Wellcome Witnesses
to Twentieth Century Medicine

CHILDHOOD ASTHMA AND BEYOND

A Witness Seminar held at the
Wellcome Institute for the History of Medicine,
London, on 4 April 2000

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Key

Front cover photographs, L to R from the top:
Dr Harry Morrow Brown
Dr Jim Cox (1931–2001), Mr John Bell
Dr Mark Levy, Professor Simon Godfrey (chair), Professor Sean Hilton
Dr Alistair Brewis, Professor John Warner, Professor Tim Clark
Professor John Warner, Dr Archie Norman
Dr Harry Morrow Brown, Dr Bill Frankland
Dr Paul McCarthy, Professor Simon Godfrey (chair)
Professor Chris O'Callaghan, Sir Ian Jack

Back cover photographs, L to R from the top:
Dr James McCracken, Sir Christopher Booth
Dr Donald Lane, Professor Jack Howell, Professor Mike Silverman, Dr Alistair Brewis, Dr Jill Warner
Professor Jack Howell, Professor John Warner
Professor Abe Guz
Dr George Russell, Dr Ian Gregg (1925–2009), Dr Mark Levy, Dr James McCracken
Dr Bob McKinley, Professor Ross Mitchell, Dr George Russell
Mrs Greta Barnes, Professor Mike Silverman

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INTRODUCTION

One Sunday morning earlier this year, I was offered a potent and disturbing reminder of current trends in childhood asthma. Our one-year-old son, Conall, had developed a loud expiratory wheeze and persistent nocturnal cough following a series of debilitating upper respiratory tract infections and, perhaps significantly, coinciding with the extremely high pollen counts recorded that month. We had attempted to relieve the symptoms with a salbutamol inhaler delivered through a spacer and mask but to no effect. That morning, he began exhibiting signs of severe respiratory distress and I took him to the accident and emergency department in the small local hospital. He was given nebulized salbutamol which immediately eased both his (and my) distress and the wheeze, he was prescribed a short course of oral steroids and a follow-up steroid inhaler, and we were advised to see our GP later that week.

Of course, our experience was by no means unusual. We all know families where young children suffer recurrent episodes of wheezing and nocturnal coughing, and where the use of both β-agonist and steroid inhalers is commonplace. When we lived in Manchester, where our older son, Riordan, first developed symptoms of asthma three or four years ago, our GP was insistent that the number of wheezy children seen in her surgery had increased dramatically over the previous ten years, particularly in those areas of Manchester close to major roads. Indeed, when we moved from Manchester to Exeter in 1998, one of our hopes was that fresh sea breezes drifting along the south-west coast, which had been renowned as a respiratory resort during the late nineteenth century, would afford our son some relief. Although such attempts at geographical or climatic management of asthma and hay fever have numerous historical precedents,[1] they are not always successful. In the modern world, asthma in children and adults is clearly not merely an urban disease. The receptionist at the school in Exmouth currently attended by our two older children, for example, is inundated with different coloured inhalers to be given to various children at various times. And if we are to believe the media, in the last decade of the twentieth century an 'inhaler culture' has emerged in playgrounds around the country.

Significantly, such anecdotal stories of the modern increase in wheezing and asthma in children are supported by epidemiological evidence. Recent research has clearly demonstrated not only a prominent rise in the incidence and prevalence of asthma in all age-groups worldwide, but also, at least until very recently, a rising mortality rate.[2] As both the levels and severity of asthma in the general population rose in the last decades of the twentieth century, asthma emerged as a major clinical, public health, and socioeconomic concern. Hospital admissions for asthma have risen, partly in response to

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[1] See, for example, Walshe W H. (1871) *A Practical Treatise on the Diseases of the Lungs: Including the principles of physical diagnosis, and notes on climate*. London: James Walton.

[2] Chadwick D, Cardew G. (eds) (1997) *The Rising Trends in Asthma*. Ciba Foundation Symposium 206. Chichester: John Wiley and Sons.

rising levels of morbidity and mortality from asthma, and partly as the result of changing hospital admission policies (such as self-referral), greater GP awareness, and the introduction of novel practices (such as asthma clinics) during the 1980s and 1990s. The current cost of treating 3.4 million asthmatics in the UK is estimated at £23 million – a figure that includes physician time, and the cost of hospitalization and medication.

One of the paradoxes of modern asthma is that such trends in incidence, prevalence, and severity have occurred at precisely the time when treatment options have improved significantly. As contributors to this Witness Seminar make clear in their testimony, during the last half of the twentieth century there were dramatic developments both in the symptomatic relief of wheezing and in the organization of asthma services: the introduction of selective β-agonists such as salbutamol by Allen and Hanburys in the late 1960s; the development of sodium cromoglycate around the same time; the availability of inhaled corticosteroids from the early 1970s; the expansion of asthma clinics and asthma nurses from the 1980s; and the growing educational role of organizations such as the National Asthma Campaign, formerly the Asthma Research Council, established in 1927 as a means of promoting and funding clinical research. As evidence presented to this seminar also demonstrates, these developments owed a great deal to the persistent visionary zeal of innovators and motivators such as Roger Altounyan, Sir David Jack, Greta Barnes, and many others.

It is important to remember, however, that while pharmaceutical developments in particular have dominated recent approaches to asthma management, other strategies, mentioned only in passing in the seminar, have also played a major role in the history of childhood asthma. First, it is important to recognize that until concerns about its safety emerged in the 1980s, allergen immunotherapy was an approach to asthma favoured by many allergists (pages 44–45, 50). Initially introduced for the treatment of hay fever by John Freeman and Leonard Noon in 1911, immunotherapy or desensitization for asthma, hay fever, and bee stings in particular became the cornerstone of clinical allergy in the middle decades of the twentieth century. Its practice in the UK was dramatically curtailed by the controversial intervention of the Committee on Safety of Medicines in 1986, after reports of deaths in asthmatics following the procedure, although its role is currently being re-evaluated.[3]

Secondly, while Professor Godfrey refers to the role of Alpine schools for Italian asthmatic children (page 47), we should remember that open-air schools also played a crucial role in the treatment of asthmatic children in this country. First developed for the treatment of tuberculous children in the early years of the twentieth century,[4]

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[3] For a discussion of the history of immunotherapy, see Jackson M. (2001) Between scepticism and wild enthusiasm: the chequered history of allergen immunotherapy in Britain, in Moulin A M, Cambrosio A. (eds) *Singular Selves: Historical issues and contemporary debates in immunology*. Amsterdam: Elsevier, 155–164.

[4] Bryder, L. (1992) 'Wonderlands of buttercup, clover and daisies': tuberculosis and the open-air school movement in Britain, 1907–39, in Cooter R. (ed.) *In the Name of the Child: Health and welfare, 1880–1940*. London: Routledge, 72–95.

open-air schools were increasingly used to treat a variety of other respiratory conditions, including asthma and bronchitis, at least until the introduction of more effective medication in the 1960s. In Birmingham, for example, the schools at Uffculme and Cropwood regularly admitted children with asthma, and routinely sent children abroad to the Davos Alpine School in Switzerland.[5] Of course, open air was only one part of the therapeutic regime. The children also received better nutrition and more exercise and, according to some commentators, benefited from being removed from both their home environment and their parents. The adoption and demise of 'parentectomy', which proved popular on both sides of the Atlantic in the middle decades of the century, would be worthy of more extensive historical study.

While the startling rise in asthma in the face of improvements in treatment constitutes one paradox in the history of the disease, there are many other complexities and ambiguities to be considered. First, it is not entirely clear to what extent the current epidemic of asthma is the product of changing definitions and shifting diagnostic labels. It has often proved difficult to define the precise functional and pathophysiological features that differentiate asthma from other chronic obstructive lung diseases.[6] In addition, it is evident that during the late 1960s and 1970s, doctors increasingly labelled as asthmatic children who previously would have been diagnosed as having 'wheezy bronchitis' (page 61).[7] Such diagnostic shifts, accentuated by contrasting national approaches to classification and the elaboration of diagnostic criteria, have made epidemiological generalizations more problematic.

Secondly, while much is known about the epidemiology of asthma, it remains difficult to account precisely either for recent rises in asthma morbidity at a population level or for exacerbations in individual patients. Changing diet, carpets, double-glazing, central heating, the rise in allergies, maternal smoking, changing family size, improved standards of hygiene, medication, industrial and traffic-related pollution, and other factors have all been implicated in modern trends in childhood asthma, eczema, and hay fever. While many of these factors may operate at an epidemiological level, it is not always apparent precisely what triggers the development of asthma or the occurrence of an attack in a particular child. It is also important to remember that debates about the causes of recent trends in asthma have become deeply political, firmly shaped by millennial anxieties about controlling both the domestic and outdoor environments, shifting notions of individual and state responsibility for

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[5] Wilmot F, Saul P. (1998) *A Breath of Fresh Air: Birmingham's open-air schools 1911–1970.* Chichester: Phillimore.

[6] The classification and differential diagnosis of chronic respiratory diseases proved a prominent focus for international conferences particularly during the 1950s and 1960s. See Ciba Symposium Report (1959) Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions. *Thorax* **14**: 286–299. Scadding J G. (1963) Meaning of diagnostic terms in broncho-pulmonary disease. *British Medical Journal* **ii**: 1425–1430.

[7] Pereira Gray D J. (1980) Gale memorial lecture 1979: Just a GP. *Journal of the Royal College of General Practitioners* **30**: 231–239.

healthcare, and concerns about the detrimental effects of modern civilization, including modern medicine.

Finally, there remain tense debates about the involvement of allergy (or more accurately, atopy) in asthma (page 47) and about the importance of psychological factors in triggering attacks. In the late nineteenth and early twentieth centuries, asthma was commonly understood to be neurogenic, that is the product of imbalances in the nervous system. With the development of more sophisticated studies of the immunology and biochemistry of allergic reactions and of the pathogenesis of asthma, neurological and psychogenic theories of asthma fell into disrepute. They generally surfaced only in marginal or alternative approaches to treatment, shaped largely by psychoanalytical concepts of the mind–body relationship.[8] In recent years, however, the contribution of the mind has once again become a focus, both for scientists interested in the interplay between mental processes and the nervous, immunological and endocrine systems, and for clinicians keen to reduce reliance on medication and improve patients' own control of their symptoms.

Unfortunately, in spite of evident clinical, scientific, epidemiological, political and media interest in asthma, there have been few studies of its history in either adults or children. Apart from some useful overviews by Alex Sakula, the marvellous collection of classic papers edited with an introduction by Alistair Brewis,[9] and the on-going research of Ian Gregg into mortality figures and hospital admissions, asthma (like many chronic conditions) has figured only rarely in recent histories of medicine.[10] At the turn of the millennium, when allergic diseases, including asthma, appear to have reached epidemic proportions, the time is ripe for closer historical scrutiny of asthma in a manner that effectively incorporates and integrates the work of historians, epidemiologists, immunologists, and clinicians.

We should be grateful to Dr Chris O'Callaghan and Dr Daphne Christie and to the Wellcome Trust's History of Twentieth Century Medicine Group for beginning the process of historical reconstruction so energetically by organizing this Witness Seminar 'Childhood Asthma and Beyond', and to Dr Tilli Tansey and Mrs Lois Reynolds for its conversion into print. Chaired with considerable insight, enthusiasm, and humour by Professor Simon Godfrey, the contributions to the discussion from leading figures in the fight against asthma shed light on many crucial issues in the history of asthma, notably the discovery and development of new pharmaceutical

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[8] See Kimball C P. (1970) Conceptual developments in psychosomatic medicine: 1939–1969. *Annals of Internal Medicine* **73**: 307–316. Inglis B. (1981) *The Diseases of Civilization.* London: Hodder and Stoughton, 218–226.

[9] See transcript notes 7 and 11.

[10] For some historical articles, see Keeney E L. (1964) The history of asthma from Hippocrates to Meltzer. *Journal of Allergy* **35**: 215–226. Sakula A. (1988) A history of asthma: The Fitzpatrick Lecture 1987. *Transactions of the Royal College of Physicians* **22**: 36–44. Emanuel M B, Howarth P H. (1995) Asthma and anaphylaxis: a relevant model for chronic disease? An historical analysis of directions in asthma research. *Clinical and Experimental Allergy* **25**: 15–26.

agents in the 1960s and 1970s, and, perhaps more interesting from a social history perspective, the emergence of a new culture of disease surveillance and healthcare provision with the establishment of asthma clinics and the training of specialist asthma nurses from the 1980s. More broadly, the range of questions raised as well as answered during the seminar should remind us of the nature and complexity of the challenges faced by both historians and clinicians in their quest to understand the causes of modern trends in asthma.[11]

Mark Jackson
University of Exeter

[11] For further information on asthma mortality statistics and hospital admission rates, see the excellent *Factsheets,* published regularly by the Lung and Asthma Information Agency in the Department of Public Health Sciences at St George's Hospital Medical School, London, or visit their website (www.sghms.ac.uk/depts/laia/laia.htm; visited 30 July 2001). Regular updates on asthma statistics are also available from the National Asthma Campaign, either through their subscription newsletter, *Asthma News*, or via their website (www.asthma.org.uk; visited 30 July 2001).

WITNESS SEMINARS: MEETINGS AND PUBLICATIONS[1]

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 meet together to discuss, debate, and agree or disagree about their memories. To date, the History of Twentieth Century Medicine Group has held over 25 such meetings, most of which have been published, as listed in the table on page viii.

Subjects for such meetings 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 of time 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 their 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.

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[1] The following text also appears in the 'Introduction' to recent volumes of *Wellcome Witnesses to Twentieth Century Medicin*e published by the Wellcome Trust and the Wellcome Trust Centre for the History of Medicine at University College 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.

1993	**Monoclonal antibodies**[1] Organizers: Dr E M Tansey and Dr Peter Catterall
1994	**The early history of renal transplantation** Organizer: Dr Stephen Lock
	Pneumoconiosis of coal workers[2] Organizer: Dr E M Tansey
1995	**Self and non-self: a history of autoimmunity**[1] Organizers: Sir Christopher Booth and Dr E M Tansey
	Ashes to ashes: the history of smoking and health[3] Organizers: Dr Stephen Lock and Dr E M Tansey
	Oral contraceptives Organizers: Dr Lara Marks and Dr E M Tansey
	Endogenous opiates[1] Organizer: Dr E M Tansey
1996	**Committee on Safety of Drugs**[1] Organizers: Dr Stephen Lock and Dr E M Tansey
	Making the body more transparent: the impact of nuclear magnetic resonance and magnetic resonance imaging[4] Organizer: Sir Christopher Booth
1997	**Research in General Practice**[4] Organizers: Dr Ian Tait and Dr E M Tansey
	Drugs in psychiatric practice[4] Organizers: Dr David Healy and Dr E M Tansey
	The MRC Common Cold Unit[4] Organizers: Dr David Tyrrell and Dr E M Tansey
	The first heart transplant in the UK[5] Organizer: Professor Tom Treasure
1998	**Haemophilia: recent history of clinical management**[6] Organizers: Professor Christine Lee and Dr E M Tansey

[1] Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds) (1997) *Wellcome Witnesses to Twentieth Century Medicine,* vol. 1. London: The Wellcome Trust, 135pp.

[2] P D'Arcy Hart, edited and annotated by E M Tansey. (1998) Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–1942). *Social History of Medicine* **11**: 459–468.

[3] Lock S P, Reynolds L A, Tansey E M. (eds) (1998*) Ashes to Ashes – The history of smoking and health*. Amsterdam: Rodopi B V, 228pp.

[4] Tansey E M, Christie D A, Reynolds L A. (eds) (1998) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 2. London: The Wellcome Trust, 282pp.

[5] Tansey E M, Reynolds L A. (eds) (1999) Early heart transplant surgery in the UK. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 3. London: The Wellcome Trust, 72pp.

[6] Tansey E M, Christie D A. (eds) (1999) Haemophilia: Recent history of clinical management. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 4. London: The Wellcome Trust, 90pp.

Obstetric ultrasound: historical perspectives[7]
Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey

Post penicillin antibiotics[8]
Organizers: Dr Robert Bud and Dr E M Tansey

Clinical research in Britain, 1950–1980[9]
Organizers: Dr David Gordon and Dr E M Tansey

1999 **Intestinal absorption**[10]
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[11]
Organizers: Professor Osmund Reynolds and Dr E M Tansey

British contributions to medicine in Africa after the Second World War[12]
Organizers: Dr Mary Dobson, Dr Maureen Malowany,
Dr Gordon Cook and Dr E M Tansey

2000 **Childhood asthma, and beyond**[13]
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[14]
Organizers: Dr Irvine Loudon and Dr Daphne Christie

2001 **Leukemia**
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 screening
Organizers: Professor Doris Zallen and Dr Daphne Christie

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[7] Tansey E M, Christie D A. (eds) (2000) Looking at the unborn: Historical aspects of obstetric ultrasound. *Wellcome Witnesses to Twentieth Century Medicine,* vol. 5. London: The Wellcome Trust, 80pp.

[8] Tansey E M, Reynolds L A. (eds) (2000) Post penicillin antibiotics: From acceptance to resistance? *Wellcome Witnesses to Twentieth Century Medicine*, vol. 6. London: The Wellcome Trust, 71pp.

[9] Reynolds L A, Tansey E M. (eds) (2000) Clinical research in Britain, 1950–1980. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 7. London: The Wellcome Trust, 74pp.

[10] Christie D A, Tansey E M. (eds) (2000) Intestinal absorption. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 8. London: The Wellcome Trust, 81pp.

[11] Christie D A, Tansey E M. (eds) (2001) Origins of neonatal intensive care in the UK. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 9. London: The Wellcome Trust Centre for the History of Medicine at UCL, 84pp.

[12] Reynolds L A, Tansey E M. (eds) (2001) British contributions to medical research and education in Africa after the second world war. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 10. London: The Wellcome Trust Centre for the History of Medicine at UCL, 93pp.

[13] Reynolds L A, Tansey E M. (eds) (2001) Childhood asthma and beyond. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 11. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp.

[14] Christie D A, Tansey E M. (eds) (2001) Maternal care. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 12. London: The Wellcome Trust Centre for the History of Medicine at UCL, 88pp.

ACKNOWLEDGEMENTS

'Childhood Asthma, and Beyond' was suggested as a suitable topic for a Witness Seminar by Dr Chris O'Callaghan and Sir Christopher Booth – members of the Programme Committee of the Wellcome Trust's History of Twentieth Century Medicine Group. Dr Chris O'Callaghan and Dr Daphne Christie provided many of the names of individuals to be invited, and assisted us in planning the meeting, and deciding the topics to be discussed. We are very grateful to them for their input. We are particularly grateful to Dr Mark Jackson for writing such a useful introduction to these published proceedings, for reading through earlier drafts of the transcript, and offering us helpful comments and advice. For additional help, we thank Professor Mike Silverman.We are equally grateful to Professor Simon Godfrey for his excellent chairing of the occasion.

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, Mrs Liza Furnival, and our readers, Ms Lucy Moore, Mr Simon Reynolds and Dr John Henderson and Mr Mark Krüger for bibliographic research. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Dr Daphne Christie assist us in running the meetings. Finally we thank the Wellcome Trust for supporting this programme.

Tilli Tansey
Lois Reynolds
Wellcome Trust Centre for the History of Medicine at UCL

CHILDHOOD ASTHMA AND BEYOND

The transcript of a Witness Seminar held at the
Wellcome Institute for the History of Medicine,
London, on 4 April 2000

Edited by L A Reynolds and E M Tansey

PARTICIPANTS

Mrs Greta Barnes
Mr John Bell
Sir Christopher Booth
Dr Alistair Brewis
Dr Harry Morrow Brown
Professor Tim Clark
Dr Jim Cox*
Dr Bill Frankland
Professor Simon Godfrey (Chair)
Dr Ian Gregg
Mrs Eleanor Hickie
Professor Stephen Holgate
Professor Jack Howell
Sir David Jack
Dr Donald Lane
Dr Mark Levy
Dr Paul McCarthy
Dr James McCracken
Professor Tony Milner
Professor Ross Mitchell
Dr Archie Norman
Professor Chris O'Callaghan
Dr George Russell
Professor Michael Silverman
Dr Jill Warner
Professor John Warner

Others attending the meeting: Dr Mark Everard, Dr Chris Griffiths, Professor Abe Guz, Professor Sean Hilton, Dr Warren Lenney, Dr R K McKinley, Professor Tom Oppé, Dr Martyn Partridge, Dr Robert Pearson, Dr Dermot Ryan

Apologies: Professor Peter Barnes, Dr David Bellamy, Professor Michael Burr, Dr Gordon Cochrane, Dr Christopher Corrigan, Dr Graham Crompton, Mrs Susan Cross, Dr Gordon Cumming, Professor Sir Richard Doll, Sir Colin Dollery, Dr David Heaf, Dr Edmund Hey, Dr Sheila Howarth (Lady McMichael),† Professor Sir David Hull, Professor W H W Inman, Dr Mark Jackson, Dr Ron Neville, Professor Søren Pedersen, Dr David Price, Dr Barbara Rashbass, Dr Andrea Swarbrick, Professor Anne Tattersfield, Professor Dame Margaret Turner-Warwick, Dr Peter Weller

*Deceased 19 January 2001

†Deceased 31 July 2000

Professor Chris O'Callaghan:[1] I am a paediatrician from Leicester, and have been asked to introduce this Witness Seminar on the history of childhood asthma. This meeting has been organized by the History of Twentieth Century Medicine Group at the Wellcome Trust. The group was established to promote interaction between clinicians, scientists, and historians interested in modern medical history. The Programme Committee of the group led by Dr Tilli Tansey decides on the programme. Dr Daphne Christie has been instrumental in the organization of this meeting. The seminars are intended to stimulate debate and discussion of events in contemporary medical history between scientists and historians. The meeting is being taped and it is very important that you say your name every time you speak to aid the transcriber. You may say what you want, as your permission will be required before publication. The tapes will be archived.[2]

It gives me great pleasure to introduce Professor Simon Godfrey, who is now Professor of Paediatrics and Director of the Institute of Pulmonology at Hadassah University Hospital in Jerusalem. Simon has been a leader in this field for many years. He saw many of the major developments in childhood asthma while working at the Hammersmith and the Brompton Hospitals, London, and was instrumental in some of them.

