult Support Services Committee (FASS) of the Cystic Fibrosis Trust.

**Sir Wilfred Sheldon**

KCVO FLS FRCP FAAP FRCOG  
MMSA HonFRS (1901–83) was  
Consultant Paediatrician at King's  
College Hospital, London, and  
Consultant Physician at the Hospital  
for Sick Children, Great Ormond  
Street, London. From 1952 to 1971  
he was Physician–Paediatrician to  
the Queen and President of the  
British Paediatric Association. See  
Stroud (1984).

**Professor Margot Shiner**

(1923–98) worked in the  
Hammersmith Hospital in London  
in the 1950s and in 1956 invented  
a technique of small bowel biopsy  
that could be used to diagnose  
coeliac disease. She was Consultant  
in Gastroenterology at the Central  
Middlesex Hospital (1971–83) and  
Head of Paediatric Gastroenterology,  
Assof Harofe Medical Centre, Israel,  
and Professor of the University of  
Tel Aviv (1983–98).

**Professor Harry Shwachman**

(1910–86) founded the first special  
treatment centre for patients with  
cystic fibrosis at the Children's  
Hospital Medical Center in Boston,  
USA, just after the Second World  
War. In 1965 he started the  
National Cystic Fibrosis Research  
Foundation and worked as Chairman  
of the Scientific/Medical Advisory  
Council of the International Cystic  
Fibrosis Association. His work is  
described in Dietzsch (1994).

**Dr Kevin Southern**

FRCPCH (b. 1964) has been Senior  
Lecturer in Paediatric Respiratory  
Medicine at the University of  
Liverpool since 1 January 2000.

**Dr David Stableforth**

FRCP (b. 1942) qualified at  
University of Cambridge and St  
Mary's Hospital, London, in 1967.  
From 1975 to 1977 he was Senior  
Registrar in respiratory medicine at  
the Brompton Hospital, London,  
under Dr (now Sir) John Batten. He  
developed CF adult care in the West  
Midlands, working closely with the  
Birmingham Children's Hospital.  
He has been Director and  
Consultant Physician to the Adult  
Cystic Fibrosis Centre at  
Birmingham Heartlands Hospital  
since 1977.

**Sir John Sulston**

Kt FRS (b. 1942) was a staff  
scientist at the MRC Laboratory of  
Molecular Biology, Cambridge,  
from 1969 to 1992. From 1992 to  
2000 he was Director of the Sanger  
Centre, Hinxton, Cambridge, where  
he oversaw the Human Genome  
Project. He shared the 2002  
Nobel Prize for Physiology or  
Medicine with Sydney Brenner  
and Robert Horvitz.

**Dr Maurice Super**

FRCP FRCPCH (b. 1936) is  
Honorary Consultant Paediatric  
Geneticist at the Royal Manchester

Children's Hospital. He was the Head of the Department of Clinical Genetics and Honorary Lecturer in the Department of Medicine at the University of Manchester (1979–2001), and worked as a consultant paediatrician in South West Africa (now Namibia) (1967–78), where he researched his MD thesis, 'Cystic fibrosis in South West Africa' (1978).

**Professor Lap-Chi Tsui**  
FRSC FRS (b. 1950) has been Director of the Centre for Applied Human Genomics, Hospital for Sick Children, Toronto, Canada, since 1998. He has been Geneticist-in-Chief and Senior Research Scientist at the Centre since 1983.

**Mr Ron Tucker**  
OBE was appointed as the Cystic Fibrosis Trust's first Executive Director and retired in 1983 after 18 years' service. In 1990 he became Vice President of the Trust.

**Dr Bernard Valman**  
FRSM FRCP FRCPCH (b. 1934) was consultant paediatrician at Northwick Park Hospital and the Clinical Research Centre, Harrow, (1972–99). He was Secretary to the Royal College of Physicians Paediatric Committee from 1981 to 1991.

**Professor Selman Waksman**  
(1888–1973) became Professor of Microbiology at Rutgers University in 1930 and was awarded the Nobel Prize in Physiology or Medicine in 1952 for his discovery of streptomycin. His 1916 MSc thesis focused heavily on actinomycetes.

**Professor John Walker-Smith**  
FRCP FRACP FRCPCH (b. 1936) was appointed Consultant/Senior Lecturer in Child Health at St Bartholomew's and Queen Elizabeth Hospital for Children in 1973, and became Professor of Paediatric Gastroenterology in 1985. He transferred to the Royal Free Hospital, London, in 1995 and spent a sabbatical in history of medicine at the Wellcome Institute for the History of Medicine in 1993. He retired in October 2000, and has been Emeritus Professor of Paediatric Gastroenterology and Research Associate in the History of Medicine since October 2000, and a member of the History of Twentieth Century Medicine Group since 1993.