Professor Simon Godfrey:[3] Chris, thank you very much. First of all I must thank the Wellcome Trust for organizing this Witness Seminar and for inviting me along to chair. I discussed this at length with friends and family to know whether this was a great honour to be asked, or whether they asked me to do it because they reckoned I was the most senile person around, just *compos mentis* enough to do it. But that we will see as time goes by, but it really is a pleasure to be here and it's wonderful to see so many of you – friends and teachers, my teachers – here. I am delighted to see them here and I hope we are going to hear from them. I think we all know about what has happened from 1960 to now, but I personally think it is going to be very interesting to hear people reminisce about what happened from 1900 to 1960. This seminar is

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[1] Professor Chris O'Callaghan (b. 1959) has been Professor of Paediatrics at the Department of Child Health and Institute of Lung Health, University of Leicester, since October 2000 and had been Senior Lecturer and Consultant Paediatrician at the University of Leicester. He has been a member of the Wellcome Trust's History of Twentieth Century Medicine Group Programme Committee from 1998 to 2001, following a Wellcome Trust Short-term Leave Fellowship in the History of Medicine for Clinicians and Scientists from June to October 1997 researching the history of metered dose inhalers.

[2] Many participants provided additional material for their contributions in more detail than can be included here, but all correspondence related to this meeting is deposited, along with tapes, and other records received during the editorial process, in Archives and Manuscripts, Wellcome Library, London.

[3] Professor Simon Godfrey FRCP FRCPCH (b. 1939) qualified at the London Hospital Medical College in 1962, undertook further research and obtained his PhD and later his MD from the University of London. He worked chiefly at the Hammersmith and Royal Brompton Hospitals in London from 1963. In 1977 he moved to Jerusalem as Professor of Paediatrics at the Hadassah University Hospital and in 1991 was appointed Director of the Institute of Pulmonology.

intended to be informal. People are invited to join in and make comments. There are one or two people who have been volunteered to say things at various points, but please, the idea is that you all join in and have as much fun as you can and reminisce or make your comments. I think it will be nice not to be too litigious or whatever the word might be in discussing various controversial issues, but I think we can carry on in a friendly atmosphere. Now I thought I would just start the ball rolling by quoting something not from the twentieth century, but from the twelfth century and I imagine there is only one other person in this room, maybe two, who will be able to tell me afterwards where it came from, and it goes like this:

> 'in this aphorism it is my purpose to bring before you something well deserving your examination and belief. If anyone declares to you that he has actual proof from his own experience of something of which he requires for the confirmation of his theory, even though he is considered a man of great authority, truthfulness, earnest words and morality, yet just because he is anxious for you to believe his theory, you should hesitate'.[4]

Now I like that, although that was not Karl Popper,[5] beloved of my teacher Moran Campbell,[6] and I imagine many others here, but it was in fact Maimonides who was born in 1135 and died in 1204. He was a philosopher, a rabbi, and a physician, and I think that's absolutely wonderful, because of course it is what Karl Popper and scientific philosophers of our own day are saying. Just because you say something forcefully, doesn't necessarily mean it is correct, and I think it will be interesting today to hear what people remember of others saying something forcefully that has not proved to be correct, and perhaps also some of the things that have been proved to be correct. With that little introduction, I would like to ask Chris [O'Callaghan] to give a formal historical background for the Witness Seminar.

O'Callaghan: This is just very brief and hopefully brings us up to the beginning of the last century. We don't really know when man first developed asthma. Descriptions of the disease date back well over 3000 years and various rather strange remedies were given. The ancient Egyptians used enemas and camel and crocodile dung to treat their patients. The ancient Greeks and Romans also recognized the disease and it was the blind poet Homer who first coined the term 'asthma' which, as we know, is the Greek word for panting [ασθμα]. Little progress was made in the treatment or knowledge of

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[4] Moses Maimonides (1135–1204) was court physician to the Sultan Saladin, whose son suffered from asthma. For a review of his work see Rosner R. (1981) Moses Maimonides' *Treatise on Asthma. Thorax* **36**: 245–251.

[5] Sir Karl Popper (1902–1994) was a British philosopher of science, born in Austria. See Popper K. (1945) *The Open Society and its Enemies*, 2 vols. London: Routledge. Susser M. (1986) The logic of Sir Karl Popper and the practice of epidemiology. *American Journal of Epidemiology* **124**: 711–718. See also Medawar P. (1977) The philosophy of Karl Popper, in Pyke D. (ed.) (1991) *The Threat and the Glory: Reflections on science and scientists.* Oxford: Oxford University Press, 91–101.

[6] Dr Edward James Moran Campbell (b. 1928) held the founding chair of the Department of Medicine at the University of McMaster, Hamilton, Ontario, Canada, from 1968 to 1975 and was an internationally renowned researcher in diseases of the lung. See Campbell E J M. (1988) *Not Always on the Level*. Cambridge: Cambridge University Press for the Memoir Club.

asthma until the twelfth century, when Moses Maimonides wrote a really excellent work on asthma in relation to the asthmatic son of the Sultan Saladin. His treatment advice was to avoid emotional turmoil, sexual activity, and he recommended chicken soup ['Jewish penicillin'] as a recipe. I guess chicken soup is quite safe.

Godfrey: I think it was excessive sexual activity, actually.

O'Callaghan: It's obviously been modified over the years. It's interesting that many of the best descriptions were by doctors who had the disease themselves. Sir John Floyer,[7] an eminent doctor, was an asthma sufferer and the first to differentiate the condition from other types of dyspnoea. Floyer recognized that there were several factors underlying the asthmatic state and he described these in the 1700s as heredity, weather, seasons and atmospheric pollution, including tobacco, occupational influences, personal idiosyncrasies and emotions. He also recognized the importance of nocturnal asthma.

It was in 1808 when Reisseissen of Strasbourg[8] demonstrated that the bronchial wall contained a distinct layer of muscle fibre, which when contracted led to constriction of the airways. This finding was exploited by Laënnec,[9] a brilliant French physician, who clarified the nature and diagnosis of asthma by physical examination of the thorax, using the stethoscope that he had invented. The foremost authority on asthma during the nineteenth century was Henry Hyde Salter,[10] who described bronchial hyper-reactivity and recommended stramonium[11] and strong coffee. A clear description of the disease was given, again probably based on the fact that he himself had severe asthma.

In terms of drug therapy, it was in 1900 when Solomon Solis-Cohen[12] injected crude adrenal extracts into patients with asthma or hay fever. Shortly afterwards Jessie Bullowa and David Kaplan[13] reported successful adrenaline injections that took over

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[7] Sir John Floyer (1649–1734) was a physician, living in Lichfield. See Sakula A. (1984) Sir John Floyer's 'A treatise of the asthma' (1698). *Thorax* **39**: 248–254. For a facsimile version of the paper, see Brewis R A L. (ed.) (1990) *Classic Papers in Asthma*. Volume 1: The evolution of understanding. London: Science Press, 30–52.

[8] Reisseissen F D. (1808) *Ueber den Bau der Lungen*. Berlin: Rucker.

[9] René Théophile Hyacinthe Laënnec (1781–1826) invented the stethoscope. See Laënnec R T H. (1819) *L'auscultation mediate*, reproduced as a facsimile copy in Brewis R A L. (ed.) (1990), note 7, 84–100.

[10] Salter H H. (1860) *On Asthma: Its pathology and treatment*. London: John Churchill. For a facsimile copy of Chapter 2, see Brewis R A L. (ed.) (1990), note 7, 106–142. For example, see also Cohen S G. (1997) Asthma among the famous: Henry Hyde Salter (1823–1871), British physician. *Allergy and Asthma Proceedings* **18**: 256–258. Neale A V. (1963) Some thoughts and experiments on respiration and on asthma, with special reference to Henry Hyde Salter. *Medical History* 7: 247–257.

[11] Stramonium is derived from the poisonous *Datura stramonium* or jimson weed. In minute doses, administered internally or by inhaled smoke, it acts as an antispasmodic giving temporary relief in asthma. See Sims J. (1812) Communications relative to the *Datura stramonium*, or thorn apple: as a cure or relief of asthma. *Edinburgh Medical and Surgical Journal* **8**: 364–367. See Brewis R A L. (ed.) (1991), *Classic Papers in Asthma*. Volume 2: Treatment. London: Science Press, 1–4.

[12] Solomon Solis-Cohen (b. 1857) was Professor of Clinical Medicine and Therapeutics, Philadelphia Polyclinic and College for Graduates in Medicine from 1887 to 1902. See Solis-Cohen S. (1900) The use of adrenal substances in the treatment of asthma. *Journal of the American Medical Association* **34**: 1164.

[13] Bullowa J J M, Kaplan D M. (1903) On the hypodermic use of adrenaline chloride in the treatment of asthmatic attacks. *Medical News* **83**: 787–790. See Brewis R A L. (ed.) (1991), note 11, 106–109.

in terms of the treatment of asthma. In terms of modern management and aerosol drug delivery,[14] it wasn't until 1929 when Camps, a surgeon to the Teddington Cottage Hospital, described giving his patients what appears to be nebulized or atomized adrenaline. To quote him:

> '...the medicine was administered at bedtime for three to five minutes, at seven litres of oxygen per minute, after a few nights the nocturnal attacks were prevented and the asthma habit was broken. Cessation of treatment was not followed by any return while the patient was living an ordinary life, until some gross error of living or other accident, such as contagion of a cold or family anxiety, brought back attacks which yielded again at once to the treatment.'[15]

I think this brings us up to the current treatment and some of the drugs that we still use.

Godfrey: I would just add one point to that. A few months ago I was at a meeting in Marburg, Germany, and came across an antique shop selling antique medical equipment, and books, and one of the things was a nebulizer dating from 1910. It had a little kettle that heated water and sent a jet of steam across a T-piece, which is exactly like a jet nebulizer, and the medication went into a mouthpiece. It was thought to be about 1910, but of course they had nothing to put in it. But there were jet nebulizers at least 90 years ago.

Chris, thank you very much for that introduction. We wondered at this time whether Dr Frankland might like to tell us something, reminiscing a little bit about the history of asthma in his youth, or before his youth, about childhood asthma and what he can remember of its management.

Dr Bill Frankland:[16] Thank you, Mr Chairman. My name is Bill Frankland and I think, along with Archie Norman, I am probably the oldest person here. Oh, I am sorry, and Chris Booth (we could have a contest).

I thought I would describe what I was seeing 63 years ago and I would like briefly to describe three patients. They were all connected to the extent that there's something that goes wrong with the definition of asthma. And I must remind you of course, this

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[14] For a recent review of aerosol delivery systems, see Taburet A M, Schmit B. (1994) Pharmacokinetic optimisation of asthma treatment. *Clinical Pharmacokinetics* **26**: 396–418.

[15] Camps P W L. (1929) A note on the inhalation treatment of asthma. *Guy's Hospital Reports* **79**: 496–498, quote on page 497. See Brewis R A L. (ed.) (1991), note 11, 115–117.

[16] Dr Bill Frankland FRCP (b. 1912) began working in the Allergy Clinic at St Mary's Hospital, London, in 1946. He started the Daily Pollen Count in 1949 and gave it to the news media by 1951. In 1953 he published the first double-blind controlled trial of an allergic disease, namely, seasonal hay fever. In 1956 he became Consultant at St Mary's Hospital, in charge of the Allergy Clinic. On retirement, he worked for 20 years at Guy's Hospital, London, as an Honorary Consulting Allergist. He has been Vice-President of the National Asthma Campaign and President of the Anaphylaxis Campaign.

is the pre-antibiotic era, and although I had seen Leonard Colebrook[17] treat puerperal sepsis with Prontosil rubrum at Queen Charlotte's Hospital. Sixty-three years ago we didn't have a sulphonamide to treat asthmatics.

I was called from my room before 4 o'clock in the morning. My room, incidentally, was the room where penicillin had been discovered in 1928. If I could just waste a little more of your time by saying, of course, that the mould spore, *Penicillium notatum,* which contaminated that plate had flown in from the allergy department beneath Fleming's laboratory. At that time the allergy department was looking into the possible causes of mould spores causing asthma. Anyhow, I went down at 6 o'clock to see a patient and this infant was 12 months old, and the mother said that her boy had been wheezy and coughing nearly all his life; every cold caused severe wheezing. He had developed a cold two days previously and she was going to bring it along to the hospital (they all just came along to the hospital to the casualty department as it was then called), but with her eight other children she was so busy she didn't have time. That particular morning the child had changed a lot, the coughing and wheezing had stopped and he had changed colour and she was worried. And here was I at 6 o'clock in the morning seeing my first case of what I thought was acute asthma. This story was all lies, the child was quite cold; he had obviously been dead for some considerable time. I remembered my previous teacher, Dr Wilson – you know him better as Lord Moran,[18] Churchill's doctor – had said that history was so important, but no one had ever suggested that the history you take might be a packet of lies.

Now briefly, the next case I saw two months later, I was on duty at 2 o'clock in the afternoon, and the nurse said would I please urgently see a boy who was having difficulty in breathing. She thought that I might have to admit this child to the ward, because it had acute asthma. In fact, this boy aged 12, didn't have acute asthma. He had had a sore throat the previous day and that morning speech was difficult, eating was difficult, and now breathing was difficult. I gave one look at the throat and saw a diphtheritic throat, I thought, and the reason I remember this particular case is that I had never used force on any patient before or since, or ordered so much force to be used. As soon as I said to the mother, 'He will have to go to the Western Fever Hospital, because he has got diphtheria, I think, and I have to take a swab before he goes,' the boy shut his lips very tightly and would not allow this to be taken. So I got three hefty medical students, two of them in St Mary's rugger team, two nurses and

[17] Leonard Colebrook FRCOG FRCS FRS (1883–1967) joined Almroth Wright at St Mary's Hospital in 1906, becoming interested in puerperal fever in women following childbirth. In 1935 he successfully treated a woman with puerperal fever with the newly discovered antibacterial drug Prontosil. He was responsible for the clinical trials, under the MRC, that established the efficacy of sulphonamides (derivatives of Prontosil).

[18] Charles McMoran Wilson (first Baron Moran of Manton from 1943) MC Kt FRCP (1882–1977) was Consulting Physician, St Mary's Hospital, London, and Dean of St Mary's Hospital Medical School from 1920 to 1945, and President of the Royal College of Physicians from 1941 to 1950. See Lovell R. (1992) *Churchill's Doctor: A biography of Lord Moran.* London: Royal Society of Medicine Services. See also his autobiography, Moran C M W. (1984) *The Anatomy of Courage.* London: Keynes Press for the British Medical Association. First published in 1945 by Constable and Company Ltd.

myself, and while I held his nose, we got a very good view of that throat. I took a swab and said, 'Let go', as I was causing acute obstruction with the tongue depressor and he went almost blue. The first cough that he took, very near my face, went all over me. Now that is another story, the bilateral membranous conjunctivitis that I had three days later, that's something different. I apologized to the mother that we had to use force, but I said that it was essential that I got a good view of that throat, and she said, 'Oh what a pity'. The reason he was so difficult, of course, was that his school friend had been sent to the same fever hospital three days earlier with diphtheria. This was a bit of the history that I hadn't got. And she added, 'And from his form two days before, he had difficulty in breathing and was given an operation on his throat, and he died on the table. That's why my son didn't want to go to this fever hospital.'

My third and final case – am I allowed a third case? I was asked to see a boy in the ward because my boss then was Dr W D W Brooks[19] of the Brompton, and I suppose they thought I would know something about asthma. This boy, aged five, had his eighth admission in about ten weeks to the children's ward with acute asthma and I had never seen so many notes as on this one boy, all from the social workers. His mother was a prostitute, she wasn't even a Paddington one, she had a place just off the square in Mayfair – upmarket – and she was actually very pleasant. The father, on the other hand, was an alcoholic, but generally in prison. The story was that the boy had this intense fear of his father, he really was terrified of his father. I don't know if anyone here has ever seen a one-cause asthma due to emotional causes, but everyone agreed that this was the cause. The reason I was asked to see this boy was that a new houseman had noticed that during his first admission and the last two admissions, the father was in prison (in fact he got a two-year sentence the last one), so he couldn't be the cause. I took a different history and the boy, of course, had a cat and he knew he was cat-sensitive, it had caused trouble to his eyes, to his nose, and if the cat scratched him, to his skin, and also caused him asthma. So I said, 'Why didn't you tell anyone, you have been in here eight different times and you know the cause of your asthma and you have never told anyone?' He said, 'No one has asked me whether I have a cat at all, you are the first person.' I said, 'Why didn't you tell them that you knew the cause?' He started crying and said, 'Well my cat produced kittens on my bed two days before I came into hospital, I know what you will advise, you will advise me to get rid of the cat,' and he cried and cried and cried. I think somehow that he had one-cause asthma due to allergy. In retrospect, St Mary's Hospital, where this was happening, had an outpatient allergy clinic at the beginning of the century run by Dr John Freeman, and after a few years he got in Dr Leonard Noon to help him with his work. Dr Noon wrote the first paper on desensitization.[20] The only difference between Noon and his investigations and possibly ours, was that he did conjunctival tests and we did

[19] Dr Donald Brooks CBE FRCP (1905–1993) was a physician specializing in chest diseases at St Mary's Hospital, London, from 1935 to 1970 and from 1938 on the staff of the Royal Brompton Hospital, London. See Lovell R R H. (1994) William Donald Wykeham Brooks. *Munk's Roll* **9**: 57–59.

[20] Noon L. (1911) Prophylactic inoculation against hayfever. *Lancet* **i**: 1572–1573. Freeman J. (1911) Further observations of the treatment of hay fever by hypodermic injections of pollen vaccine. *Lancet* **ii**: 814–817.

skin-prick tests on this boy to confirm that he was allergic to cats. We didn't use a histamine-positive control, because 60 years ago, of course, antihistamines hadn't come along. Those are three patients where the history was not quite what one thought it might be.

Godfrey: Thank you. My father was a medical student and later a doctor at St Mary's Hospital about that time, so the names are very familiar to me. Dr Norman, could we encourage you to say a word or two about how asthma was treated as long ago as you can remember.

Dr Archie Norman:[21] Thank you very much, Simon. My memory of almost all the things you want to hear about is extremely faulty and where it is not faulty, it tends to be erroneous, so don't trust too much. To cap Bill Frankland's story, I just happen to remember I recommended that a dog should be taken away from the house because an asthmatic child appeared to be sensitive to the dog. The family came back to see me a month later and said that they had had a burglary the next day.

My impression when I was a student and a houseman is that asthma in childhood then was very much what you might call an 'orphan disease'. Nobody was that interested in it. There was no adequate treatment and children didn't ordinarily die from it, so the principal physicians really tended to pay it little attention. What treatment there was, as I can remember just after the war, was ephedrine and things of that sort. Potassium and stramonium were very popular, for asthma and for whooping cough. Antihistamines were tried extensively with, I think, no success, although we thought there was some. But there was no really effective safe treatment until, I would have thought, the 1950s or 1960s.

Concerning steroids in the 1960s and the 1970s,[22] I saw a number of children with extremely severe asthma – stunted, ill, never at school. When treated with prednisone,[23] say 5–10 mg daily, they could return to what appeared to be a normal life and normal schooling and this was a great result because they were no longer thought to be dim and unfit for school. They were normal children for that time. But of course after a year or so, it was becoming manifestly unsafe to continue with an asthma-controllable dose of prednisone or steroids and one had to stop.

Godfrey: I think Dr Morrow Brown is going to talk a little bit about steroids later.

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[21] Dr Archie Norman MBE FRCP (b. 1912) was assistant Tuberculosis Officer to the Middlesex County Council in 1939, before his War Service from 1940 to 1945. He was appointed Physician to the Great Ormond Street Hospital in 1950, where he developed the Respiratory Unit, until his retirement in 1977. He was Chairman of the Research Committee of the Cystic Fibrosis Trust from 1978 to 1984.

[22] For early use of corticosteroids see the Introduction to Brewis R A L. (ed.) (1991) *Classic Papers in Asthma*. Vol. 2: Treatment. London: Science Press.

[23] Prednisone, a systemic glucocorticoid taken orally, is used as an anti-inflammatory to treat acute asthma, becoming active only after conversion in the liver to prednisolone.

Norman: What I would like to add is that we had a number of deaths, and my impression was that the danger was in diminishing and stopping the dose. It was after that, that the children became suddenly ill and there were occasional sudden deaths. I think that's really all you want to hear at the moment.

Godfrey: Thank you very much. I am sure you will join in later. I actually went to a library and got out a couple of papers from Great Ormond Street about that time, a little bit before your time actually. In the fifth volume of the *Archives of Disease in Childhood*, 1930, there is a paper by Bray on childhood asthma.[24] It is no less than 18 pages long, it has a 111 references, and not a single word, not one word, about treatment. The only thing it does have is about prevention, prophylaxis, and it says here, 'Allergics shouldn't marry each other'.

Norman: I think your friend Maimonides and others, later, did a great deal of harm by saying that asthma was an emotional condition. Even in the 1930s, I have a little book, *The Nervous Child*, by Hector Charles Cameron of Guy's, saying just the same thing.

Godfrey: In 1928, also from Great Ormond Street, Pearson and Wyllie talk about the treatment of asthma in *Recent Advances in Disease of Children*. They talk about prevention, which is no different from Maimonides – hygiene, fresh air and not too much sex or whatever, except that's irrelevant, as it was paediatrics. They do actually talk about treatment of acute attacks which include potassium iodide, stramonium, and during an attack adrenaline. If this fails, morphia, one-twelfth of a grain for a child of six years, hypodermically to be effective, or ephedrine hydrochloride, a quarter to a half a grain by mouth, was recommended.[25]

The other interesting thing, from Great Ormond Street of that time, was a survey of paediatrics outpatients, of whom only 1 per cent were asthmatic in the early 1930s. I suspect it is probably a little higher than that these days. What was it like in your day, Professor Warner?

Professor John Warner:[26] I just wanted to say something about morphine, Simon. It's interesting that even into the 1960s and early 1970s, there were still physicians who believed that a very small dose of morphine was an appropriate treatment for acute asthma. When I was a registrar at the Queen Elizabeth Hospital in Hackney in 1973 there was still a consultant there who insisted that his patients should be given a small dose of morphine when admitted with acute asthma. All the SHOs and registrars would carefully steer him away from these patients because they were absolutely

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[24] Bray G W. (1930) The asthmatic child. *Archives of Disease in Childhood* 5: 237–258.

[25] Pearson W J, Wyllie W G. (1928) *Recent Advances in Diseases of Children*. London: J & A Churchill, 336–337.

[26] Professor John Warner FRCP FRCPCH FMedSci (b. 1945) has been Professor of Child Health in the University of Southampton since 1990, having qualified at the University of Sheffield and worked at the Hospital for Sick Children, Great Ormond Street, London, and the National Heart and Lung Institute, London (part of the Imperial College of Science, Technology and Medicine's new Biomedical Science Faculty from 1995). His main interests are in the early-life origins of asthma and related allergic disorders.

petrified of ever using morphine, and would use various forms of subterfuge to avoid confrontation over the issue. Such comments as, 'The patient was admitted just before your take started', or 'Casualty had already given him some nebulized salbutamol. The patient improved so much it was not necessary to administer morphine.'

Professor Tony Milner:[27] Can I follow that? When I was a medical student, we used to go down to Pembury, where there was a certain Dr Jacoby who knew how to treat asthma: [**Godfrey**: That was him! The only paediatrician to do his own surgery for pyloric obstruction.] He certainly gave good doses of morphine and it certainly seemed to work. I have seen children admitted with really severe asthma, who were given morphine. A look of satisfaction came on to their faces, they stopped wheezing and they didn't go blue!

Godfrey: Anybody else like to mention the advantages of morphine?

Professor Ross Mitchell:[28] I am based in Dundee now, but in 1947 I was in Liverpool. I wasn't going to talk about morphine, but, taking up Professor Godfrey's second point about the frequency of asthma in hospital, I would say that in Liverpool in 1947 we thought of Great Ormond Street and St Mary's Paddington as rather rarified atmospheres. In the rough and tumble of provincial hospitals like the Royal Liverpool Children's Hospital, the wards were full of children with tuberculosis, leukaemia, rheumatic carditis, empyema and bronchopneumonia, and we considered asthma as a comparatively minor condition to be treated for the most part in general practice and seldom admitted to hospital. If children came in status asthmaticus, we gave them adrenaline in the outpatient department. By contrast with the children who were ill and dying in the wards, we didn't rate asthma so highly then and it was that much less common. Even in 1953 when I was working in the Allergy Section of the Mayo Clinic, allergy and asthma were looked upon rather disdainfully by other specialities.

Mrs Eleanor Hickie:[29] I developed asthma at the age of four in 1943. Two things happened then: my father was shot down, missing and presumed dead, and my mother started smoking all on the same day. And although my father returned at the end of the war, my mother didn't stop smoking. I remember from four until 17 I spent my life in a frenzy of atropine and adrenaline and then being sedated until I could barely breathe, so I can't actually say much for the idea that sedation did help at all. On the last occasion I was actually given two tablets of Soneryl and I managed to

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[27] Professor Anthony Milner FRCP (b. 1938) was Professor of Neonatology at the Guy's, King's and St Thomas' Hospital Medical School of King's College, London, from 1990 to 2000, later Emeritus. He had been Professor of Paediatric Respiratory Medicine at the City and Queen's Medical Centre, Nottingham, from 1982 to 1990.

[28] Professor Ross Mitchell FRCPEd FRCPCH (b. 1920) trained in paediatrics in Liverpool, Edinburgh, and London, and held a Rockefeller Research Fellowship at the Mayo Clinic, Rochester, Minnesota, USA. He was Professor of Child Health in the University of Aberdeen from 1963 to 1972 and in the University of Dundee from 1973 until his retirement in 1985, later Emeritus.

[29] Mrs Eleanor Hickie (b. 1939) has been a staff nurse at the Queen's Medical Centre, Nottingham, from 1992 to 2001.

secrete them in the back of my mouth and didn't swallow them. In the morning the consultant almost decapitated the registrar and I have never been sedated since. My asthma has almost improved since I stopped eating nuts four years ago. I don't use a nebulizer or inhaler at all.

Professor Tim Clark:[30] If we are talking of sedation and asthma, just briefly I can remember Mac Cochrane and I carried out a survey of deaths from asthma in London[31] in what was then known as the GLC [Greater London Council, 1964 to 1986], this was [Ken] Livingstone's era. I can't remember the percentage, but we found a considerable proportion of those who died in the GLC area had taken sedation in one form or another. We then decided we should try to do what was a very rudimentary case control study and look at other patients admitted who hadn't died and found that an equally large proportion had also had the sedation. We included that in the paper published in *Thorax* but that section was rejected by the editors as being without interest. So it never appeared.

Professor Jack Howell:[32] Dr Pearson's name has been mentioned and I associate his name with the recognition of nocturnal dyspnoea and there may not be another opportunity to bring this in,[33] but I think it is such an important observation, such a crucially important symptom in asthma, that it's worth mentioning, and if I am correct, I think in this country at least, he takes credit for it. [**From the floor**: He shouldn't.]

Godfrey: I am into this in a big way at the moment because this is what my sabbatical is about. Sir John Floyer wrote that the fit begins about two in the morning, induced by the heat of the bed or words to that effect. He very clearly described nocturnal asthma.

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[30] Professor Tim Clark FRCP (b. 1935) has been Professor of Pulmonary Medicine at Imperial College, London, from 1990 and its Pro-Rector from 1995 to 1997 as well as serving as Provost of Imperial College at Wye from 2000. He qualified in 1961 and was Consultant Physician at Guy's Hospital, London, from 1968 to 1990 and at the Royal Brompton Hospitals, London, from 1970 to 1998. He was Dean of the United Medical and Dental Schools of Guy's and St Thomas' Hospital (Guy's, King's and St Thomas' School of Medicine, Dentistry and Biosciences since 1998), London, before becoming Dean of the National Heart and Lung Institute (merged with Imperial College of Science, Technology and Medicine as part of its School of Medicine in 1995), London. He was President of the British Thoracic Society from 1990 to 1991 and Vice-Chairman of the National Asthma Campaign from 1992 to 2000.

[31] Cochrane G M, Clark T J H. (1975) A survey of asthma mortality in patients between ages 35–64 in the Greater London Hospitals in 1971. *Thorax* **30**: 300–305.

[32] Professor J B L (Jack) Howell CBE FRCP (b. 1926) qualified at the Middlesex Hospital, London, in 1950 and held an MRC Fellowship at Johns Hopkins Hospital, Baltimore, Maryland, from 1957 to 1958. He was Senior Lecturer and Consultant Physician at the Manchester Royal Infirmary from 1960 to 1969 and Foundation Professor of Medicine at the University of Southampton from 1969 until his retirement in 1991, later Emeritus, and Dean of the Faculty of Medicine from 1978 to 1983. He was President of the British Thoracic Society from 1988 to 1989 and of the British Medical Association from 1989 to 1990 and Chairman of the Southampton Health Authority from 1983 to 1998.

[33] Professor Jack Howell wrote: 'I must accept that I was mistaken because I have searched the *Quarterly Journal of Medicine* throughout the 1930s–1950s and the paper I thought I recalled was not there. So I can't even confirm that I was confusing nocturnal dyspnoea with a study of exercise-induced asthma, which is my alternative thought. In any event, I precipitated half-a-dozen subsequent entries based on this error.' Letter to Mrs Lois Reynolds, 1 April 2001.

Howell: I believe that this paper which I think was in the *Quarterly Journal of Medicine* was really on a different plane. I think it is worth recording it, if true. I would like to go back and check it.

Godfrey: Was that before Margaret Turner-Warwick and the Brompton people with the morning dipping?[34]

Clark: Henry Hyde Salter recognized the diurnal variation. I agree Floyer did before him, but I doubt if Floyer was the first.

Godfrey: We started discussing asthma deaths, deaths from asthma and as everybody here is aware the epidemic of asthma deaths affected primarily children, young people, and we thought this would be an important topic to consider and I have asked Chris O'Callaghan to lead off and then we will all add our little bits and I think he is going to read some information he received from Charlie Thiel.

O'Callaghan: I would like to relate to you some written information we received from Charlie Theale, who was one of the chemists at Riker 3M in 1956 when the first metered dose inhaler was developed. The drug used was isoprenaline, developed in the 1940s and released in 1951 from Boehringer-Ingleheim. I looked through the various journals to find information on asthma at this time, particularly the *British Medical Journal*, and found very few articles during the 1950s and the early 1960s on asthma. The great increase in articles on asthma appeared to go hand in hand with the development of the first metered dose inhaler. In fact the adverts for Guinness outweighed those for asthma by a factor of ten in 1962, but that rapidly changed.

This is from Charlie Thiel.[35] Early in the spring of 1955 one of his bosses, Dr Maison, who I understand also invented the G-suit for fighter pilots, had a 13-year-old daughter with asthma, whose name was Susie. She used to frequently complain that the glass squeeze-bulb nebulizer she used for her isoprenaline kept breaking. She asked her father, 'Why can't they put my asthma medicine in a spray can like they do hair sprays?' Dr Maison was President of Riker Laboratories and the next day he approached Mr Irving Porush, head chemist in their three-person pharmaceutical development laboratory, to see if he could make a pressurized inhaler of a bronchodilator. Literally down the corridor was a cosmetics laboratory where he went for advice from colleagues who formulated hairsprays. They provided Porush with some background materials, equipment and supplies. In April 1955 he ordered some propellants from DuPont, borrowed an old ice-cream freezer from the Rexall drug store downstairs, bought an empty case of cola bottles and a bottle capper. Thus equipped he set out to formulate pressurized aerosols of epinephrine and isoproterenol. Before

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[34] Al-Damluji S, Thompson P J, Citron K M, Turner-Warwick M. (1983) Effect of naloxone on circadian rhythms in lung function. *Thorax* **38**: 914–918

[35] Thiel C G. (1996) From Susie's questions to CFC free: An inventor's perspective on 40 years of MDI development and regulation. *Respiratory Drug Delivery* **5**: 115–123, material above from 115–117.

coming to Riker Irving [Porush] had been a chemist for the Coca-Cola™ bottling plant. He knew that the cola bottles could hold about 1300 pounds per square inch internal pressure and they would be ideal for experimenting with. Irvine's formulation consisted of a drug with ascorbic acid, as an antioxidant, dissolved in alcohol and diluted to weight with propellants. Just prior to this, in about 1954, Phillip Meshberg had patented a metering valve that he envisaged would be useful for perfumes. They negotiated the use of his patent and together with the Wheaton Glass Company, who made little glass phials with a vinyl plastic around them, they assembled the first pressurized metered dose inhaler. It consisted of a Meshberg valve, a Wheaton Glass perfume bottle, and the drug inside. The actual plastic coating had a hole in the bottom and they thought that if it got overheated and exploded, the contents would come out of the little hole in the bottom and the glass wouldn't fragment into the patient.

Simple animal exposure studies were done as safety checks. The first clinical trial was carried out by Dr Karr at the Veterans Administration Hospital in Long Beach, California, in 1955. The treatment seemed to be effective and on 9 March 1956 the MedihalerIso and the MedihalerEpi, were launched. Around this time they patented various things to put in metered dose inhalers, including nicotine, which never got launched. They trialed insulin, and although it made animals hypoglycaemic, it was considered far too variable to launch on the public. They also formulated ergotamine [Medihaler Ergotamine, 3M], which was launched and I believe it either is still available or was available until recently for the treatment of migraine. The actual solution was of alcohol, and the metered dose inhaler had a long pipe in front of it to reduce the unpleasant effect of 50 per cent ethanol hitting the back of the throat.

A couple of years later Charlie Thiel reformulated these drugs as suspensions. This nearly cost Riker their business, as patients had associated the foul taste of alcohol with feeling better. The suspension without a foul taste had to prove itself again. In terms of popularity from that stage onwards, the metered dose inhalers have grown phenomenally. Over 500 million are sold per year. Unfortunately during the 1960s it was noticed that there was an epidemic of asthma deaths that seemed to be strongly linked to the development and the use of metered dose inhaler.[36]

Godfrey: Well I think maybe we could ask Dr McCracken at this stage to say something about his personal experience of asthma deaths in young people and then we will discuss more generally the whole question of the epidemic of asthma deaths.

Dr James McCracken:[37] My contribution really originates from a memorable patient article published in the *British Medical Journal* of 1997.[38] It's one thing to read these

[36] Committee on Safety of Drugs. (1967) Aerosols in asthma: Vaccines. *Adverse Reactions Series* No. 5. London: HMSO.

[37] Dr James Spowart McCracken MBE FRCGP (b. 1930) is now a retired principal and lecturer in general practice at the University of Nottingham. He edited two volumes of *Sport, Exercise and Medicine* in 1995 and was President of the Nottingham Medico-Chirurgical Society from 2000 to 2001.

[38] McCracken J. (1997) A memorable patient: Death in the Scottish Highlands. *British Medical Journal* **315**: 408.

anecdotes, but another to listen to them being read. One tends to feel that it's like watching paint dry, so what I would like to do is to briefly describe it and use my contribution as a means of jogging your memories about the level of our awareness of asthma during the 1950s. I understand that you all have a copy of the article in your folders. It was called 'Death in the Scottish Highlands'.

I graduated in the late 1950s in Aberdeen and was at that time working as a locum, my first locum. At around 2 o'clock in the morning, I was called to a patient's bedside from my hotel where I was staying. All I knew was that the patient was having an asthma attack, a 16-year-old, who was well known to us in the town as an attractive girl who used to serve the teas at the local cricket club. I knew all about asthma, my goodness I had learned it all up by then. So, driving along at 2 o'clock in the morning, I remember thinking that the village was on the other side of the world from Buckie, ten miles away in my Morris Eight. I was a bit peeved and I kept thinking to myself, 'Has she taken her tablets containing phenobarbitone – Franol tablets?'[39] (Everybody who had the slightest suggestion of bronchospasm was on Franol tablets for the next 20 years.) 'Was I expected to give her subcutaneous adrenaline,' because to do so would medicalize the problem and succeeding emergencies would have to be dealt with in the same way? 'No, I didn't feel inclined to do that'. 'Was her mother being over-protective?' After all we had been taught, 'Get rid of the mother and you cure the child's asthma.' 'Couldn't she have waited until the next morning?'

I eventually arrived at the village, but how to find the house? By God, it wasn't difficult. There was a loud wailing, banshee-like, spine-chilling lament coming from one of the cottages and when I went in, the girl's aunt who was looking after her, threw herself at me, battering me on the chest to help, and the child was as dead as a post on the floor, a 16-year-old. Of course, I gave the subcutaneous adrenaline that I had intended not to give. I knew full well she was dead by then. It was long before the days of mouth-to-mouth resuscitation. End of story. I went home a chastened man. I found that I knew less about asthma than I thought I knew. The village mourned and the practice went on with its ministry. Just one small corollary to that. The editor of the *British Medical Journal* asked me if I could possibly arrange to have confirmation of any relatives' agreement to this being published. Now, this was 40-odd years later and I didn't think that it had been the girl's mother, but I contacted the senior partner whom I still knew. We regularly exchange Christmas cards and although he'd retired by then, he well remembered the case. No way had the case been forgotten up there. He put me in touch with the senior nursing sister in the practice who was a 56-year-old, and yes, you've worked it out, she well remembered the young girl. She had been in her class at school. She remembered the house. She remembered the lot. It wasn't history up there, I can assure you.

That's the background to the story, but as I say I would like it to act as a sort of entrée to what was happening in asthma awareness at that time. I would like you to look back

[39] Franol is currently a proprietary combination of ephedrine hydrochloride and theophylline manufactured by Sanofi Winthrop. In the 1950s it also contained phenobarbitone.

and think – the Clean Air Act only came in, in 1958. The profession, far less the public, was certainly not aware of any hazards from cigarette smoking. Life was lived at a different pace. I still have a hand-written letter, addressed in the 1950s to a GP from a consultant paediatrician in Nottingham (Professor Morrow Brown and Professor Tony Milner will remember Dr Pat Page), where the last sentence reads, 'Please excuse the handwriting, but the hospital secretary is on holiday at present'. Life, as I said, was lived at a different pace.

I wonder if anybody who has graduated since 1960 remembers Tucker's Cure? Tucker's Cure was actually used very effectively to alleviate bronchospasm. It was cocaine and atropine given in a nasal atomizer. The term 'snorting' wasn't in use then! In the treatment of acute episodes of bronchospasm at that time, at least in the adult, your first consideration was to identify between bronchial and cardiac asthma. In the first, you really were dealing with the later effects of chronic bronchitis and emphysema, so common in those days. With the other, the patient was drowning of acute congestive cardiac failure. After all, digoxin had only just started to replace *Digitalis folia*. The patient requiring diuretics could only get treatment by intramuscular injection in the morning given by the district nurse. And hypertension was 'treated' only by barbiturates. Congestive cardiac failure was common. Good old aminophylline[40] you will remember, was given in a long large slow intravenous dose, 500mg in 20ml, and worked wonders. If cardiac asthma was suspected we used morphine or diamorphine added to the aminophylline.

I say in my article that my knowledge of asthma I had in those days had been gleaned from my tutor and mentor in general practice, a wonderful old man. As an undergraduate I had spent a month shadowing him. He was never without his atomizer – a large rubber bulb with a glass reservoir – containing, I think, adrenaline and ephedrine, but it might have been isoprenaline. [From the floor: Rybar was it?] Every house we went into he would flop down in the nearest, most comfortable armchair, puffing away at his atomizer. He would introduce me to the patient, 'I have brought a young specialist with me' and I was a specialist in whatever the problem happened to be. If it was the left knee I was a specialist not only in knees, but in the left knee. He subsequently died in status asthmaticus in the mid-1960s, in the middle of the dress circle, in the middle of an evening performance at the local theatre, still clutching his atomizer. I say he was a wonderful old boy, although in retrospect when he died he was probably a good ten years younger than I am today. They still say those were the good old days.

Godfrey: That's an excellent introduction and I am going to ask Professor Michael Silverman to read a piece that we have received from Professor Inman relating obviously to the asthma epidemics of the 1960s. He unfortunately was unable to be here because of his illness, but he very kindly wrote in and we have asked Michael to present the material.

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[40] See note 131.

Professor Michael Silverman:[41] I am the voice of Bill Inman.[42] This is in return for a free lunch, I think. And he writes:

> 'As my lack of mobility prevents me from attending this meeting in person, I have been asked to record a few words by way of introduction to what in a recent book I have called 'The Silent Epidemic'.[43] The epidemic was silent in its approach. It was massively damaging to the asthmatics of the mid-1960s who were using pressurized aerosol bronchodilators. The epidemic passed away with practically no publicity, in striking contrast with our experience with oral contraceptives, which was occupying us very much at that time. The problem was first identified by my former chief at the old Addenbrooke's Hospital in Cambridge, Dr Martin Greenberg, who wrote to the Committee on Safety of Drugs to say that he was concerned that patients using the new isoprenaline aerosols might be dying suddenly. Rather than rush into print, he had reported his concern to the Committee, but I warned him that the Committee would not act without further evidence and I advised him to write to the *Lancet*. In children in the 5–14-year age group for example there had been an increase in mortality rate of 330 per cent. In June 1967 the Committee on Safety of Drugs issued a low-key warning, advising parents to contact their doctors if their child had failed to achieve the normal response to its inhaler. Because of the one to two-year delay in publication of the UK vital statistics, Dr Adelstein,[44] the Chief Medical Statistician of the Registrar General's office and myself were only able to publish a paper which we called the 'Rise and Fall of Asthma Mortality' in 1969.[45] We reported that there had been a steady rise in asthma mortality running parallel to the increase in the sales of isoprenaline inhalers. It peaked in mid-1965 at the time of Dr Greenberg's first publication[46] and then fell gradually during the next three to four years. After the peak I noticed in the

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[41] Professor Michael Silverman (b. 1943) has been Professor of Child Health at the University of Leicester since 1995. He was at the Royal Postgraduate Medical School, Hammersmith Hospital, London, as Senior Lecturer in Paediatrics from 1977 to 1992 and Professor of Paediatric Respiratory Medicine from 1992 to 1995.

[42] Professor Bill Inman (b. 1929) qualified at Cambridge, acted as medical adviser to Imperial Chemical Industries from 1960 to 1964, joined the Ministry of Health's Committee on Safety of Drugs in 1964 as Senior Medical Officer, later Principal Medical Officer, to develop its voluntary reporting system, and was Medical Assessor of Adverse Reactions at the Ministry of Health until 1980.

[43] Inman W H W. (1999) *Don't Tell the Patient: Behind the drug safety net*. Los Angeles: Highland Park Productions. Chapter 3, The Silent Epidemic, 61–79.

[44] Abe Adelstein FRCP (1916–1992) was Chief Medical Statistican for England and Wales from 1975 to 1981 and Visiting Professor at the London School of Hygiene and Tropical Medicine from 1981 to 1984. He arrived in England in 1961 from South Africa, having been director of research and medical statistics of the South African Railways. See Marmot M. (1992) Obituary: A M Adelstein. *Lancet* **340**: 1463. Professor Jack Howell wrote: 'He was also statistical adviser to Howell and Altounyan in their first clinical study of cromoglycate in 1965.' Letter to Mrs Lois Reynolds, 6 July 2001. See note 87.

[45] Inman W H W, Adelstein A M. (1969) Rise and fall of asthma mortality in England and Wales in relation to use of pressurized aerosols. *Lancet* **ii**: 279–285. *idem* Asthma mortality and pressurized aerosols. ibid. **ii**: 693.

[46] Greenberg M J. (1965) Letters to the Editor: Isoprenaline in myocardial failure. *Lancet* **ii**: 442–443.

Hospital In-Patient Enquiry (HIPE) estimates of discharges and deaths that although the deaths were diminishing the hospital admissions and the discharges continued to rise. This suggested that we were dealing not so much with drug toxicity, but with over-confidence in a normally effective form of treatment. When children became tolerant to the isoprenaline so that it lost its effect, the danger was recognized too late and admission to hospital was delayed.