**Professor Warren Warwick**  
(b. 1928) is Annalisa Marzotto Professor of Cystic Fibrosis in the Department of Pediatrics, University of Minnesota, USA. He graduated from the University of Minnesota Medical School in 1954, and was Associate Professor of Pediatrics at

the University of Minnesota from 1966 to 1978. Since 1962 he has been Director of the Cystic Fibrosis Care, Research and Teaching Center at the University of Minnesota Medical Center.

**Professor Kevin Webb** (b. 1946) is Clinical Director of the Manchester Adult Cystic Fibrosis Centre, which currently cares for around 250 patients. He founded the Centre in 1982 with Mrs Mary Dodd.

**Dr Peter Weller** FRCP FRCPCH is Consultant Paediatrician in Respiratory Medicine at Birmingham Children's Hospital. He qualified from St Thomas' Medical School, London, in 1969.

**Professor John Widdicombe** FRCP (b. 1925) was Foundation Professor and Chairman of Physiology, at St George's Hospital Medical School, London, from 1972 to 1992. He is now 'retired' and an Emeritus Professor of Physiology in the University of London.

**Dr Jonathan Widdicombe** (b. 1949) worked in the Cardiovascular Research Institute, San Francisco (1975–95), and is now at the University of California, Davis, Sacramento.

**Professor Robert (Bob) Williamson** FRCP FRCPATH FRS (b. 1938) was Professor of Biochemistry at St Mary's Hospital Medical School, London, from 1976 to 1995. He has been Research Professor of Medical Genetics, University of Melbourne School of Medicine, and Director, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, since 1995.

**Dr Winifred Young** FRCP DCH (1909–69) was a research clinician at the Queen Elizabeth Hospital for Children, London, from 1948 to 1969. She started a special clinic for children with cystic fibrosis at the hospital in 1950. She established the importance of prolonged intensive therapy of lung infections in affected babies. See Wilmers (1982).



## Glossary

Note the use of bold for items in glossary.

### Actinomycetes

A group of bacteria that grow slowly as branched filaments. Together with the mycobacteria they make up the Actinomycetales; Streptomycetaceae are the source of most **antibiotics**.

### Aminoglycosides

A group of **antibiotics** used to combat bacterial infections, especially infection from *Pseudomonas* sp. and *Staphylococcus* sp. Examples include **gentamicin** and tobramycin.

### Antibiotic

A medication that is used to treat infections caused by bacteria. They have no effect on illnesses caused by viruses.

### Antibiotic resistance

When bacteria can no longer be killed by a particular antibiotic, for example, **MRSA**.

### Aureomycin (chlortetracycline hydrochloride: Lederle)

A yellow crystalline **antibiotic** used to treat certain bacterial and rickettsial diseases.

### *Bacillus pyocyaneus*

An earlier name for *Pseudomonas aeruginosa*.

### Biopesticide

A pesticide in which the active ingredient is a virus, fungus, or bacteria, or a natural product derived from a plant source. Its mechanism of action is based on biological effects and not on chemical poisons.

### Bronchiectasis

The irreversible, abnormal structural dilatation of one or more bronchi, accompanied by chronic infection.

### Bunyan bag

A plastic bag used to enclose severely burned limbs.

### *Burkholderia cepacia* (*Pseudomonas cepacia*)

A species of *Burkholderia*. It is considered to be a human pathogen with serious consequences for people with **cystic fibrosis**. It can cause rapid decline in lung function, resulting in severe lung disease that may lead to death.

### Chlortetracycline hydrochloride

See **Aureomycin**.

### Carbenicillin

A semisynthetic penicillin that is acid labile and the first penicillin to be active against *Pseudomonas*.

### CFTR

See **cystic fibrosis transmembrane conductance regulator**.

### Chloramphenicol

An **antibiotic** produced synthetically and from cultures of *Streptomyces venezuelae*. It is used as an antibacterial agent.

### Cholecystokinin (pancreozymin)

A hormone secreted by the duodenal and upper jejunal mucosa. It stimulates the gall bladder to contract, and release pancreatic enzymes and bile.

### Cotazym

An older preparation of **pancreatin**.

### Crohn's disease

A chronic inflammatory bowel disease involving the small intestine, the colon or both, and characterized pathologically by transmural inflammation, deep linear ulceration and often granulomas.

### Crossed immunoelectrophoresis

A method of demonstrating antibodies in the blood.

### Cystic fibrosis (Mucoviscidosis)

An inherited disorder that causes widespread dysfunction of the exocrine glands, resulting in chronic lung disease, abnormally high levels of electrolytes (e.g. sodium, potassium, chloride) in sweat, and deficiency of pancreatic enzymes needed for digestion.

### Cystic fibrosis transmembrane conductance regulator (CFTR)

The protein product of the **cystic fibrosis** gene. Functionally the gene encodes a protein that is responsible for regulating the opening and closing of chloride channels. This protein is the most important apical membrane transporter for chloride.

### Delta F508

One of the abnormal alleles, the most common, within the **cystic fibrosis** gene; a deletion of phenylalanine (F) at amino-acid position 508 of **CFTR**.

### Electrolyte

A substance that yields ions in solution so that its solutions conduct electricity.