For several years I was a member of the Medical Research Council's Asthma Death Committee[47] and I remember at one of our meetings suggesting that we should look at the toxicity of the CFCs, the fluorocarbon propellants used in the pressurized aerosols. I could see that Colin Dollery[48] was fidgeting in his chair and Sir Cyril Clarke, the Chairman, had hardly got to the end of 'Any Other Business' when Colin grabbed his coat and briefcase, and rushed out of the room. Two weeks later he had an article in the *Lancet*.[49] The story was confirmed by Charles George who told me years later that when Colin got back to his laboratory at the Hammersmith, he was pressed into service as a volunteer. There was apparently no significant effect of CFCs and many other hypotheses proposed at these MRC meetings failed to explain this extraordinary epidemic. To conclude, I believe that both doctors and patients had been lulled into a false sense of security by a new treatment that was normally very effective, but that occasionally, once the patient became tolerant to it, led to a delay in resuscitation. The increase in mortality was relatively greatest in young patients, but all ages were affected, except children under five, who were too young to use the aerosols. The figures suggested that more than 3000 people died from asthma during the epidemic, in excess of the expected or baseline mortality of perhaps one-third this number and I have always been concerned that there could be another

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[47] 'The Council's Committee on Deaths from Asthma (Chairman: Sir Charles Stuart-Harris), which was set up in February 1968 to keep under review the problem of deaths from asthma and to advise the Council on further steps which might become necessary in the light of accumulating evidence, reported in June 1971. The Committee recommended that doctors should be alerted to the risk of death in patients in unrelieved status asthmaticus, and that the potential dangers of the excessive use of pressurized aerosols should be the subject of reminders to doctors and warnings to patients. The Committee is to remain in existence for a further period to hold a watching brief on deaths from asthma – particularly in young people – and to monitor the effects of changes in therapy; it hopes to stimulate detailed clinical studies of patients in status asthmaticus and further work on the mechanism of resistance to bronchodilator drugs.' House of Commons. (1972) *Medical Research Council Annual Report, April 1971– March 1972*. HoC 326. London: HMSO, 31.

[48] Professor Sir Colin Dollery Kt FRCP FMedSci (b. 1931) has been a senior consultant in Research and Development at Smithkline Beecham plc since 1996. He was Consultant Physician at the Royal Postgraduate Medical School, Hammersmith Hospital, London, from 1962 to 1996 and Lecturer in Medicine from 1962 to 1965, Professor of Clinical Pharmacology from 1965 to 1987, Professor of Medicine from 1987 to 1991 and Dean of the Royal Postgraduate Medical School from 1991 to 1994 and Pro-Vice-Chancellor for Medicine and Dentistry at the University of London from 1992 to 1996. He was a member of the Committee on Safety of Medicines from 1966 to 1975.

[49] Dollery C T, Davies D S, Draffan G H, Williams F M, Conolly M E. (1970) Blood concentrations in man of fluorinated hydrocarbons after inhalation of pressurized aerosols. *Lancet* **ii**: 1164–1166.

> 'silent epidemic'. I remember the aggressive way which salmeterol was promoted more recently, with the help of so-called post-marketing surveillance studies, in which doctors were paid to include large numbers of asthmatics, the majority of whom were probably being well controlled with their current antiasthma therapy. I cannot resist the temptation to plug my book, in which I recall the asthma epidemic and several other accidents with drugs. It's called *Don't Tell the Patient*[50] and you can find out more about it on the Internet.'

Thank you very much.

Godfrey: Would anybody like to comment on the epidemic? I would like to make just one small comment and that is that those who don't learn from history are doomed to repeat it. Of course we have seen the epidemics, or apparent epidemics, of asthma deaths with the fenoterol and probably other bronchodilators that occurred 20 or 25 years later in a similar fashion and disappeared and have generated the same argument as to whether it really is or isn't the drug or what's the problem? So there was the 1960s epidemic and, at least in New Zealand, although I believe in Canada too, the 1980s to 1990s epidemic.[51]

O'Callaghan: I wasn't around at that stage, but just reading through a variety of literature on the asthma deaths, I think the propellants in the inhalers and the drugs coming out of them were implicated. The background for that is the various work that was done on animals – they used to get animals to inhale the propellants, the fluorocarbons, and then exercise them in a laboratory. Provided they had inhaled enough propellants, they would drop dead of a ventricular tachycardia. Similarly, if they gave them propellants and then injected them with adrenaline, instead of exercising them, they again got ventricular tachycardia and died.

Godfrey: You mean Colin Dollery got it wrong?

O'Callaghan: Well, I am not sure. In the anecdotal reports children were reported to be seen clutching their empty metered dose inhalers. They would frequently go through 200 shots in three or four days. So in some cases at least, they were using them in excess. Dollery's work[52] suggested that the myocardium didn't get the levels of propellant that would sensitize it to these effects. In fact it got a tenth of that.

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[50] See note 43. See also, for example, www.societyguardian.co.uk/news/story/0,7838,438227,00.html or www.open.gov.uk/mca/aboutagency/regframework/mc/mcsm900.pdf (visited 7 June 2001).

[51] Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, Ball M, Beasley R. (1989) Prescribed fenoterol and death from asthma in New Zealand, 1981–1983: a case-control study. *Lancet* **i**: 917–922. Suissa S, Ernst P, Boivin J F, Horwitz R, Habbick B, Cockroft D, Blais L, McNutt M, Buist A S, Spitzer W O. (1994) A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *American Journal of Respiratory and Critical Care Medicine* **149**: 604–610.

[52] Dollery C T, Williams F M, Draffan G H, Wise G, Sahyoun H, Patterson J W, Walker S R. (1973) Arterial blood levels of fluorocarbons in asthmatic patients following use of pressurized aerosols. *Clinical Pharmacology and Therapeutics* **14**: 59–66.

However, if you got somebody to inhale the aerosol, as one of his volunteers did, on every breath for 30 seconds at the rate of 12 breaths per minute, the actual amount in the myocardium well exceeded the amount that would sensitize a dog's heart to injected adrenaline. Although people say that it's very safe, in fact the work that he did suggests that it may not be safe in excess. In the animal studies they found that one or two of the dogs were highly sensitive and would die following exposure to very small concentrations. So I think the jury is still out on what exactly caused the deaths.

Professor Stephen Holgate:[53] Around that time when the theory was being advanced, there was another name that ought to be mentioned – Dr Szentivanyi. He advanced a theory, based on an experimental animal model, that sensitization to allergens could lead to downregulation of adrenoceptor function. At that time there was an intense debate as to whether or not the fundamental cause of asthma was a decrease in adrenoceptor function and that the reason why these patients needed to use so much bronchodilator drug was because they had an impaired intrinsic response to it (adrenergic resistance). However, by taking an excess of bronchodilator to achieve a therapeutic effect, they were enhancing the cardiac side-effect of the propellants. It is interesting to note that this theory has never really gone away, despite the fact that it was based purely on an animal model. It remains in the literature to this day as to whether or not there is a fundamental abnormality of the adrenoceptor system that's behind some of the pathophysiology of asthma. It's fascinating to think that those observations, which I think date back to the late 1950s when Szentivanyi first did his experiments, have not really ever been disproven.[54]

Warner: It's interesting if you look through historical publications on asthma, that in the twelfth century Moses Maimonides's book, *Treatise on Asthma*, where asthma deaths were recognized to occur. He wrote that if, 'the rules of management go unheeded, asthma may well end in death'.[55] Yet Osler[56] at the beginning of the twentieth century is supposed to have said that he had never seen an asthmatic die, he talked about 'asthmatics panting on into old age'. At least he recognized it was a chronic condition that was life-long, even if he didn't recognize deaths. Did he truly miss all asthma deaths and ignore them or was it that there have been cycles increasing and decreasing risk of asthma deaths? Even in the 1950s asthma was not viewed as a

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[53] Professor Stephen Holgate FRCP FIBiol FRCPath FMedSci (b. 1947) has been MRC Clinical Professor of Immunopharmacology at the School of Medicine in Southampton since 1987. He has been Director of the Respiratory Cell and Molecular Biology Division within the Medical School at the University of Southampton from 1968. He chaired the Department of Health's expert group, the Committee on the Medical Aspects of Air Pollutants, from 1992 to 2001. See Holgate S T. (1994) Antihistamines in the treatment of asthma. *Clinical Review of Allergy* **12**: 65–78.

[54] Szentivanyi A. (1968) The β-adrenergic theory of the atopic abnormality in bronchial asthma. *Journal of Allergy* **42**: 203–231.

[55] See note 4.

[56] Sir William Osler FRCP FRS (1849–1919) was Regius Professor of Medicine at the University of Oxford from 1904 until his death. See Osler W. (1892) *The Principles and Practice of Medicine: Designed for the use of practitioners and students of medicine.* Edinburgh: Young J Pentland.

potentially fatal disease. I have an extract from a ship's captain's medical guide from 1952, talking about asthma:

> '...attacks are considered to be due to peculiar sensitiveness of the patient to nervous upset or to certain irritants like dust. Although often very distressing, asthma is not a dangerous disease.'[57]

Sir David Jack:[58] I'm formerly of Allen & Hanburys and Glaxo. We also did studies in dogs and found that normal animals tolerated multiple inhalations of isoprenaline delivered from pressurized inhalers. The propellants were therefore unlikely to be a primary cause of the unexpected deaths associated with excessive use of inhalers. However, when repeated inhalations of the isoprenaline aerosols were given to hypoxic dogs some of them died with cardiac arrest in diastole.[59]

I believe that hypoxia was also a critical factor in the deaths of patients who used their isoprenaline inhalers increasingly despite a waning response to the drug and steadily worsening asthma. Unfortunately for the victims, these were consequences of progressive physical occlusion of the airways and not of pharmacological tolerance to isoprenaline. Further inhalations of the drug were lethal because they increased the oxygen requirement of an already hypoxic heart and, at the same time, may have reduced its oxygen supply by lowering the blood pressure and, therefore, coronary flow. The outcome was death, probably following cardiac arrest in diastole. All of this emphasizes the need for appropriate steroid treatment to contain inflammation in the airways of asthmatics.

Dr Ian Gregg:[60] Referring to Professor Warner's remarks about Sir William Osler's dictum that asthma never caused deaths, I believe that in the context of Osler's

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[57] Ministry of Transport and Civil Aviation. (1952) *The Ship's Captain's Medical Guide*. London: HMSO. Quote on page 167.

[58] Sir David Jack Kt CBE FRSE FRS (b. 1924), a pharmacologist, has been associated with new medicines for asthma (Queen's Awards for salbutamol, 1973; inhaled beclomethasone dipropionate, 1975), hypertension, peptic ulcer (Queen's Award for ranitidine, 1985), nausea and migraine. He was a scientist in the Glaxo Laboratories from 1951 to 1953; Head of Product Development at Smith Kline and French from 1953 to 1961; Research Director of Allen & Hanburys, a constituent part of Glaxo, from 1961 to 1973 and Managing Director of Allen & Hanburys from 1973 to 1978; and Research and Development Director of Glaxo Holdings from 1978 to 1987.

[59] Sir David Jack wrote: 'A similar sensitivity to β-agonists was found by Shanks and his colleagues in Belfast in anaesthetized dogs made hypoxic by inhaling nitrogen-enriched air.' Comment on draft transcript, 15 January 2001. Shanks R G. (1966) The effect of propranolol on the cardiovascular responses to isoprenaline, adrenaline and noradrenaline in the anaesthetized dog. *British Journal of Pharmacology* **26**: 322–333. Black J W, Duncan W A, Shanks R G. (1965) Comparison of some properties of pronethalol and propranolol. *British Journal of Pharmacology* **25**: 577–591.

[60] Dr Ian Gregg FRCP FRCGP (b. 1925) was in general practice in London from 1958 until his retirement in 1987. Much of his research was carried out in association with the then Cardio-Thoracic Institute (later Royal Brompton Hospital, London), where he was Director of an extramural Department of Clinical Epidemiology. His special interests have been the assessment of bronchial airflow by PEF (peak expiratory flow) in collaboration with Dr Martin Wright (1912–2001), the inventor of peakflow meters, the roles of bacterial and virus infection of the bronchi and the epidemiology of asthma worldwide. See Anonymous. (2001) Martin Wright. *The Times*, 23 March, 25; Wright C M. (2001) Basil Martin Wright. *British Medical Journal* **322**: 1308. For details of Wright's work at the MRC, see Reynolds L A, Ness A, Tansey E M. (eds) The MRC Epidemiology Unit (South Wales). *Wellcome Witnesses to Twentieth Century Medicine*. vol. 13. London: Wellcome Trust Centre for the History of Medicine at UCL, in press.

experience of asthma in hospital practice, his observation was correct.[61] At the time he wrote those words, there seems very little evidence that deaths from asthma in hospitals were at all common. I have studied the records of three London hospitals from 1880 to 1930 and found that before the First World War almost no children and very few adults were admitted with asthma, and there were no deaths. From 1919 onwards, admissions of children increased, but to a much greater extent in adults, in whom there were 11 deaths.[62]

But going back to the whole question about the cause of death in the so-called epidemic of asthma deaths that occurred in the 1960s, there appeared at the time to be a strong temporal association between deaths and the use of pressurized metered aerosols containing isoprenaline, particularly the stronger of the two preparations, iso-forte. It has been my understanding that when these deaths were reviewed some years later, only about a third of them were linked with the taking of isoprenaline.[63] I think that comes back to really a more fundamental question still, and that is this: when one considers the relative frequency of asthmatic attacks and fatality, why, in the absence of treatment or what we would now regard as good modern treatment, why were deaths so uncommon? So, why is it that once an attack has begun, it does not invariably progress to total obstruction of airflow and death? Is there some mechanism that can terminate the process but occasionally fails to do so and in that case, death follows?

Finally when Simon [Godfrey] referred to the treatment of acute asthma in children at Great Ormond Street in the 1930s with injected adrenaline or ephedrine by mouth,[64] I was reminded of a discussion we once had many years ago about the relative merits of selective adrenoceptor agonists and ephedrine. My argument was that whereas they may have been selective agonists and had fewer cardiac effects, ephedrine is an analogue of adrenaline and therefore has '*pan*-adrenergic' properties.[65] Would someone like to comment on these two issues?

Dr Alistair Brewis:[66] I was only just going to add a comment to balance the focus that we had earlier on the toxicity or possible toxicity of the components of the

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[61] Dr Ian Gregg wrote: 'In the first edition of his *Principles and Practice of Medicine*, 1892, Osler wrote, "Death during the attack is unknown".' Letter to Mrs Lois Reynolds, 30 March 2001.

[62] Dr Gregg has been undertaking a study of deaths from asthma from 1700 to the present and the prevalence of asthma from the 1920s, supported in part by a grant from the Wellcome Trust.

[63] See note 45.

[64] See note 24.

[65] Gregg I. (1970) Clinical experience with disodium cromoglycate and assessment of its steroid-sparing action, in Pepys J, Frankland A W. (eds) *Disodium Cromoglycate in Allergic Airways Disease: A symposium held at the Royal Society of Medicine, London, on 5th March 1969*. London: Butterworths, 177–187.

[66] Dr Alistair Brewis FRCP (b. 1937) qualified at Newcastle upon Tyne in 1960 and trained at the Royal Victoria Infirmary, Newcastle, the Hammersmith Hospital, London, the Royal Brompton Hospital, London, and Manchester Royal Infirmary, before returning to the Royal Victoria Infirmary as Consultant Physician in 1970, specializing in respiratory medicine. He edited *Thorax* from 1982 to 1986.

bronchodilator aerosols and to back up what Ian Gregg has just been saying that many of us at the time felt that the whole issue was much more complex. I was terribly impressed by a paper by Speizer, Doll, Heaf and I think Leonard Strang was the last author, in which they had suspected at the outset that the cause of the deaths might be overuse of steroids that were getting a bad press at the time. They found to their surprise that there was relative underuse of steroids in this group of supposedly terribly severe asthmatics who had died from it. I forget the figures, but there were 177 deaths that they looked at. I think there were 16 who had been on high-dose steroids, but the rest had been on either a non- or a low-dose of steroid which hadn't been put up or those that had been put up only received the increased dose on the day before death, something of that sort.[67] There was striking underuse of steroids in this group, so certainly they were pressurized-aerosol users. Perhaps that had given them an undue sense of security. And the other thing that came up then, and was focused on in other studies of death, was the element of surprise. Doctors were surprised. That came out at that time as well. So many people, I think, were not just looking at whether those who died were being poisoned by the aerosols, but at a much more complex effect of the bronchodilator aerosols on the rest of treatment and how patients were managed.

Godfrey: I remember the arguments going around at that time, and one I remember being put forward was that the epidemics were not seen in all countries using the same drugs, and this was very difficult to explain. I think it was Scotland that had fewer deaths, that needs to be checked, but I think it was much less in Scotland and greater in England and Wales.[68] This seemed to be regional. Again the similarity to the New Zealand fenoterol epidemic.[69] But in fact that wasn't correct because it was also seen in Canada and it was also seen in fact with other bronchodilator drugs when it was looked at more closely, and I personally think that it comes back again to what you were saying, the underestimation of the severity of the asthma or masking of the severity of the asthma or underuse of steroids was almost certainly a major contributing factor both to the original 1960s epidemic here and to the more recent epidemics.

Clark: Yes, this is *déjà vu* all over again. I was on the MRC Committee on Asthma Deaths which went on for quite some time,[70] because there was endless debate about the mechanisms, whether it was the constituent parts of the aerosol other than the

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[67] Speizer F E, Doll R, Heaf P, Strang L B. (1968) Investigation into use of drugs preceding death from asthma. *British Medical Journal* **i**: 339–343. Information received on 177 out of 184 deaths, revealed that two-thirds of the patients had received corticosteroids before the terminal episode, and 84 per cent were known to have used pressurized aerosol bronchodilators. The paper concluded that more information was needed about the usage of these drugs. See also Speizer F E, Doll R, Heaf P. (1968) Observations on recent increase in mortality from asthma. *British Medical Journal* **i**: 335–339.

[68] See Speizer F E, Doll R, Heaf P, Strang L B. (1968), note 67, 337, indicating that the Scottish death rate at ages 5 to 34 was generally lower than England and Wales, but the increase in the number of deaths was similar. See also Fraser P, Doll R. (1971) Geographical variations in the epidemic of asthma deaths. *British Journal of Preventive and Social Medicine* **25**: 34–36.

[69] See note 51.

[70] See note 47.

pharmacological agents, whether it was the high-strength isoprenaline, whether it was the hypoxia induced by the use of the inhalers? The whole thing gradually fizzled out as the epidemic waned. No one was quite sure why it had waned, other than the view that gradually gained hold, as Alistair Brewis has said, that it was more of a behavioural response to the treatment. The immediate acute effect on relieving symptoms beguiled patients into believing that they needed no other treatment, and it was relative undertreatment with steroids that led to death. And this came up in the recent Saskatchewan study[71] of near death and deaths that were originally related to fenoterol and after endless arguments the view again came back to the idea that it was asthma being under treated. Indeed subsequent analysis of the Saskatchewan deaths has shown that when they looked at all the treatments at the time the odds ratio of death associated with treatment was increased for virtually all the bronchodilators. It was as high with theophylline as with the others and the only treatment that was associated with fewer deaths was inhaled steroids, which is now being followed up. There is now evidence accumulating that regular use of inhaled steroids is associated with a reduction of deaths in any community. So the whole history of the original epidemic of deaths has been recycled with New Zealand, Saskatchewan and this afternoon. I suspect it will continue for another 50 years.

Dr Paul McCarthy:[72] I just want to make a comment on the certification of death from asthma. I think we do need to remember that certification in different countries is at different levels. I was at a presentation last week on the Scottish Confidential Inquiry into Asthma Deaths[73] and they found that a third of the deaths recorded as asthma were in fact not from asthma at all, but asthma was on the certificate because the patient suffered from asthma. To comment on what Professor Clark has said, I think we are in great danger sometimes of blaming the obvious culprit, and one might say that if a patient is found dead in a desert clutching a water bottle then they might have died from excess water intake; and we are in danger of saying, if patients are clutching their empty β-agonist inhalers, that that is the cause rather than the under-treatment of the underlying disease.

Godfrey: Professor Holgate is a joint author of a paper of age-specific trends in asthma mortality in England and Wales by Campbell, Cogman, Holgate and Johnston, which was published in the *British Medical Journal* in 1997, and that actually shows that asthma mortality rates are decreasing.[74] Do you stand by that, sir?

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[71] Spitzer W O, Suissa S, Ernst P, Horwitz R I, Habbick B, Cockcroft D, Boivin J F, McNutt M, Buist A S, Rebuck A S. (1992) The use of β-agonists and the risk of death and near death from asthma. *New England Journal of Medicine* **326**: 560–561.

[72] Dr Paul McCarthy MRCPCH MRCS (b. 1942) was in general practice, first in the Republic of Ireland and subsequently in Suffolk, from 1974 to 1993. In 1987 he developed the McCarthy mask, the first mask for attachment to large volume spacers for the administration of inhaled medication to small children. In 1993 he was appointed Regional Medical Adviser by GlaxoWellcome, later Associate Medical Director from 1997. He is an Associate Specialist in Respiratory Medicine at the Norfolk and Norwich Hospital, Norwich, and in Paediatric Respiratory Medicine at Addenbrookes Hospital, Cambridge.

[73] Bucknall C E, Slack R, Godley C G, Mackay T M, Wright S C on behalf of SCIAD collaborators. (1999) Scottish Confidential Inquiry into Asthma Deaths (SCIAD), 1994–96. *Thorax* **54**: 978–984.

[74] Campbell M J, Cogman G R, Holgate S T, Johnston S L. (1997) Age-specific trends in asthma mortality in England and Wales, 1983–95: results of an observational study. *British Medical Journal* **314**: 1439–1441.

Holgate: Only to the point that the statistics derived from death certificates, if we can believe them in the UK, show that the number of deaths are decreasing. If you look at the age-related mortality, the confidence of a diagnosis of asthma as a cause of death increases as one gets into the young adults as opposed to the older generation. In this younger age group the mortality from asthma also seems to be falling and, as far as I am aware, I think the trends are continuing, which is encouraging. Now whether the decline in mortality is due to a change in asthma management or the delivery of healthcare on the ground, we can spend a long time debating, but certainly the trends are encouraging.

Godfrey: Well, Sir David, could you tell us whether the sales of metered-dose bronchodilators are decreasing?

Jack: They should not be, because they are key drugs for asthmatics, but as one of yesterday's men, I do not really know. I have, however, no doubt that the proposition being made about under-usage of steroids is right. I used to have the sad job of sending company doctors to inquests on patients who died after excessive use of their inhalers. Virtually without exception, the post-mortem results showed very clearly why they died. Their bronchi were so occluded by the products of inflammation that no bronchodilator could create an open airway. The only drugs known to me that can prevent gross physical occlusion of the airways are the systemic and inhaled anti-inflammatory steroids. There may be others in development today but I am unaware of them.

Godfrey: Anybody else like to join in? The point I was really making here was that I am sure that we are not using fewer bronchodilators, in fact we are using even other kinds of longer-acting bronchodilators. The UK statistics, which I believe are very good, and Professor Holgate and his colleagues' data look very solid, show the death rate at least is not increasing, so someone is doing something better, but we are still using the bronchodilators.

Sir Christopher Booth:[75] I wanted to comment about the pathology of the situation. When somebody dies of asthma what is the pathology of the bronchioles? I can recollect when I was a medical student in Dundee many years ago seeing an autopsy on a patient who died of asthma and the striking thing was the hypertrophy of the muscle in the bronchioles. There was a gross hypertrophy of the muscles, and one was puzzled to know how on earth one could conceivably dilate such a situation. I don't know what the pathology is in fatal asthma. Anybody like to comment on that?

Godfrey: Well, that has stunned you all into silence.

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[75] Sir Christopher Booth Kt FRCP (b. 1924) trained as a gastroenterologist and was Professor of Medicine, 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, and Harveian Librarian at the Royal College of Physicians from 1989 to 1997. He was the first Convenor of the Wellcome Trust's History of Twentieth Century Medicine Group from 1990 to 1996.

Holgate: I think there are two important issues here. The event that causes the crisis leading to death is to do with occlusion of the airway lumen and that is as much about secretions and air-trapping as it is about contraction of the spiral smooth muscle. But I think the point you make, Chris [Booth], is a valid one, and it is one which, in our rush towards the great pro-inflammatory theory of asthma, we have left behind, namely that in established asthma there are major changes to the structure of the airway wall, referred to as 'remodelling'. We are only just beginning to go back and look at the mechanisms responsible for this now and in particular trying to understand what it is in the asthma syndrome that leads to this structural change and how this interacts with the inflammatory components of the disease.

Godfrey: We would like to move on to talk a little bit about Intal®,[76] sodium cromoglycate and the famous Intal story, because that's certainly one of the exciting events of twentieth-century asthma treatment in the UK. I like to think that all the best inventions in asthma treatment came from the UK and the poor Americans were years behind. They get very upset when I say that. Mr Bell, can you tell us something about cromoglycate and Roger?

Mr John Bell:[77] I am from Loughborough and I just happened to be an employee of Fisons Pharmaceutical Division at the time that Intal was being developed, so this is a bit of a third-party story. The story of sodium cromoglycate, of course, is the story of Roger Altounyan.[78] Roger was a physician at the Monsall Hospital in Manchester where he had an asthma clinic and another clinic. He had a number of patients that he had characterized very thoroughly, in fact he could play tunes on them, whatever that meant, but he really understood this set of patients very well. At the time he was employed by Benger Laboratories, at Holmes Chapel in Cheshire. The treatment of asthma at that time of course was by isoprenaline, administered by pressurized inhaler. As we have already heard this afternoon, the Riker Medihaler was the dominant dosage form I think. Asthma at that time was a rather mysterious condition and I can remember Roger describing to me that schoolboys would be told by the headmaster to 'brace up', there was nothing really wrong with them. This seemed to be the picture of the disease at that time. Roger was looking for a long-acting isoprenaline and he worked with chemists in the research division, as is well known now, on derivatives of khellin and ultimately they

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[76] Intal® (disodium cromoglycate, sodium cromoglycate, cromolyn; Fisons) was synthesized in 1965 from khellin, a chromone that is a derivative of the plant *Ammi visnaga*. See, for example, Shapiro G G, König P. (1985) Cromolyn sodium: A review. *Pharmacotherapy* **5**: 156–170.

[77] Mr John Bell (b. 1934) was Pharmaceutical Development Manager in Fisons Pharmaceutial Laboratories from 1965 to 1979.

[78] Dr Roger Altounyan FRCP (1922–1987) joined Benger Laboratories, later Fisons Pharmaceuticals, Loughborough, Leicestershire, as a medical liason officer where he continued his research until his retirement. He became a consultant chest physician at Monsall Hospital in Manchester in 1957. See Anonymous. (1988) Obituary: Roger Ernest Collingwood Altounyan. *Lancet* **i**: 193. Fuchs E. (1988) Roger E Altounyan. *Allergologie* **11**: 522. Orr T S. (1989) Roger Altounyan: the man and his work. *Respiratory Medicine* **83** (Suppl. A): 3–6. See also a 30-minute drama-documentary of episodes from the life of Dr Roger Altounyan entitled *Hair Soup*, broadcast in 1992 by Yorkshire Television and produced by Swallow Productions. The part of Roger was played by David Suchet and Barbara Altounyan, Roger's daughter, narrated.

came across sodium cromoglycate, a bis-chromone derivative developed from materials in khellin. Again I think it is pretty well known that he used to screen these materials on himself. He'd take the research compound from a nebulizer and then administer his own antigen, and there are many stories of Roger being found slumped across his desk at work, whether they are apocryphal or not, I don't know. One of the features in the development of Intal, which I think Professor Black[79] always reckons to be a good feature in the development of a drug, is that management stopped the project. Roger continued working at weekends with a chemist called Colin Fitzmaurice and they moved slowly on in this research outside company authorization, if you like.

On the base of his personal use Roger arrived at a dose of about 20mg for this compound, which exceeded the capability of the pressurized inhaler and Roger was the first person really to realize the need for coordination – synchronization of dose administration with inhalation in portable inhalers – and he also is the inventor of the Spinhaler®. He worked with a colleague in the workshop[80] on the thesis of putting a capsule of drug on to a propeller, so when the propeller rotated the powder was thrown out. I happened to come across the patents for this recently at this wonderful place just along the road here, the British Library, where you can read the original patents that were filed in 1963, which is the same year that the patent on sodium cromoglycate was filed. So Roger effectively developed both the drug itself, and certainly invented the delivery device.

About this time [1964], internal in the company, Benger [Laboratories] was taken over by another Fisons company called Genatosan [in Loughborough]. It isn't really enough to discover these drugs, there really has got to be drive behind them from a management point of view to do it. A young research director called Dr J S G Cox,[81] an ex-Glaxo synthetic chemist, took over the project and it was really Jim Cox and Roger Altounyan who took this through to market. The product Intal was first marketed in the UK in 1967 which isn't a bad record, 1963 to 1967 to market, but the period between 1963 and 1967 was manic inside the company. The drug had to be synthesized and all the industrial processes scaled up. The mechanism of the Spinhaler turned out to be complex, and it had to be understood, the design developed, and the powder technology comprehended.[82]

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[79] Professor Sir James Black Kt OM FRCP FRS (b. 1924) was Professor of Analytical Pharmacology at King's College Hospital Medical School, London, from 1984 to 1993, later Emeritus. He has been Chancellor of Dundee University since 1992. He shared the 1988 Nobel Prize for Physiology or Medicine for 'discoveries or important principles for drug treatment' with George Herbert Hitchings Jr (1905–1998) and Gertrude Belle Elion (1918–1999).

[80] Mr John Bell wrote: 'Roger approached the problem in his entirely unique way, together with a very resourceful engineer in the R&D workshop called Harry Howells. Together they essentially developed the prototype of the current Spinhaler®. Because of the plastic capsule filling problem, the drug was put into standard gelatin capsules. These were then mounted in a cup at the end of a shaft above a fan blade or propeller, and the shaft mounted on a pin. Sometimes it worked and sometimes it didn't.' Note prepared for the Witness Seminar, 27 March 2000.

[81] For biographical details, see note 96.

[82] Mr John Bell wrote: 'We know now that we were working at the limits of powder science in those formulations and the procedures we developed have continued to the present day in products like the Rotahaler, Accuhaler, and Turbohaler.' Note prepared for the Witness Seminar, 27 March 2000.

The clinical work itself had to be planned and carried out and there are a number of people in this room who are much more familiar with that side of it than I am. The regulatory scene itself was undergoing great change, of course, in the wake of thalidomide, and the Committee on Safety of Drugs[83] was just growing up and finding its feet. The Medicines Act of 1968 was imminent, which changed the nature of drug development forever. All this work was done prior to getting the drug to market.

A couple of other just brief points I thought I would mention while talking about Roger. There was the Fisons setup in Loughborough and round the corner was Riker, and shortly after Intal was marketed a deputation arrived [at the Derby Road headquarters of Fisons] from Riker who were of course concerned with the impingement on their own product, the Medihaler range. They claimed that the isoprenaline in Intal, which Roger had put in to prevent impact, was actually having the effect.[84] He considered the impact of powder particles on the bronchial walls might cause bronchospasm.

The other point about Roger that I thought I would mention was that Roger vehemently opposed the use of steroids for asthma and he considered it would lead to *Candida* overgrowth, but of course I guess we can all be wrong sometimes.[85]

Milner:[86] The first publications on disodium cromoglycate, as it was first known, came out in a rather topsy-turvy manner in 1967. The first one was by Dr Jack Howell, and came out in the *Lancet* in the September.[87] In this paper he described a randomized double-blind study on ten asthmatic adults aged between 30 and 63. Essentially these ten adults were given inhalations of isoprenaline through a Spinhaler for two weeks, then for a further two weeks they either had isoprenaline, or they had isoprenaline and sodium cromoglycate. Then the patients were interviewed weekly, and in addition to various symptom scores, the clinicians decided whether they were better on treatment A or on treatment B. All ten were better on treatment with sodium cromoglycate.

The next paper was one written by Dr Cox which came out in *Nature* and essentially described the pharmacology and toxicology of the drug, showing that it was very effective in the animal model, with the exception of the poor old guinea-pig, who

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[83] See also Tansey E M, Reynolds L A. (eds) 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.* vol. 1. London: The Wellcome Trust, 103–132.

[84] Mr John Bell wrote: 'Included in the SCG [sodium cromoglycate] formulation was 100µg of IPS [isoprenaline]. The purpose of this was a concern of Roger's that impact of powder particles inhaled from the Spinhaler would produce bronchoconstriction and the IPS was to combat this. Riker argued that this was the actual active ingredient in the product. Later, when we were confident that RA's concern was unfounded, the IPS was dropped.' Note prepared for the Witness Seminar, 27 March 2000.

[85] Mr John Bell wrote: 'David Jack told me later that the activity of steroids was like a lighthouse beacon compared with SCG.' Note prepared for the Witness Seminar, 27 March 2000.

[86] For biographical details, see note 27.

[87] Howell J B L, Altounyan R E C. (1967) A double-blind trial of disodium cromoglycate in the treatment of allergic bronchial asthma. *Lancet* **ii**: 539–542. See Brewis R A L. (ed.) (1991), note 11, 184–187.

apparently got no benefit.[88] The only animal that showed really toxic effects was the dog, who apparently developed bradycardia, hypotension and apnoea but recovered fairly quickly. But in terms of the safety pattern it was really quite remarkable. You have to give vast amounts of sodium cromoglycate to harm even the small animals.

The third paper was the very short paper by Altounyan himself that is just over 200 words. This came out in *Acta Allergologica* and was essentially describing what we have already heard about, how he investigated this drug and its apparent effects in blocking deterioration after inhaling mixed pollens.[89]

However, after just those three publications, the drug was released. Obviously there had been a lot of other studies subsequently, but I don't think there would be many drugs that would be released nowadays after results on only ten patients had been reported. Inevitably over the next couple of years, there were a lot of randomized trials carried out, but it was not until 1970 that we get the first reports on the use of sodium cromoglycate in children. These were in an edition of *Respiration* after a number of investigators were brought together and of the two investigators who spoke English as their first language, one of them is our current chairman.[90] Over the next one to two years there were a number of different double-blind studies carried out to show that sodium cromoglycate was indeed an effective drug for use in children and probably more so than in adults. By the mid-1970s we had comparisons with the inhaled topical steroids, suggesting that perhaps it wasn't quite as good. The study which led to the acceptance of sodium cromoglycate in the States was one our chairman carried out in combination with Weinberger showing that sodium cromoglycate seemed to be just as good as theophylline and considerably less toxic.[91] But there was then a slightly odd paper by Dick Jones in 1979,[92] in which he claimed that if you looked at particular sorts of asthmatic children, you could show that sodium cromoglycate was a mild bronchodilator drug, but I don't think anybody has managed to show that

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[88] Cox J S G. (1967) Disodium cromoglycate (FPL 670) ('Intal'®): A specific inhibitor of reaginic antibody–antigen mechanisms. *Nature* **216**: 1328–1329. See Brewis R A L. (ed.) (1991), note 11, 188–189.

[89] Altounyan R E C. (1967) Inhibition of experimental asthma by a new compound – disodium cromoglycate 'Intal'®. *Acta Allergologica* **22**: 487. See Brewis R A L. (ed.) (1991), note 11, 183. Professor Anthony Milner wrote: 'This article describes how a large number of compounds were investigated for their antiasthma effects by one investigator (Roger himself) who at three- to four-day intervals inhaled the test drugs prior to inhalation of mixed pollen antigens which normally produced a 45 per cent reduction in forced expiratory volume in one second (FEV_1). Intal was identified as a drug that was highly effective, producing a 70 per cent reduction in fall in FEV_1 at a dose of 1mg, and a 40 per cent reduction at 0.15µg. [See note 100, 767, for details.] He recommended the use of 20mg six hourly. He also stated that the compound was ineffective if given after the challenge. Despite the fact that data had only been published on ten patients, Intal was launched later that year.' Notes prepared for Seminar, 4 April 2000.

[90] Godfrey S. (1970) The physiological assessment of the effect of disodium cromoglycate (DSCG) in the asthmatic child. *Respiration* **27** (Suppl.): 353–356.

[91] Hambleton G, Weinberger M, Taylor J, Cavanaugh M, Ginchansky E, Godfrey S, Tooley M, Bell T, Greenberg S. (1977) Comparison of cromoglycate (cromolyn) and theophylline in controlling symptoms of chronic asthma. A collaborative study. *Lancet* **i**: 381–385.

[92] Chung J T, Jones R S. (1979) Bronchodilator effect of sodium cromoglycate and its clinical implications. *British Medical Journal* **ii**: 1033–1034.

again. Anyway over this period sodium cromoglycate had gained a reputation that it was an effective drug in all except severe asthmatic children and was very safe. So when the asthma guidelines began to be developed both nationally and internationally sodium cromoglycate had a very strong place at stage 2, that is if you couldn't control the patient on just the occasional dose of a β_2 agonist, they ought to be on sodium cromoglycate. They ought also to have been shown to have failed on sodium cromoglycate before they went on to the next level. And it's only really in the very latest of the guidelines[93] that things are now beginning to change, so that now we are given an option of either having sodium cromoglycate or low-dose inhaled steroids as our first prophylactic level. I think the reason for this is partly that sodium cromoglycate isn't always effective, it has to be taken at least three or four times a day, and is less pleasant to take. Now just one or two other bits of information about Roger Altounyan. Apparently he was dyslexic and had a lot of problems at school, and this has been put forward as an explanation why perhaps his article was only 200 words when it was such an important topic. He also, as I am sure everybody in this room knows, was part of a family who used to go on sailing holidays in the Lake District and there he met up with Arthur Ransome,[94] and became Roger in the stories. But I don't know whether the rest of the family also have those funny names or not.

Finally in addition to developing the Spinhaler, as far as I can make out he was the first one who actually used hypotonic solution for generating broncho constriction. I found a nice paper by him on this topic.[95] But he was a remarkable man and I am sure a lot of us remember him with a lot of affection.

Godfrey: I also remember Roger with great affection, he was one of my favourite people, a most extraordinary man, with bad asthma, who used to suck away on his Spinhaler which did him absolutely no good at all although he insisted it was wonderful and I used to say, 'Why don't you just take some steroids?' No, no, he would suck on his Spinhaler and wheeze away. A few years ago there was a meeting in Jerusalem, he grabbed hold of me and he said, 'This is boring, get in your car, I want you to take me to see where I lived'. I said, 'What do you mean?' He said that during the Second World War his father was stationed in Palestine as it was then with the British Forces and Roger was a young man, he must have been a teenager and they lived for a while in Jerusalem. I said, 'With pleasure' and so we got in the car and I said, 'Well, where is it?' He had never been back since, this must have been probably 40 years later and he said, 'Well, first of all go to the railway station'. So we drove to the railway station and he said I think you take that fork and then we go left and we

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[93] British Thoracic Society. (1997) The British guidelines on asthma management. *Thorax* **52** (Suppl. 1): S1–S21. A table on the management of acute severe asthma in general practice is reproduced from this article in section 3 on the respiratory system in the *British National Formulary*, published by the British Medical Association and the Royal Pharmaceutical Society of Great Britain.

[94] Ransome A M. (1930) *Swallows and Amazons*. Jonathan Cape: London.

[95] Schoeffel R E, Anderson S D, Altounyan R E. (1981) Bronchial hyperreactivity in response to inhalation of ultrasonically nebulized solutions of distilled water and saline. *British Medical Journal* **283**: 1285–1287.

came to some crossroads, and he said, 'I am sure this used to be a roundabout'. He said, 'Take the third exit' and he said, 'There it is' and we stopped outside this house and the owner of the house came out, very suspicious, because there were these two sort of prowlers prowling around outside their house and I explained what it was and that seemed to satisfy her. Also at the time my children were much younger and they were fascinated to meet Roger of *Swallows and Amazons*, and they thought he looked a bit strange for a little boy. Who else would like to chip in? Please, yes. One of the heroes of the story.

Dr Jim Cox:[96] I wanted to add one or two comments on the development of Intal. One for me was a very salutary lesson in the importance of the basic scientist sitting in on clinics. I remember one of the early trials on Intal and I was talking to the clinician and he called the child and his mother in and I said, 'Well, how did you find the result?' 'Oh a wonderful drug, very good'. I then said, 'Well, what about the Spinhaler? Did you have any difficulty with that?' The child looked at his mother and neither knew what to say, as they hadn't been given the Spinhaler, they had just taken the capsule as it was. There was no way that they could have got a result. The other comment also relates to the development of Spinhaler, because in many ways more effort was put into that, than into the development of the actual drug. We were very determined that the Spinhaler should be as efficient as possible and it so happened that the professor in the Department of Aeronautical Engineering in Loughborough was very keen on this and he looked at the Spinhaler and did various measurements of it. He said, 'The propellers are round the wrong way, you will have to turn it round,' that it couldn't possibly work as it was. We spent a long time doing this and tried it out again and it just didn't work at all. So I think the importance of this is that sometimes you have to bear in mind that there are many other factors that come into play in the development of a drug, it is not always objective and clear as the battle we have described.

Godfrey: Professor Silverman was my research fellow who did all the work for which I took the credit on the trial of Intal in children.

Silverman: Yes, that's quite true, that's where I started my life in respiratory paediatric medicine, with Simon [Godfrey] who was my boss and has remained so ever since. I just want to make a general point, because it is quite intriguing how a number of drugs, such as theophylline and Intal (sodium cromoglycate), have been thought to have their beneficial effects in asthma by a particular mechanism, only later to be shown to have effects which differ, and which may well explain their antiasthmatic benefits. It's intriguing how a number of drugs have evolved in asthma by trial and error and the explanation for their benefit has been based on some associated pharmacological effect which may or may not be the correct one. I don't know

[96] Dr Jim Cox (1931–2001) was Director of Research and Development at Fisons Pharmaceuticals from 1963 to 1978. He retired in 1999. See Cox J S G. (1970) Review of chemistry, pharmacology, toxicity, metabolism, specific side-effects, anti-allergic properties *in vitro* and *in vivo* of disodium cromoglycate. In op. cit. note 65, 13–25. See also Cox J S G, Beach J E, Blair A M J N, Clarke A J, King J, Lee T B, Loveday D E E, Moss G F, Orr T S C, Ritchie J T, Sheard P. (1970) Disodium cromoglycate (Intal). *Advances in Drug Research* 5: 115–196.

whether that problem still exists, because there is now a resurgence of interest in obtaining drugs from various plants around the world and trying them out in various ways. This does have disadvantages, for example one of the sidelines was that which followed as a result of the work on Intal and its potential effect in stabilizing mast cells, which seems, as far as I can see, to have been a dead end. The original mechanism by which it had its effect led to the screening of vast numbers of other drugs, using that particular mechanism, to try to determine or identify antiasthmatic drugs. I suppose that history possibly continues to repeat itself in the way in which drugs continue to be screened as a result of effects that may not be relevant in their clinical benefits.

Godfrey: Does anybody here now believe or disbelieve that chromones and cromoglycate works by inhibiting mediator release from mast cells?

Holgate: There's little doubt that it works by inhibiting mediator release from mast cells, but this may not be its only mechanism of action. Sodium cromoglycate is now known to activate particular phosphorylation pathways in the mast cell which are intimately related to the degranulation processes. It has been suggested that sodium cromoglycate interferes with a chloride channel present not only in mast cells but also in other cells such as epithelial cells.[97] Its highly acidic and hydrophilic properties imply that it works on the cell surface, but the precise molecular target still has not been defined. I absolutely agree with the comments you made earlier, that sometimes one believes one has identified a critical mediator or a pathway that is involved in asthma pathogenesis but further research proves this not to be the case. A good example of this is platelet-activating factor (PAF), receptor antagonists which wasted a huge amount of resources in the pharmaceutical industry, based on animal studies and not understanding the complexities of human disease. So I would agree entirely with the comment, but I wouldn't like the record to go unmarked saying that this drug has no effect on mast cells – it does.

Godfrey: Well I would just like to come back to the paper by Silverman and Andrea – Andrea was our lab technician – showing that cromoglycate inhibited exercise-induced asthma only if you gave it before the exercise, but not if you gave it at the end of the exercise yet before the attack had developed. And I wonder how you could relate that to its effect, other than by releasing mediators from something?

Silverman: It seems reasonable to assume that because it has to be given before the challenge, before the effect of that challenge has developed, that it probably doesn't work by some sort of neurological mechanism which would be more likely to be relatively rapid, (although there are some neural actions of sodium cromoglycate). I think that the hypothesis that it blocks the release of some sort of mediator is probably the correct one. But I have to say that I think that the attempt to screen lots of other

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[97] Holgate S T, Davies D E, Lackie P M, Wilson S J, Puddicombe S M, Lordan J L. (2000) Epithelial–mesenchymal interactions in the pathogenesis of asthma. *Journal of Allergy and Clinical Immunology* **105**: 193–204.

drugs for their effect in inhibiting mast-cell release of histamine and various other agents has seemed in practice not to lead very far. I think that that may not be its principal beneficial effect in asthma.