### Epithelium

The cellular covering of the skin and mucous membranes.

### Fibrosis

The deposition of collagen, usually in the form of a scar, surrounding parenchymal cells.

### G551D

One of the abnormal alleles within the **cystic fibrosis** gene.

### Genotype

The total genetic information in a somatic cell, or the total genetic information in a germ cell or organism.

**Gentamicin**

A broad-spectrum **antibiotic** that inhibits bacterial protein synthesis and is active against many Gram-negative and Gram-positive bacteria, particularly *Pseudomonas aeruginosa*.

**Glycoprotein**

Any type of protein that possesses a sugar within the molecule.

**Intralipid**

An intravenous fat emulsion used to treat people who are unable to eat properly.

**Intussusception**

The telescoping of one segment of the intestine within a neighbouring segment, most commonly the ileum into the colon.

**Jaundice**

A phenotypical expression caused by the presence of bilirubin in body fluids, which results in the yellowing of eyes and skin. This can be a result of excess destruction of red blood cells or of liver failure.

**KM19**

A marker within part of the **cystic fibrosis** gene (exon 6).

**Meconium ileus**

The intestinal obstructive variant of **cystic fibrosis** or mucoviscidosis. Approximately 15–20 per cent of infants with cystic fibrosis also

present with intestinal obstruction related to **meconium ileus**.

**Messenger RNA (mRNA)**

The RNA that carries the information encoded in a DNA sequence to the site of protein biosynthesis, where it specifies the order of amino-acid residues.

**Methicillin-resistant *Staphylococcus aureus* (MRSA)**

A subgroup of *Staphylococcus aureus* that cannot be killed by many frequently-used **antibiotics**, including methicillin.

**Mucin**

Any mucoglycoprotein secreted by cells which raises the viscosity of the medium around them.

**Mucolytic**

An agent that dissolves or destroys **mucin**.

**Mucoviscidosis**

A term for **cystic fibrosis** commonly used in continental Europe.

**Nebulizer**

A device for converting liquid into a mist or cloud, used primarily for direct inhalation.

**Pancrease**

An early acid-resistant pancreatic enzyme preparation. See page 26.

**Pancreatin**

A product derived from hog or ox pancreas and containing enzymes such as amylase, protease and lipase, which have the same actions as pancreatic juice. When administered to patients with pancreatic insufficiency it improves their ability to metabolize starches, protein and fats.

**Pancreozymin**

See **cholecystokinin**.

**Penicillin**

A group of  $\beta$ -lactam **antibiotics**. The naturally occurring penicillins (penicillin G) are active chiefly on Gram-positive organisms.

**Phagocytosis**

The ingestion of materials from the outside of the cell into its exterior.

**Polysaccharide**

A complex carbohydrate consisting of many smaller monosaccharide components.

*Pseudomonas aeruginosa*

A Gram-negative organism characteristic of, but not exclusive to, **cystic fibrosis** lung infections.

*Pseudomonas cepacia*

An earlier name for *Burkholderia cepacia*.

**Recombination**

Any process occurring during reproduction which results in an

offspring with a combination of two or more genes that is distinct from the arrangement of those genes in either parent.

**Secretagogue**

An agent that stimulates a secretory action, especially for example the exocrine glands.

**Secretin**

A type of hormone that promotes the secretion of bile from the liver.

*Staphylococcus aureus*

A type of **bacteria** commonly found in the environment and sometimes found in the nose and on the skin of healthy people. It can cause several types of infections, including skin and wound infections, and less commonly pneumonia.

**Steatorrhea**

The presence of excess fat in the stool. It is generally an indication of malabsorption.

*Stenotrophomonas (Pseudomonas) maltophilia*

An aerobic Gram-negative bacillus that is an infrequent pathogen in humans and is found in a variety of aquatic environments. It is multidrug resistant and occasionally causes bacteraemic and organ-specific infections in humans.

**Sweat test**

This test determines the amount of chloride in the sweat. A chemical, known to cause sweating is applied to a small area on an arm or leg. An electrode is then attached and a weak electrical current applied to the area to stimulate sweating. The sweat is then collected and analysed. Children and adults with CF have an increased amount of sodium and chloride (salt) in their sweat. In general, sweat chloride concentrations less than 40 mmol/L are normal (does not have CF); values between 40 to 60 mmol/L are borderline, and sweat chloride concentrations greater than 60 mmol/L are consistent with the diagnosis of CF.

**Tetracycline (Terramycin, oxytetracycline: Pfizer)**  
A broad-spectrum **antibiotic**.

**Terramycin**  
A trade name for **tetracycline**, see above.

**Trypsin**  
A pancreatic proteinase that hydrolyses polypeptides on the C-terminal side of arginine and lysine residues.

**Xerophthalmia**  
Abnormal and severe dryness of the surface of the cornea and conjunctivae as may occur in

vitamin A deficiency or some autoimmune syndromes.

**XVC2 (gene locus)**  
A sequence of DNA very close to the **cystic fibrosis** gene.



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