Godfrey: How do you think the antileukotriene drugs work, if they do work?

Holgate: They are highly selective receptor antagonists or inhibitors of leukotriene production. Leukotrienes are the components that comprise a slow-reacting substance of anaphylaxis (SRS-A) that is released by inflamed asthmatic airways and originally was described by Feldberg and Kellaway in 1938.[98]

I am glad you mentioned that because Roger Altounyan was the first person to describe the clinical use of an antagonist to slow-reacting substance of anaphylaxis (SRS-A) in 1958, following a paper he heard in 1956 by Walter Brocklehurst[99] who had been working at Mill Hill at the time with Sir Henry Dale and Frank Austin. This was before he [Altounyan] made the dichromone, using the single agent. When administered to himself, he showed that a new chemical entity, K18 (which was structurally derived from khellin extracted from the seeds of the Mediterranean plant *Ammi visnaga*) inhibited the immediate bronchoconstriction triggered by inhaled allergen. He further showed addictive inhibition with mepyramine when combined with K18.[100] Although Dr Altounyan gave K18 to 25 outpatients and showed efficacy in asthma, this development had to be discontinued on account of hepatotoxicity. This was the first description of the clinical use of an SRS-A (or cysteinyl leukotriene) antagonist and was the precursor of the classical *in vitro* SRS-A antagonist FPL55712 as well as part of the search that eventually led to the discovery of sodium cromoglycate.

Howell: Could I first say that there is a widely held misconception that Roger [Altounyan] invented the Spinhaler to deliver Intal. I am almost certain this was not the case. He told me that he invented it several years earlier in the late 1950s to deliver another therapy by inhalation, a mixture of pancreatic enzymes called Lomulase[101] for the treatment of chronic bronchitis. He had the idea that if a chronic bronchitic inhaled these enzymes – trypsin and chymotrypsin – they might help to liquefy the

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[98] Feldberg W, Kellaway C H. (1938) Liberation of histamine and formation of lysocithin-like substances by cobra venom. *Journal of Physiology* **94**: 187–226. See also Feldberg W. (1954) Review Article: On some physiological aspects of histamine. *Journal of Pharmacy and Pharmacology* **6**: 281–301.

[99] Brocklehurst W E. (1956) A slow reacting substance in anaphylaxis – 'SRS-A', in Wolstenholme G E W, O'Connor C M. (eds) *Histamine*: Ciba Foundation symposium jointly with the Physiological Society and the British Pharmacological Society, held at the Ciba Foundation, 6–7 April 1955, in honour of Sir Henry Dale. London: Churchill, 175–179. Brocklehurst's thesis, entitled 'The formation and release of a slow-reacting substance in the course of the anaphylactic reaction' was completed in 1958.

[100] See Edwards A M, Howell J B L. (2000) The chromones: history, chemistry and clinical development. A tribute to the work of Dr R E Altounyan. *Clinical and Experimental Allergy* **30**: 756–774.

[101] Mr John Bell wrote: 'Benger had already developed and marketed a device called the Lomuliser, a bulb-operated powder inhaler, with IPS [isoprenaline] in competition to Medi-haler. This was a difficult device to manufacture. The drug was contained in plastic capsules, filled on a special machine devised and built by the Chief Engineer, Frank Wright.' Note prepared for the Witness Seminar, 27 March 2000.

sputum and make it easier to expectorate. These enzymes were readily available because they were the 'bread and butter' of the Benger Company for the preparation of the predigested protein food, Benger's Food. He tried it out in a test tube and showed that they would liquefy sputum from chronic bronchitics. His next task was to deliver the powdered enzymes in quite large quantities into the bronchi of chronic bronchitics. My understanding is, and this was from him, that he invented the Spinhaler to deliver this.[102] Unfortunately the research director had his own idea about how the enzymes should be delivered, and it was not by the Spinhaler. So it was put to one side, but clearly it was resurrected subsequently, for the FPL670 [Intal] administration, if the patent was taken out in 1963. But I don't think many people realized that. They associated him with Intal and the Spinhaler.

I had the immense good fortune to meet Roger in 1961 in Manchester where we were both based at that time and he told me about the work that he had been doing at Benger's over the previous four or five years.[103] I have to confess that my interests were more physiological and I listened, but I did not get enthusiastic. In 1963 he telephoned me to say that he had now tried out on himself this new compound he'd been trying to develop and it had all of the properties that he was looking for. The question he was really interested in now was if this [Intal] inhibits the allergic reaction that follows the inhalation of an antigen, how might one use it therapeutically in a patient with asthma? We talked about this on the phone and later together, and decided that since he had shown that, for the compound to be effective it had to be delivered before the antigen, the only way to test its efficacy was to administer the drug continuously for as long as possible, even though it was impractical as a treatment. The first thing to establish was 'did it work?'

He had a red-haired Irish patient with very severe disabling, chronic asthma requiring high doses of corticosteroids who was prepared to try anything. We took him into one of Sir Douglas Black's[104] beds in the Manchester Royal Infirmary one Friday night, put him into an oxygen tent over the weekend and nebulized the new compound into it continuously for 72 hours. On the Monday morning when we finally took him out of the tent the result was unequivocal: it had done absolutely nothing. Roger was intensely disappointed. He went back to his lab at Monsall, tested it again on himself and it didn't work at all. He went back to Benger's at Holmes Chapel [Cheshire] to discover that they had had to make a new batch, the first batch had been used up or thrown away or something, and this new batch just didn't work and nobody knew

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[102] Professor Jack Howell wrote: 'The idea of the Spinhaler came to him when he remembered sitting in his Spitfire with the propeller whirring in front of him.' Letter to Mrs Lois Reynolds, 1 April 2001. See also note 80.

[103] Professor Jack Howell wrote: 'This was based on what he had noticed in a series of *in vitro* studies carried out since 1957 by his pharmacologist colleagues who were attempting to synthesize a better bronchodilator preparation.' Letter to Mrs Lois Reynolds, 1 April 2001.

[104] Professor Sir Douglas Black Kt FRCP FRCPath FRCPsych FRCOG (b. 1913) was appointed to the Department of Medicine at Manchester University in 1946, becoming Professor of Medicine from 1959 to 1977, later Emeritus. He was Chief Scientist at the Department of Health and Social Security from 1973 to 1977, a member of the MRC from 1966 to 1970 and 1971 to 1977 and President of the Royal College of Physicians from 1977 to 1983.

why. Roger's reputation with top management, quite unfairly, had not been high but was now even worse and about this time support for the project was withdrawn. Fortunately he still had the confidence of the pharmacologists and chemists who were willing to work unofficially in continuing to synthesize new compounds. Jim Cox will correct me if I have the details wrong, but I understand that for a time because of these problems they had to work in relative secrecy until in 1965,[105] in early February, he rang me up again to say, 'I have got it, it really does work'[106] and that was FPL670, the 670th compound and chemically it was disodium cromoglycate.

He gave me some to try on a couple of patients of mine, just two of them. Both improved symptomatically, but only one of them had improvement in lung function tests and this had a profound effect upon me and the way in which we designed the subsequent double-blind cross-over trial, which has been referred to.[107] The next thing was to persuade the company that they had something good. Roger had been associated with two projects soon after he joined the company in 1956. In the first, he was given the project to study the ability of the iron-dextran compound, Imferon, to prevent anaemia in rapidly growing piglets and hence to improve their rate of growth. While it prevented anaemia, unfortunately it did not improve their growth rate and therefore was not commercially useful. He felt he was blamed for this result. I already mentioned the second project involving the inhalation of pancreatic enzymes for the treatment of chronic bronchitis. Before the drug was launched into clinical practice, a number of trial patients developed severe asthmatic reactions and he advised the delay of its launch. But this was not done and it had to be withdrawn within months.

Roger knew that he did not carry the confidence of many senior people in the company, and that there might be difficulties in persuading them to pursue the development of disodium cromoglycate. They had recently appointed a new research director, Dr James Cox, and it was vitally important to convince him that this was a drug worth pursuing. Roger asked me if I would go with him to see Jim Cox and we went to Holmes Chapel. What I remember most vividly was the thickness of the pile of the carpet and the young Dr Cox behind his large desk. I can remember saying to him finally that using this drug reminded me of the introduction of corticosteroids. I don't know what his thoughts were, but the response was enthusiastic. I asked if we

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[105] Professor Jack Howell wrote: 'Roger wondered if some highly active "contaminant" had been synthesized inadvertently on the first occasion, and one of the chemists suggested that two of the molecules might have joined together to form a bis-chromone. So they deliberately made a bis-chromone which Roger tried out on himself in January 1965.' Letter to Mrs Lois Reynolds, 1 April 2001.

[106] Professor Jack Howell wrote: 'Roger found it completely blocked the asthmatic reaction which followed inhalation of extracts of guinea-pig hair or grass pollens, even when taken four hours before the challenge, but rapidly lost its effectiveness if it was inhaled after the challenge. He himself continued to inhale the compound four times a day with substantial clinical improvement and he was able to lower his daily dose of prednisolone. He gave the new compound to half a dozen of his severely asthmatic patients with similar improvement.' Letter to Mrs Lois Reynolds, 1 April 2001.

[107] See note 87.

could have more of the compound to do a formal controlled study – this mammoth study on ten patients that was referred to earlier – and he agreed. His decision was absolutely crucial to the development of cromoglycate, because he had the capacity at that point to say 'Run away little boys, don't waste my time' as I think some other people were tending to do before that. We owe a lot to Jim Cox for immediately seeing the potential of the drug and his enthusiastic support which led to the drug being available for clinical use only a few years later.

One further episode that sheds light on Roger's character: he wanted to know what happened when cromoglycate was given intravenously and he asked me if I would inject him with it. I refused. But he was very persistent and said he had tried it on pretty well every animal species without adverse effect, but admitted that they hadn't tried it on primates. A few months later he said they had now given it intravenously to a marmoset without ill effect and would I please give him the injection. I felt I could resist no longer and with considerable reluctance agreed. He came to our clinical room at the Royal Infirmary where first he did skin tests on himself, blew into the spirometer to measure his forced expiratory volume in one second (FEV1). He lay on the couch, I then attached ECG leads and a blood pressure cuff and started a slow injection. Roger said I gave him 12mg, my recollection was 7mg. For about half a minute nothing appeared to happen but then he said in quick succession, 'I'm feeling something on my skin, my face is burning, I'm burning all over'. His pulse rate and blood pressure went up, so did mine. But the burning sensation quickly subsided and Roger jumped off the couch, repeated his skin tests and measured his FEV_1 as if nothing happened. Later I told Roger jokingly, that my main concern was what I was going to say to his wife Hella and he embellished this to 'Hella, I'm afraid I have killed Roger – with some of his own medicine'. There is no doubt that I was foolish to agree to do it, but Roger was a very persuasive, very courageous, absolutely single-minded man and I wonder how many of you in this room would have been able to refuse to give that injection to him.

Cox: I must make one comment. I don't remember the depth of the carpet, but those of you who know Jack [Howell] very well, it's very difficult to say no when he asks for something.

Godfrey: I am glad that you mentioned its number I have been trying all day to remember what it was called, FPL-something or other, because when Tim [Clark] and I must have been housemen or registrars around the Hammersmith at that time, even Moran Campbell tried some of this stuff on some asthmatics who were doing exercise tests. I don't think it worked at all, but that had to be something special.

Howell: Can I come back on one little point? As some of you may know Roger had extensive atopic eczema, but he didn't have his first attack of asthma until 1950, when he was a medical student. This frightening attack happened one night and recurred the following night. So he went to see the Casualty Medical Officer at the Middlesex Hospital, who after diagnosing asthma proceeded to test his knowledge of its causes,

eventually adding, pointing to his temple, the psyche. Roger was not impressed with its implication. This young doctor went on to become a very distinguished respiratory physician, Dr Moran Campbell.[108]

Godfrey: Well, this has been fascinating. I would like to ask Sir David Jack to introduce the discussion or reminiscences concerning another British invention, the salbutamol story, Ventolin.

Jack: I too knew Roger Altounyan and well remember a hilarious lecture he gave in York about how he developed 'Intal' despite everything his management would do to stop him. I was luckier. I can say in all honesty that I did not lack support from management in Allen & Hanburys or in Glaxo. The pattern was set during one of the early conversations I had in 1962 with C W Maplethorpe,[109] the man who hired me as Research Director of Allen & Hanburys. A member of the Glaxo Board, he was a great man but also very impatient. I had found that there was not a single viable project in the research portfolio and, after a while, I went to see him to explain what I wanted to do. Within two minutes he held up a hand and said, 'David, I don't care what you do so long as you are successful.' I acted on that basis for the next 26 years in Glaxo.

Today I want to outline some highlights of the development of selective β-adrenergic and anti-inflammatory steroid activities in the lung. First, however, I would remind you of what Ehrlich,[110] the greatest-ever drug hunter, had to say about drug discovery. The three essentials were: sound, practicable, original ideas; money to pay for the required resources; and luck. As I outline how salbutamol and other products were found, you will find that all three played their part.

Our first asthma research objective was a long-acting analogue of isoprenaline for use by inhalation. Isoprenaline is, of course, an extremely effective but short-acting bronchodilator. It was also a dangerous drug because patients used it increasingly despite worsening asthma. The key idea came from Larry Lunts,[111] a senior medicinal chemist with a Midas touch in research. He decided to make non-catechol analogues of isoprenaline because the cause of its brief effect is inactivation in the body by mechanisms that are catechol specific.

Unfortunately the chemistry proved to be difficult and it was not until 1966 that AH3021, the saligenin analogue of isoprenaline, was first tested in the pharmacology

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[108] For biographical details, see note 6.

[109] See Tweedale G. (1990) *At the Sign of the Plough: 275 years of Allen & Hanburys and the British pharmaceutical industry, 1715–1990*. London: Murray. See also Davenport-Hines R P T, Slinn J. (1992) *Glaxo: A history to 1962*. Cambridge: Cambridge University Press. Jones E. (2001) *The Business of Medicine: The extraordinary history of Glaxo, a baby food producer, which became one of the world's most successful pharmaceutical companies*. London: Profile Books.

[110] Professor Paul Ehrlich (1854–1915) won the Nobel Prize in Physiology or Medicine in 1908 for his work on immunity. See Himmelweit F. (ed.) (1956–60) *The Collected Papers of Paul Ehrlich*. Four vols. London: Pergamon Press.

[111] Hartley D, Jack D, Lunts L H C, Ritchie A C. (1968) New class of selective stimulants of β-adrenergic receptors. *Nature* **219**: 862.

laboratory. The primary tests were done by a new graduate, Valerie Cullum (now Valerie Alabaster) who is now head of cardiovascular research in Pfizer Research. Very soon Valerie reported to Roy Brittain, head of pharmacology, 'This is a funny β-agonist. It is pretty active on bronchial muscle but is virtually inactive on the heart'. Roy replied, 'That cannot be right. Go and do it again.' This she did with the same result and Roy still sceptical then did the tests himself. Thus it was that we stumbled upon the first highly active, highly selective β_2-adrenoceptor stimulant.[112] The truth is that the drug really found us, surely the kind of luck that Ehrlich spoke about. The next member of the series was salbutamol (AH3365), which is more active at β_2-receptors and even more selectively acting on bronchial muscle. First made in 1966 it was marketed in 1969 as the 'Ventolin' inhaler and in time became the most prescribed bronchodilator in the world.

I have regularly been asked how we managed to market salbutamol only three years after its first synthesis. The simple answer is that in the early stages we experimented on one another, a procedure that I commend to all responsible for recommending new medicines to other people. I was first to take salbutamol by inhalation and by mouth under the supervision of Wilfred Simpson, a bold and intelligent clinical pharmacologist, who was then our medical director. He had the drug next under my supervision! Salbutamol was obviously innocuous in us but neither of us is asthmatic. The first asthmatic to take salbutamol was Desmond Poynter, our friend and colleague, who was head of pathology. Desmond had unwisely told me that he was very sensitive to sulphur dioxide. Since he knew more than anybody else about his condition and the toxicology of salbutamol, I had no hesitation in inviting him to inhale a small amount of sulphur dioxide to see if inhaled salbutamol relieved bronchoconstriction. Desmond readily agreed and we soon established that salbutamol is an effective bronchodilator with minimal cardiovascular side-effects.

In the next stage, Colin Dollery[113] agreed to test the effects of salbutamol on two asthmatic volunteers in his 'body box'[114] at the Hammersmith. The volunteers were Anne Ruffel and Graham Williams who were researchers in Allen & Hanburys. Within a month we knew the effective doses of salbutamol, by inhalation and by mouth, the duration of the action and the probable use-limiting side-effects. Thus it took only six months from the date of first synthesis to establish the probable efficiency and safety of the drug. Today that would take at least two years which, in my view, is an unnecessary self-inflicted wound.

When we knew that small inhaled doses of salbutamol gave near-maximal bronchodilation for three to four hours without use-limiting side-effects we asked

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[112] Brittain R T, Farmer J B, Jack D, Martin L E, Simpson W T. (1968) α-[(*t*-Butylamino) methyl]-4-hydroxy-*m*-xylene-α^1, α^3-diol (AH3365): a selective β-adrenergic stimulant. *Nature* **219**: 119–120. Refers to unpublished work of J B Farmer, V A Cullum and G P Levy on aerosolized acetylcholine.

[113] For biographical details, see note 48.

[114] For a historical review of the whole-body plethysmograph, see Comroe J H Jr. (1977) Man-Cans. (Conclusion). The body plethysmograph (body box). *American Review of Respiratory Disease* **116**: 1091–1099.

ourselves how similarly selective glucocorticoid activity might be achieved in the lungs. Wilfred Simpson provided the answer.

Wilfred reasoned that the airways in asthma are simply another inflamed body surface and might, therefore, respond well to potent anti-inflammatory steroids of the kind used to treat eczema, psoriasis and other skin diseases. Their most serious side-effects in dermatology are 'thinning' of the skin and, if used on large areas of the skin, systemic glucocorticoid activity.

The essential properties of a selectively acting topical steroid were thought to be (i) persistent binding to glucocorticoid receptors in the lung, (ii) lack of adverse effects on the lung and (iii) low oral bioavailability because at least 80 per cent of every inhaled dose is swallowed.

By great good fortune, beclomethasone dipropionate (BDP),[115] the only potent topical steroid readily available to us, proved to have the necessary characteristics. It had been made available to us by Glaxo Research for the 'Propaderm' topical steroid products. We already knew it to be about 600 times more active than cortisol acetate in the McKenzie skin-blanching test,[116] which measures the intensity of binding to glucocorticoid receptors in the skin. We then established that the lungs were not adversely affected in dogs made obviously 'Cushingoid'[117] by repeated daily inhalations of large doses of BDP for 12 weeks. This reassured us that the drug would probably be safe in man. Our next step was to assess the oral bioavailability of BDP by measuring reductions in early morning plasma cortisol levels after oral and intravenous administration of the drug to ourselves. It was about five times more active by the intravenous route and so its bioavailability was only about 20 per cent.

Exploratory open clinical trials of the BDP inhaler were carried out in Ian Grant's unit in Edinburgh[118] and later in Harry Morrow Brown's clinic in Derby.[119] The Edinburgh results were at best equivocal. However, Harry resolved our doubts in a remarkable clinical publication in the *British Medical Journal.*[120] I will say no more about this because Harry [Morrow Brown] is here in person and more than able to speak for himself. I am most grateful for all he did.

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[115] Beclomethasone dipropionate (Becotide; Allen & Hanburys) was put on the market in 1972.

[116] The McKenzie skin-blanching test is commonly used to evaluate the biochemical potency of topical corticosteroids. See McKenzie W A, Stoughton R B. (1962) Method for comparing percutaneous absorption of steroids. *Archives of Dermatology* **86**: 608–610.

[117] Symptoms and signs of Cushing syndrome are caused by an excess of cortisol hormone. See Cushing H. (1932) The basophil adenomas of the pituitary body and their clinical manifestations. *Bulletin of the Johns Hopkins Hospital* **50**: 137–195.

[118] Choo-Kang Y F, Cooper E J, Tribe A E, Grant I. (1972) Beclomethasone dipropionate by inhalation in the treatment of airways obstruction. *British Journal of Diseases of the Chest* **66**: 101–106.

[119] For biographical details, see note 124.

[120] Brown H M, Storey G, George W H S. (1972) Beclomethasone dipropionate: A new steroid aerosol for the treatment of allergic asthma. *British Medical Journal* **i**: 585–590.

The BDP inhaler was marketed as 'Becotide' in 1972. It was generally well received, but its use was reserved for patients inadequately controlled by bronchodilators or theophylline. Indeed, it took nearly 20 years for inhaled BDP to be accepted as a safe primary treatment for asthma. Amazingly, at that very time after 30 years of clinical experience, regular use of inhalers containing selective β_2-agonists, the standard primary treatment, was reported to be unsafe because it caused the asthma to worsen! More of this anon.

During the 1970s all our efforts to find better treatments for asthma failed. When I assessed the situation in 1981 the patents on salbutamol and BDP were uncomfortably close to expiry. I, therefore, decided that our best option was to try to improve the drugs we already had. The only obvious fault with inhaled salbutamol is that its duration of action is not long enough to persist throughout the night. A truly long-acting alternative was clearly a worthwhile objective. Similarly, the only obvious weakness with BDP treatment was weak systemic glucocorticoid side-effects associated with high dosage with the drug. A more selectively acting BDP was required.

To obtain a long-acting β_2-agonist for use by inhalation I asked my colleagues to make a β_2-agonist which would bind irreversibly to its receptor protein, because I expected its duration of action to be determined by the life of the occupied receptors. Others were less sure because of the vast literature on desensitization of continuously activated β receptors. If the literature was right, my occupied receptors would be rapidly desensitized. In the event, the required drug [salmeterol] was found by replacing the N-substituent of salbutamol by a long flexible nonpolar chain.

Salmeterol did bind irreversibly to the β_2-adrenoreceptor protein and was found by Nils Svedmyr and his colleagues[121] to be effective for at least 12 hours when inhaled by asthmatic patients. All subsequent studies confirmed this, and also that repeated doses did not induce tolerance. When I retired from Glaxo in 1987, I was convinced that the pharmacological effects of salmeterol and BDP are synergistic and, administered concurrently, that they would provide a new better way to treat asthma.[122] Unfortunately it took more than ten years for this possibility to be realized.

Improving on BDP proved to be relatively easy. I simply chose fluticasone propionate (FP) from the Glaxo library of steroids, because it had been found to be about twice as active as BDP in the McKenzie test in man, but virtually inactive as a glucocorticoid after oral administration to mice. That was very unusual because the mouse was known to be exquisitely sensitive to oral glucocorticoids. My choice dismayed the director of chemistry, Barry Price, because FP was very difficult to make! The reason why FP is

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[121] Ullman A, Svedmyr N. (1988) Salmeterol, a new long-acting inhaled β_2 adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients. *Thorax* **43**: 674–678. See Brewis R A L. (ed.) (1991), note 11, 215–219.

[122] Sir David Jack wrote: 'This was stated explicitly in my 1988 Centre for Medicines Research Lecture. "In my view, the combined use of these drugs will greatly simplify treatment and satisfactorily control asthma in the great majority of patients".' Comment on draft transcript, 15 January 2001. See Jack D. (1989) The challenge of drug discovery. *Drug Design and Delivery* **4**: 167–186.

inactive in the mouse was soon found to be quantitive inactivation by first-pass metabolism in the liver and, fortunately, human beings dealt with it similarly. Products containing FP are now being increasingly used instead of BDP and similar steroids.

I regret that I have to finish by expressing my concern at how long it has taken for the value of concurrent treatment with a long-acting β_2-agonist and a topical steroid to be recognized and accepted. Much of the delay resulted from the 1990 report by Sears and his colleagues[123] that regular inhaled β-agonist treatment caused asthma to worsen. They warned against such treatment and recommended the use of such inhalers only when necessary to relieve acute symptoms. That these recommendations were immediately incorporated into the Guidelines for Asthma Treatment was surprising because their finding was based on a total of 56 assessable patients and was at odds with the results obtained in many larger, well-controlled studies, and with more than 20 years of experience with inhaled β_2-agonists. I very much hope that concurrent use of a long-acting β_2-agonist and a potent anti-inflammatory steroid by inhalation will be used increasingly by adult asthmatics and investigated further in children because it may prevent or reduce irreversible damage to the airways. The shadow of Sears's recommendations is still all too obvious in the guidelines for asthma treatment.

Godfrey: Thank you very much. When did beclomethasone become easily available on the market?

Jack: We started the work in 1966 and the inhaler was first marketed in the UK in 1972.

Godfrey: I was trying to remember with Professor Silverman the first patient I treated with beclomethasone. The first child was a little West Indian boy and he was a quite troublesome asthmatic, and we came to the conclusion that it didn't work at all, because we gave him 50 micrograms once a day or something like that. But subsequently, as you know, we found that it was quite a good drug.

Dr Harry Morrow Brown:[124] Well my story also has a lot of luck in it. It begins over 50 years ago, because in my MD thesis I proposed that allergic reactions should be regarded as manifestations of incomplete adaptation to the environment, or adaptive dysfunction. There was no opportunity to pursue this concept further in an NHS in its birth pangs, and a scramble for jobs, in which I was lucky to get a job as full-time consultant to a decrepit chest clinic in Derby in 1953, dealing mainly with

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[123] Sears M R, Taylor D R, Print C G, Lake D C, Li Q Q, Flannery E M, Yates D M, Lucas M K, Herbison G P. (1990) Regular inhaled β-agonist treatment in bronchial asthma. *Lancet* **336**: 1391–1396. Sears M R, Taylor D R. (1994) The β_2-agonist controversy: observations, explanations and relationship to asthma epidemiology. *Drug Safety* **11**: 259–283.

[124] Dr Harry Morrow Brown FRCPEd (b. 1917) was Consultant Chest Physician in Derby from 1953 until his retirement in 1982. He found sputum eosinophilia is linked with steroid responsiveness in 1958 (see note 126), leading to major interest in allergic diseases and showed the effectiveness of beclomethasone dipropionate in asthma in 1972 (see note 120). He founded the Midlands Asthma and Allergy Research Association in 1968, and has continued clinical and aerobiological research to date.

tuberculosis, for £1200 a year. Then after the TB was licked, I had to fight a battle with colleagues and administrators for beds to treat other diseases of the chest.

The conclusion of the MRC trial in 1956,[125] that oral steroids were no better than bronchodilators for asthma, was totally opposite to my own experience, but who was I, working in a deprived clinic with no equipment, to say that the MRC were wrong? However, I determined to conduct my own trial, so I scrounged a load of prednisolone from Eric Morton at Boots and treated every apparent asthmatic I could find with it. After three months I began to wonder if the MRC were right after all, as many cases just didn't improve, but those who did respond did so so obviously and so dramatically, that it seemed as if I was treating a different disease. This was actually true, because the responders had many eosinophils in the sputum and the others didn't. I seriously doubt if my 1958 paper describing this discovery[126] would have been accepted for publication today. There were no objective lung function tests, it was not double-blind, the eosinophils were not counted by somebody else, and the statistics were a simple table with an obvious result. However, 'on-the-spot' cytology enabled me to select the steroid responders, ending up with very large numbers of steroid-dependent, but very happy, asthmatics.

Because I was sentencing these people to indefinite steroid dependency with all the side-effects, I felt very unhappy. In fact, in the next few years I acquired more steroid-dependent asthmatics than almost anybody. So I decided that the logical approach was to try to identify the responsible allergens, if you could, in the hope that I could free them from steroid dependence by avoidance or by specific immunotherapy, which is a dirty word in this country.

This decision also projected me into a completely different speciality, which has been my obsession ever since, and unwittingly set the scene for the first trials of beclomethasone, which was first tried out in Edinburgh, found ineffective, and in bigger doses caused adrenal suppression, so that Allen & Hanburys nearly threw it out. Fortunately, Wilfred Simpson, the medical director, had such faith in it because of its skin activity, that he offered it to me for trial just before he left the company (in fact two hours before), I have a letter from him to this day,[127] and the late David Harris, who took over from him, continued to support me with great enthusiasm. We must also spare a thought for Sir David Jack, and his team, and how disappointing it

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[125] Medical Research Council, Subcommittee on Clinical Trials in Asthma. (1956) Controlled trial of effects of cortisone acetate in chronic asthma. *Lancet* **ii**: 798–803. *idem* Controlled trial of effects of cortisone acetate in status asthmaticus. ibid. **ii**: 803–806. Subcommittee members were: Professor R V Christie, Dr J G Scadding, Dr J T Boyd, Dr W Brockbank, Dr E T Conybeare, Dr J J R Duthie, Dr A W Frankland, Dr R Kauntze, Dr M C S Kennedy, Dr H Nicholson, Professor G W Pickering, Professor F T G Prunty, Dr R S Bruce Pearson and Sir John Taylor.

[126] Brown H M. (1958) Treatment of chronic asthma with prednisolone: significance of eosinophils in the sputum. *Lancet* **ii**: 1245–1247.

[127] Copies of the letters to Dr H Morrow Brown from W T Simpson, Head of Medical Services, Allen & Hanburys Ltd, 16 July 1969 and from Dr D M Harris, Head of Medical Services, Allen & Hanburys Ltd, 9 February 1971, are held, along with tapes, and other records received during the editorial process, in Archives and Manuscripts, Wellcome Library, London.

must have been to do all the research and find that the drug didn't work in the clinic when you expected it to work. The ability to select the allergic steroid responders, especially children, because they are often completely reversible, was crucial to the success of the first BDP trials. This time individual peak-flow meters[128] produced objective evidence that soon convinced Allen & Hanburys and other investigators – many here today – that it was really useful. In February 1971, David Harris wrote, 'I have succeeded in obtaining a new lease of life for the steroid aerosol,' and in October 1972 the Committee for Safety of Medicines became convinced of its safety and of its ability to release many patients from steroid dependence.

I don't think these open trials would have been accepted today, but those were the happy days when you could just get on with a trial without the ethics committees, elaborate and restrictive protocols, double-blinding, statistics, and all the other strictures that surround clinical trials today. I am sure many people will think of these as halcyon days. But inhaled steroids, along with all the other drugs developed in recent years, are at best only effective suppressants without serious side-effects, and in my opinion life-long dependency on drugs for health is a most unsatisfactory situation that we should not accept as normal. It makes sense, to me at least, to regard drugs as a 'chemical crutch' to control the problem while attempts are made to find the cause, yet this view is very rare indeed in the UK. If identified, the causative allergies may be eliminated, or avoided, or if unavoidable, specific immunotherapy introduced in an attempt to re-establish perfect adaptation. The recognition of allergic disease as a speciality a year ago[129] was only the first faltering step towards the time when every district general hospital has an allergy department which treats and investigates all sorts of allergies in all body systems. My fear is that by the time the first trainees are ready for a consultant post, the hospital trusts will consider allergists are unnecessary because the drugs are so effective and they want the money for something else. Sue Arnold recently wrote in the *Independent* that when she saw her doctor he always had his eyes focused on his computer, while he produced another prescription. He never actually touched or even looked at her as doctors used to do, once upon a time. I do hope this is not a glimpse of the NHS of the future.

Clark: I want to link Roger Altounyan with your very graphic tale, Harry [Morrow Brown], on how you identified the steroid response in the unresponsive. I was going to ask Jack [Howell] what happened to the Altounyan atropine test that was put forward by Roger as a very good way of predicting steroid sensitivity before giving the treatment? It has sort of disappeared. I used to love it.

Howell: The Altounyan test is a test that I was emotionally attached to because it came from Roger [Altounyan], but it took at least an hour to do. It also required an inquiring

[128] Wright B M, McKerrow C B. (1959) Maximum forced expiratory flow rate as a measure of ventilatory capacity with a description of a new portable instrument for measuring it. *British Medical Journal* **ii**: 1041–1047. Wright B M. (1978) A miniature Wright peak-flow meter. ibid. **ii**: 1627–1628. For biographical details of Wright, see note 60.

[129] Dr Harry Morrow Brown wrote: 'Agreed by the Royal College of Physicians on 7 June 1999.' Note on draft transcript, 26 June 2001.

attitude of mind, a model of what asthma is, or we believe it is, and I think most clinicians today don't have that time or that particular focus on asthma to bother with a test that takes at least an hour to do. But if you do have the time, if you really are trying to get an answer to a real question, then I still would commend this to people.

Somebody asked what the test involved. You start off with a patient with a low FEV_1 (forced expiratory volume in one second), atropine methonitrate is then administered by nebulizer, and in 45 minutes to an hour, there may or may not be a slow response to it. When that response has peaked at, say, three-quarters of an hour, isoprenaline is then administered – yes, it had to be isoprenaline at that time – and then the patient is measured for a further response. Now that means you will have a total bronchodilator response, part of it due to the atropine and part of it due to the subsequent isoprenaline, and the proportion of it due to isoprenaline represented the steroid or cromoglycate-responsive component of that patient's bronchial disease.[130]

Godfrey: I think you were basically saying that atropine is more effective in chronic obstructive pulmonary disease [COPD] and the salbutamol more effective in asthma or the equivalent.

Clark: But what was interesting was that if you started off with a patient who did not respond, you treated them with steroids and then they did respond. The Altounyan test changed to a poor response because having treated them effectively with corticosteroids, they were not going to respond any more, and that is what the result of the test would indicate when repeated. It's a very good test.

Godfrey: I think probably we are going to be all right for time, but as somebody said, you only have to mention Roger Altounyan's name and everybody gets excited and talks for two hours. Having got over that hurdle, and in a very enjoyable fashion, I would like to ask Professor Warner to talk to us a little bit about the increasing prevalence of asthma and the impact of allergy on asthma.

Warner: As I am not an epidemiologist, I am not going to talk about the epidemiology of asthma, I will leave it to you to decide how much it has increased, merely to say that all allergic diseases have increased. I wanted to reminisce a little bit about my evolving interest in allergy as it relates to asthma and to carry on from what Harry Morrow Brown had to say. I start with my mother because she had bad eczema as a child, developed moderate to severe asthma in her teens and early adulthood, and also had hay fever. I can remember her using one of those rubber bulb and glass atomizers and in the very early 1950s she had a course of desensitizing injections about the time that Bill Frankland was doing his first double-blind placebo control trials of pollen immunotherapy. She

[130] Professor Jack Howell wrote: 'In addition to predicting responsiveness to corticosteroids, Roger used the test to assess whether anti-inflammatory therapy was being maximally effective – if the response to atropine was significantly less than the total response to both drugs given in this sequence, it was an indication to increase the anti-inflammatory therapy. This is perhaps the most useful application of the test. He also showed that lack of relative response to atropine correlated with the presence of sputum eosinophilia that disappeared as atropine responsiveness appeared with effective corticosteroid therapy.' Letter to Mrs Lois Reynolds, 6 July 2001.

benefited enormously from those injections and in fact didn't have much asthma through mid-adult life. I have to admit she is now in her seventies and taking inhaled steroids. That was my first exposure to allergy in asthma. As an SHO in 1969, I can remember treating asthmatic children in the Sheffield Children's Hospital and one child comes very much to mind, who spent all of his last year of his life in hospital because his asthma was that bad. Growth stunted with continuous oral steroids, he went to school from the hospital ward. He frequently required intravenous aminophylline[131] and subcutaneous injections with adrenaline just to keep him going. He eventually died in status asthmaticus and I was left with the feeling that this wasn't the way in which we should be managing this disease. Then as a registrar in respiratory medicine in 1971, I actually took over a desensitization clinic being run by Jerry Daley, a chest physician in Sheffield. In the first year I did it with the senior registrar – lots of injections, witnessing healthy people made unwell as a result of the injections. In 1972 we decided that as Intal was now around, we would not give these injections. We would put all the patients on Intal and close the allergy clinic with the support of the consultant. Having moved to Great Ormond Street to work with Archie Norman later in 1972, I was then given the opportunity to go into research, and what should it involve? An immunotherapy trial. I want to read you a letter I found among my documents. It was written in December 1973 as part of the application to the Ethics Committee at Great Ormond Street for the trial that I was to do. The letter was written by Edmund Hey[132] and Archie Norman[133] to the Secretary of the research board and there's one section here, in the first paragraph:

> '...conventional treatments for asthma, have improved symptomatic management of this often chronically incapacitating and all too often fatal condition, but no comparable advance has been made as yet in the elimination or prevention of allergic bronchospasm.'

This provided the justification for conducting this immunotherapy trial, together with bronchial allergic challenges to monitor effects on the early and late reactions, which yielded rather interesting results.[134] It actually took ten years for anybody else

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[131] Aminophylline is an injectable treatment for severe asthma attacks that do not respond to nebulized β_2-adrenoceptor stimulants. There is a narrow margin between a therapeutic and a toxic dose. For a review of drugs used in the treatment of asthma, see Molinoff P B, Ruddon R W. (eds) (1996) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. Ninth edn. New York: McGraw-Hill, 659–682.

[132] Dr Edmund Hey (b. 1934) trained as a respiratory physiologist in Oxford and worked for the MRC with Kenneth Cross, Professor of Physiology at London Hospital Medical College; Geoffrey Dawes and Elsie Widdowson for some years before moving to Newcastle to get a grounding in paediatrics in 1968. Professor John Warner wrote: 'Dr Edmund Hey was a consultant paediatrician working at the Hospital for Sick Children, Great Ormond Street, London, who moved to continue his career in Newcastle. He is now retired. He is best known for his seminal work on temperature control in the neonate. Dr Hey was an outstanding paediatric physiologist and physician.' Letter to Mrs Lois Reynolds, 16 May 2001. See also Christie D A, Tansey E M. (eds) (2001) Origins of neonatal intensive care in the UK. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 9. London: Wellcome Trust Centre of the History of Medicine at UCL, 5, 10, 34.

[133] For biographical details, see note 21.

[134] Warner J O, Price J F, Southill J F, Hey E N. (1978) Controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with asthma. *Lancet* **ii**: 912–915.

to replicate our observations of the effect of immunotherapy on late bronchial reactions,[135] which worried me enormously because I thought that maybe my observations were totally invalid. Roger Altounyan had heard my presentation about the results, about the late reactions and the effect of immunotherapy, and he phoned me up at Great Ormond Street sometime afterwards and said, 'Look, are you still doing the research?' and I said, 'No, I am back in my training programme. I am now Senior Registrar, and have to go through the usual hoops.' He said, 'I feel this research is terribly important and I am going to sort things out for you'. About two months later he phoned back and said, 'I have organized a position for you working in Hamilton, Ontario, with Freddy Hargreave. How about going there to carry on with your challenge work?' I was, perhaps, stupid enough not to accept the offer at that stage, but I have gravitated back to allergy very much more in recent years and have become ever more convinced, like Harry [Morrow Brown], that there is more to asthma than just drugs, and that there is a great deal more that we should be doing. As Harry was speaking, I did notice some shufflings in the audience of people who perhaps don't quite hold the same view and perhaps still, like many people, look upon allergy as being a side issue in asthma. I will quote something from a book that I have found immensely valuable in my training, *Respiratory Illness in Children*, by Howard Williams and Peter Phelan, the first authors of this book, first published in 1975. These Melbourne paediatric chest physicians have been very instrumental in raising the profile of the discipline, but in the chapter on asthma, Chapter 7, there are ten pages on emotional aspects of asthma and only one page on immunological aspects. On allergy skin tests they wrote:

> 'While such procedures are routine with most allergists, many physicians are more cautious and skin testing is reserved for patients whose asthma is not well controlled pharmacologically and in whom there is no serious emotional disturbance.'[136]

Now I think it would be an interesting issue to discuss why there is this enormous diversity of views from those who are total believers that allergy is the cause of everything, to those who think it a concept totally inappropriate to think about in relation to asthma.

Godfrey: Is that all? Very good, very succinct, but you haven't told us anything about the increased prevalence of asthma.

Warner: Well, you know it has increased. Who needs to say more?

Godfrey: I am almost speechless, but I think that what I would say, personally, is I have been convinced by a lot of very good studies that at least in children, ongoing

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[135] Van Bever H P, Stevens W J. (1989) Suppression of the late asthmatic reaction by hyposensitization in asthmatic children allergic to house dust mite. *Clinical and Experimental Allergy* **19**: 399–404.

[136] Williams H E, Phelan P D. (1975) *Respiratory Illness in Children*. Oxford: Blackwell Scientific, 159–160.

exposure to allergen is a major factor in the continuation of airways inflammation which is the basis of bronchial hyper-reactivity which makes the patient susceptible to all the various environmental influences, not just allergic challenges, that provoke his asthma. And I have a very interesting recent experience with this, because as some of you know I am currently on sabbatical, working with a company who devised the hardware and software for online continuous monitoring of wheezing overnight. Some studies are being carried out with Professor Boner's children up in Misurina in the Italian Alps,[137] which is an institute for asthmatic children. I didn't believe it when I first heard about it, but I have now seen the children and seen the data, and you get standard wheezy little asthmatics from Rome and wherever it might be, who go up to an allergen-free environment up in the Alps there and a month later, they are doing cross-country skiing. Now, as those of you here who are interested in exercise-induced asthma know, cross-country skiing has to be about the worst possible sport for an asthmatic for provoking the attacks, but I have seen the kids doing it, so there has to be something – and they are off their medication, it's not just that they are taking the medication. The thing about the Misurina children is that they are symptom free, not all of them of course, but a lot of them are symptom free, off their steroids and other medication, and doing cross-country skiing. So you have to be very, very, very sceptical not to be impressed with that kind of evidence. Going on from that, and I am not going to let you get away with the increasing incidence of asthma. How can we relate the increasing incidence to exposure to allergen, different exposure to allergen, reduced incidence of infections and changes from TH1, to TH2-type, lymphocytes? What about the immunizations from Southampton and your antenatal inception of asthma, you people can't get away with this, you must talk about it. This is great stuff.

Holgate: I would like to state that the rising trend of allergy is clearly established worldwide. There is slightly more debate about the rising trends of asthma, because it appears that this differs quite markedly country by country, which is not mapped by the trends in allergy. One has to go to continents like Africa, or some of the more remote islands, to see the morbid disparity between the prevalence of atopy and of asthma. For example, when Richard Godfrey went out to The Gambia, in the early 1970s, the prevalence of atopy in schoolchildren there was in the order of 12 per cent.[138] In a recent survey conducted in the same population by Keith McAdam, Director of the MRC Unit there, and his colleagues, the prevalence of atopy had increased to 35 per cent.[139] Yet in this population the current prevalence of asthma and airways hyper-reactivity as a surrogate of a component of asthma, is only 0.3–1.0 per

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[137] Boner A L, Niero E, Antolini I, Valletta E A, Gaburro D. (1985) Pulmonary function and bronchial hyperreactivity in asthmatic children with house dust mite allergy during prolonged stay in the Italian Alps (Misurina, 1756 m). *Annals of Allergy* **54**: 42–45.

[138] Godfrey R C. (1975) Asthma and IgE levels in rural and urban communities of The Gambia. *Clinical Allergy* **5**: 201–207.

[139] Nyan O A, Walraven G E L, Banya W A S, Milligan P, van der Sande M, Ceesay S M, Del Prete G, McAdam K P W J. (2001) Atopy, intestinal parasite infection and total serum IgE in rural and urban Gambian communities. *Clinical and Experimental Allergy* **31** (in the press).

cent. So here one sees a very large disparity. There are similar data coming out of Ethiopia and Nigeria. So I think when one observes such a very different relationship between atopy and asthma, then one needs to ask some serious questions about the linear causation of asthma from atopy and allergen exposure. Thinking is beginning to develop around the existence of two parallel pathways involving susceptibility genes for atopy, the influence of which best fits with the 'hygiene hypotheses', and a separate set of susceptibility genes expressed in the airways responsible for the structural changes that occur and for sustaining the inflammation locally. For most of us who see asthmatic patients over a lifetime, this disease is not a progressive disorder. In fact it is a remarkable disorder that can vary so much from year to year. Harry Morrow Brown, I think, can speak more about this than anyone.

Warner: Stephen [Holgate] said much more eloquently what the state of the art is with relation to allergy in asthma and I think most people would now agree. The reason I made this comment about polarization of views is because I would like to look at it from a historical perspective, because that's what we are here for and it is very interesting that at a time when there were no effective drugs available for asthma, allergy was clearly the one approach that evolved from the beginning of the century that seemed to have some impact, and immunotherapy and allergen avoidance were regularly and routinely employed, not just in the first half of the twentieth century, but even in previous centuries. Once effective drugs started to appear – almost a British rather than a North American enterprise – allergy very rapidly faded into the background. Obviously, the rapid onset of active pharmacotherapy eclipsed allergy in Britain. However, in other countries pharmacotherapy has been very much slower to evolve. North America is a fine example, where the allergist retained, as it were, a hold on the scene for a great deal longer and maybe hasn't faded quite so much into the background in maintaining an interest in the allergic side of the condition.

Godfrey: I think we would be very remiss if we didn't remember Jack Pepys[140] in this gathering, who really was the father of academic allergy wasn't he? I was his houseman at the Brompton and I remember at the time nobody believed a word he said, they thought he was crazy, and of course he wasn't and he really was the first person to get going, doing academic allergy in proper scientific controlled experiments. He was years before his time.

Silverman: I think it might be worth considering some explanations as to why there has been this waxing and waning. I think, as John Warner has clearly pointed out, it relates somehow to drug availability, but I think it might also be dependent on the quantity of financial sponsorship for particular types of research. And we have been dominated for the last 20 years by the large pharmaceutical firms pushing drugs, so that very few

[140] Professor Jack Pepys FRCP FRCPath (1914–1996) came to the UK from South Africa in 1947 to sit for the MRCP. He worked in clinical immunology at the Royal Brompton Hospital, London, setting up an allergy clinic at the Institute of Diseases of the Chest, and in 1967 was appointed Professor and head of the first academic Department of Clinical Immunology in the UK. The MRC funded his Clinical Immunology Research Group, from 1960 to 1967 when financial responsibility was taken over by the Institute of Diseases of the Chest.

resources have been available for research in allergy in comparison with the amounts that are spent on drug use. It may be that there has been a lot more profit to be made out of pharmacological agents dealing with the consequences of allergic inflammation, rather than in the potential for treating or preventing allergic inflammation, and I wonder whether there is a commercial pressure that has actually diverted to some extent the type of research that's gone on over the last 25 years and possibly explains to some extent the waxing and waning of allergy as a sort of favourite topic.

Dr Donald Lane:[141] Could I just come in to give a different slant on this point. There is a very remarkable historical waxing and waning. I have just stopped working in the Osler Chest Unit in Oxford. Now Osler viewed asthma quite differently to the way we do. I am not saying he got it wrong, but he understood it differently. Asthma appears in his textbook, in the section on neurology, under the heading 'hysteria'. At that time the whole emphasis on asthma was on the emotional and neurological components, despite the fact that Henry Hyde Salter had described allergy absolutely beautifully in the 1860s.[142] By the early twentieth century allergy had gained credibility and became a second mechanism for explaining the asthma phenomenon and gradually the emotional component dropped out. It is, however, still present but, because we have been given effective drugs for controlling the disease, we have stopped asking why any individual has asthma. I think we need to start asking that question again so that we can look into causation more carefully and tailor-make our treatment for the individual. Undoubtedly some patients have a strong emotional or psychological component; others have a strong allergic component. Yet others have totally different mechanisms that half the time we don't understand at all. I would like to get back beyond the word 'asthma', which after all is only describing a syndrome, to try to find out why individual patients are asthmatic.

Morrow Brown: If the present epidemic of asthma and allergies had happened 20 or 30 years ago, there would have been many more deaths, I am quite sure, because the drugs weren't there. We now have the drugs that are papering over the cracks with the result that there is no interest in why all these children have got asthma at all. GPs used to send so many patients for skin testing and investigation that there was over a year's waiting list, but that has all evaporated since they have learned how to use inhaled steroids properly and are paid to have their own asthma clinics.[143] I would like to propose that we pay more attention to childhood asthma in particular, because if you can do something for the children, perhaps they will have a chance to grow up into asthma-free adults. My experience with effective acaricides, for example, showed that there is a minority of younger patients who, if they are in a mite-free atmosphere or a mite-free environment for long enough, will cease to respond to challenges presented by dusty environments that have not been cleared of mites. Just like the

[141] Dr Donald John Lane (b. 1935) was Consultant Chest Physician at the Osler Chest Unit, Churchill Hospital, Headington, Oxford, from 1971 to 2000. He has been Vice-President of the National Asthma Campaign since 1993.

[142] See note 10.

[143] See page 54.

children in the Alpine schools, some will lose their sensitivity to mites with long-term avoidance so that they do not relapse on returning to Rome.

Finally, I would like to say that specific immunotherapy has got a bad name, and its premature and misguided abandonment really gave asthma over totally to the drug manufacturers. But if we use immunotherapy properly it works. My approach was that they [patients] should not receive immunotherapy unless they had a positive bronchial provocation test, so that at the end of the course a negative bronchial provocation test could show that they had achieved immunity. If not, further immunotherapy could be given until the provocation test became negative. That sort of objective approach is what's been missing in the past.

Godfrey: I think the Warners, Jill and John, would say what you really need to do is to prevent the mother getting allergic and giving TH2 lymphocytes to her fetus. Like Bray says, 'Don't marry allergics'. Back to that.

Clark: I will be quick. We were just talking about historic anomalies, or possible historical anomalies, and I will avoid injecting an acerbic note into this, to try to keep it all friendly. One of the interesting distinctions, looking internationally, is the failure of allergy as a speciality in the UK and that is a very big issue that requires debate now. I personally wholly subscribe to the point of view that Harry [Morrow Brown] put forward about his patients who became steroid-dependent asthmatics. There must be something better than having patients dependent on medication. If you and the patient can avoid the cause for the medication, the patient is much better off. But whether you need a separate speciality is a very big issue and I feel that this is something that is about to be debated again. I personally don't think you do, but there are many people who think the opposite. I think we should just note the historical anomaly in this country, which is relatively unusual in not having a clinical speciality of allergy, and it may be our troubles are because we haven't had the speciality. However, I think there are other conclusions you can draw.

Brewis: I was going to bring up the dulling effect of effective treatment on curiosity, and I was going to lead on to the effect on one's life as a clinician. Much of what we have been talking about so far is in the literature and I wondered whether you would like to tap into the experience that people have had in respiratory medicine, treating asthma in childhood and adult life, which doesn't appear in the literature.

I have done 30 years, just finished. In the early years my clinics were dominated in the asthma context by what I used to characterize as a steroid confessional. People came to confess how bad they had been, allowing themselves to have just a little bit more prednisolone. On the whole people undertreated themselves, they were so fearful of side-effects, and you had to make them feel better about this. Then along came steroid aerosols, and then there was a period when I had a rush of people with hypoadrenal symptoms, although not enough to write up. There was very little written up, apart from a lot of irrelevant stuff about giving adrenocorticotropic hormone (ACTH) and

weaning people off.[144] But people used to come in as emergencies, collapsed with apparent flu or hypotension. People were investigated for diarrhoea of mysterious cause, had headaches and felt gravely unwell. They were hypoadrenal. They had their steroid aerosol, keeping their asthma absolutely fine; nobody thought that they were short of steroid, but they were. This gradually faded out during the later 1970s. After the 1970s asthma gradually became a GP disease and in hospital practice you were only really sent people who had terrible, intractable disease. Also, you no longer saw so much missed asthma. I used to see at the beginning of this 30-year period a blindness on the part of many GPs to asthma. Anybody that coughed had chronic obstructive pulmonary disease (COPD), and when I went to Newcastle 30 years ago I turned over huge amounts of apparent COPD and gave them steroid trials to show that some had asthma. Gradually practitioners and practices would learn to recognize these and you would realize that you wouldn't get any more cases from that particular practice. They had twigged. So there was quite a big change.

I would suggest almost three phases to those 30 years of experience as a respiratory consultant, and a lot of people will recognize that there must be many anecdotes, many features of life in respiratory medicine dealing with asthma that you could get from your audience here, which are not actually being published and I wondered whether you would like to try.

Gregg: Can I reinforce one or two points that have been made, particularly by Donald Lane. First of all, I think we should be rather more careful with our use of terms. We talk about asthma as if it were one disease, and yet everybody with clinical experience knows that it is shot through with contradictions and paradoxes. Hence it is most unwise to generalize about asthma. Also, when talking about allergy, are we really talking about atopy? Most of us have been, I think, this afternoon. But after all where you find no evidence of atopy at all in some of the occupational asthmas, particularly with TDI (toluene diisocyanate), there is no evidence of atopy that I know of and yet even after removal from exposure some patients continue having asthma. So presumably they are allergic.

To go back to Roger Altounyan, who I am sure would have liked us to derive as much from his experience as we can. I think that he was generally regarded as having atopic asthma. Certainly in childhood he did know from experience that eating chocolate had appalling effects. Yet he never had asthma as a child and he was passed fit for the Air Force as a fighter pilot during the Second World War, clearly indicating that he must then have been a very fit man. I always understood that was where he got the idea of the propeller of the Spinhaler. It was only towards the end of his medical studentship did he suddenly develop asthma that persisted for the rest of his life. He challenged himself repeatedly by inhaling substances that provoked acute asthma

[144] Carey R A, Harvey A M, Howard J E, Winkenwerder W L. (1950) The effect of adrenocorticotropic hormone (ACTH) and cortisone on the course of chronic bronchial asthma. *Bulletin of the Johns Hopkins Hospital* **87**: 387–414.

(thereby discovering Intal that protected him against their effects) and this would seem to suggest that the attacks were atopic in nature. I don't know what his skin tests were, I always meant to ask him and I never did. He used to smoke quite a lot too, a pipe, and the word was that it was a nonspecific effect and the Intal in him anyway was working to prevent what is usually only done in atopic people. We don't know. His chronic asthma may have been due to a different mechanism.

Dr George Russell:[145] I want to say a few things about the changing scene in the asthma clinic that Alistair Brewis referred to. I think it is fair to state that when I came back from the States in 1965, the asthma clinic in Aberdeen, started by Professor Ross Mitchell, was very heavily allergy biased and every patient who came had skin testing done, and every patient had advice on allergy. Then of course in the late 1960s and early 1970s, we got all the new drugs. We also at the same time were inundated with large numbers of patients and we hadn't the time to skin-test them all and work them up in the way that we used to do. I think one of the reasons why allergy has gone out is because it is so labour intensive. It takes time, it takes people, it can't be done by machines, and many clinicians are insecure about it. It is easier and takes much less time to manage patients pharmacologically. Now, what I have seen since then is a gradual change towards getting more and more difficult asthmatic patients who aren't responding outside hospital. Furthermore, in the last four or five years we have also seen an inundation of people who are not asthmatics, but who have been labeled asthmatics, because of all the publicity about asthma and all the enthusiasm for things like coughing asthma. Most of these patients don't respond to antiasthma therapy. They come to us and are very upset when we have to amputate the diagnosis of asthma from them and tell them that what they have is whooping cough, habit cough or whatever. [From the floor: Postnasal drip.]

Also I would just like to make a little retrospective comment on the introduction of Ventolin. I was extremely interested to hear that when Ventolin was introduced, what was being looked for was a long-acting isoprenaline, because my recollection of its initial use was that its prolonged action was indeed its scoring point.[146] Safety wasn't a major issue. The advance on isoprenaline was the fact that it lasted three or four hours instead of five to ten minutes, and children could get it first thing in the morning, were well until lunchtime when they could get more. Indeed it was often used as a sort of prophylactic much in the way that salmeterol is used nowdays.

Dr Jill Warner:[147] Listening to George [Russell] speak made me want to thank the people running those allergy clinics in 1965, because a lot of the results that have

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[145] Dr George Russell FRCP (b. 1936) was a consultant paediatrician at the Royal Aberdeen Children's Hospital from 1969 until 1996 when he retired to join the staff of Aberdeen University as Reader in Child Health. He has contributed various papers on the increasing prevalence of childhood asthma, and on its treatment.

[146] Riding W D, Dinda P, Chatterjee S S. (1970) The bronchodilator and cardiac effects of five pressure-packed aerosols in asthma. *British Journal of Diseases of the Chest* **64**: 37–45. Kamburoff P L, Prime F J. (1970) Oral and inhaled salbutamol as a bronchodilator. ibid.: 46–54.

[147] Dr Jill Warner (b. 1962) is Senior Lecturer in Allergy and Immunology and Coordinator of the MSc training programme in allergy at the University of Southampton.

come from those large cohorts have been the basis for much of the work that we are now doing. You mentioned the antenatal work. A lot of the support for that comes from the observation that you see an increased risk of mothers with asthma going on to have children with asthma. The people who made those observations have given us the opportunity to go on now and look at more of those causal factors, which must be occurring during pregnancy.

Godfrey: Would Mrs Greta Barnes like to come on and set the ball rolling, because we want to move a little bit to our next topic, the impact of, well, the role of, support organizations that have evolved and how that's affected the asthma scene over the years. I think last and by no means least we are going to talk a little bit about phenotypes of asthma and that really comes back to George Russell's point about the coughing asthmatics or nonasthmatics.

Mrs Greta Barnes:[148] Maybe it's important to say to those of you who don't know me, that I am not a doctor. I am a nurse by background, and in 1983 I was just finishing a role with the Medical Research Council, when our GP, Dr Robert Pearson, turned to me and said, 'You have looked at diabetes, you have looked at hypertension, I think we have got a major problem with asthma in the practice. We know it's increasing and patients are not getting a good deal; why don't you spend some time researching, looking at the role of the nurse in asthma?' So I did this for a year and we found that by utilizing nursing skills, we were able to reduce the acute nebulizer use, but inevitably what we did was to increase the inhaled corticosteroid use, which won't surprise any of you. Now I have to admit that I have got two heroes, one of them knows who he is because he's sitting over there, Tim Clark, but the other one I have never met before and it's this gentleman [Simon Godfrey], because I learnt all the asthma that I could possibly learn from the 'green book',[149] and you went to bed with me night after night. [**From the floor**: It gave me great pleasure.] We also visited Ian Gregg who was incredibly helpful, we went round various hospitals and I was a real nuisance, because I wanted to know what was going on, and the one thing that struck me at that time was we were giving messages that were too complicated for the patients to understand. Patients needed to have simple messages. The major requirement was that we needed to make people understand that prevention was possible, and that our goal should be having patients without symptoms.

One day in 1986 I happened to see that a tiny property opposite our medical centre was for sale. I thought that it would be ideal to use as a training centre for nurses and doctors. I am not, as some of you will know, frightened of the medical profession and I thought it would be a good idea if we could just set up a training centre for diabetes, asthma and hypertension. Three chronic disorders, wonderful, that's the way general practice should go! Perhaps historically this is quite important because we tried to get

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[148] Greta Barnes MBE (b. 1940) is the founder and Director of the National Asthma and Respiratory Training Centre in Warwick, which was established in 1986.

[149] Clark T J H, Godfrey S. (eds) (1977) *Asthma*. London: Chapman and Hall. The second edition in 1983 was green.

funding for setting up a training centre for the three conditions. We went to industry and we went to the charities and we were able to attract a very small amount of funding from what is now the National Asthma Campaign and from Allen & Hanburys. We were unable to attract funding for the other two disorders, and I suspect that things might have been very different if we had actually managed to do so. The training centre was set up with charitable status and we ran a three-day course for nurses with their GPs coming on the last day. The reason the GP was invited was to promote teamwork and it seemed what we mustn't do was to antagonize doctors. We needed to show we were working together, we were not trying to work separately. Well by 1990, several things had happened. One was that the British Thoracic Society (BTS) Guidelines were introduced,[150] secondly, there was a new GP contract that meant that GPs could get money for running asthma clinics. GPs quite like money and so this made a huge difference. And thirdly, we had introduced the Diploma in Asthma Care programme, which was six months' distance learning, including face-to-face teaching as well as a written and practical examination. I do wonder sometimes whether introduction of the guidelines resulting in the increased use of inhaled steroids, the new GP contract,[151] or possibly the fact that we were working very hard on introducing nurse-run asthma clinics, had an effect on the reduced death rate. I don't think we are ever going to know which it was, but it is likely to have been a combination of all of them. By 1992, the UK had the chronic disease management programme in place when focused on asthma and diabetes. So this meant that we were hugely in demand, because GPs wanted to run asthma clinics. By 1993 the training centre had introduced 12 different courses which ranged from essential skills workshops to diploma-level courses,[152] including allergy, where we worked very closely with the experts, including Steve Holgate. We also introduced a respiratory Master's level course in conjunction with Sean Hilton at St George's Medical School. Currently we have trained approximately 20 000 health professionals. The number has increased internationally as well as in the UK. You may say, 'How have you achieved this?' The answer is that we have a very large national training network. We have 60 trainers in this country, as well as in Canada, America, Norway, Denmark and several other countries besides. The trainers are practitioners, whom we have put through a special programme to enable them to train others effectively. We also have 250 educators in the UK as well as regional training centres. So, really, that's the way that has been achieved. It has been through the tremendous support from the nursing profession, but in addition, and I suspect the chief reason, has been the support and

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[150] British Thoracic Society et al. (1990) Guidelines for management of asthma in adults: I: Chronic persistent asthma. *British Medical Journal* **301**: 651–653. *idem* Guidelines for management of asthma in adults: II: Acute severe asthma. ibid.: 797–800. Revised and extended to include asthma in childhood in *idem* (1993) Guidelines on the management of asthma. *Thorax* **48** (2 Suppl.): S1–S24.

[151] Department of Health and the Welsh Office. (1989) *General Practice in the National Health Service: A new contract. The Government's detailed proposals for changes to the GP's terms of service and remuneration system.* London: HMSO.

[152] Barnes G. (1998) The nurse's role in asthma management. *Seminars in Respiratory and Critical Care Management* **19**: 593–601.

encouragement from the medical profession. Our trustees have been superb, two of whom are here today, as well as our medical adviser, and people like Tim [Clark] who opened our fourth and latest headquarters in Warwick.

Godfrey: Thank you very much and a great contribution it is. I beg your pardon, Dr Lane, would you like to add a few words along these lines? The organization of education.

Lane: I have worked closely with Greta [Barnes] in the training centre as a trustee, but perhaps I could put a historical perspective on voluntary organizations for asthma. The modern medical charities started in the 1890s. It's interesting that the first one, perhaps not surprisingly, was for tuberculosis, but following that, very quickly, were the two cancer charities that still remain.[153] And in fact the next one was for asthma, but that was not until 1927, when the Earl of Limerick, concerned about the lack of understanding of this disease, formed the Asthma Research Council. That organization funded research through the next 40 or 50 years at a fairly modest level, so that by the time of the introduction of Intal and the asthma deaths epidemic it was still only putting about £300 000 to £400 000 per annum into asthma research. Then, stimulated by the upsurge of asthma deaths, a lady called Helen Wilde, whose own daughter had died of asthma sometime earlier, joined the Asthma Research Council and set up the Friends of the Asthma Research Council, which was there to aid fund-raising for research. However, you can't bring together people interested in fund-raising for asthma, without their starting to inquire about their asthma, because a significant proportion of the fund-raisers were asthmatics themselves. So towards the end of the 1970s a group of us looked at other charities that had a specific patient-support function in order to decide whether we should have one for asthma. That decision was in the affirmative, and so the Asthma Society came into being in 1980. The medical background that was important, and noted at that time, was that we had two effective measures in the therapy of asthma: good controlling drugs, the steroids, and cromoglycate, as well as good relief medications. That left the issues of the delivery devices and patient education. Patients weren't taught how to use the devices properly and didn't really understand the difference between steroids and bronchodilators. And that's why the Asthma Society started with an educational programme involving patient groups,[154] the branches that brought asthmatics together for support. It was very successful. The Asthma Society and the Research Council were run from the same office for a decade, but for organizational reasons it was obviously best that they came together, which they did in 1990. The National Asthma Campaign was the result, a charity campaigning on behalf of asthmatics with Government and public bodies. It has introduced a very popular telephone helpline. The balance is shifting now from patient support groups to the service that is available through general practice asthma clinics staffed by the sort of nurses that Greta (Barnes) has trained. The National Asthma Campaign continues to fund research,

[153] The Cancer Research Campaign and the Imperial Cancer Research Fund.

[154] For another example of patient groups, see Tansey E M, Christie D A. (eds) (1999) Haemophilia: Recent history of clinical management. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 4. London: The Wellcome Trust.

which now instead of being £300 000 to £400 000, is now £3 to £4 million. Quite a success story.

Godfrey: You said that it was started by Limerick.

Lane: The Earl of. Not the one who invented the rhyme.

Godfrey: In that case, I am afraid I am irrepressible.

> There was a young man with a wheeze,
> Whose doc said asthma's a breeze,
> Just take a puff of that steroidal stuff,
> And you will be able to breathe with ease.

Dr McCarthy, please carry on in the same vein. You don't have to make up a limerick on the spot.

McCarthy:[155] I do have a limerick but I had better not repeat it. For many years I was a GP in Suffolk and, like others of my contemporaries such as Mac Cochrane, was inspired by the enthusiasm and example of Tim Clark in developing an interest in asthma. I went into practice in the late 1970s and at that time it became clear fairly quickly that asthma in primary care was dramatically undiagnosed and also under-treated. There was significant morbidity and, from publications that had come out in the late 1970s and early 1980s, also a mortality that was unacceptable because of the preventable causes that have been pointed out. There was an also an increase in prevalence and I suppose, if we talked about children in particular, there were probably about something like 15 to 20 per cent of children with asthma who were receiving some kind of appropriate treatment. I had a major interest in children as I trained in paediatrics and anaesthetics, and I think the big change in primary care came about when it was recognized that asthma was a disease of inflammation as well as of bronchial constriction. The use of cromoglycate first and then of inhaled steroids made a significant difference. Steroids were used mostly in adults and, I think, with children there was probably the difficulty of getting the drug into them. The development of the large-volume spacers really made a considerable impact on the management of younger children with asthma and enabled us to deliver both bronchodilators and prophylactic medication such as steroids to these children.

I suppose as a result of my interest in anaesthetics, I was very keen to get the drugs into the small babies and initially used an anaesthetic mask that had become attached to me when I left anaesthetics. I then attached this to a spacer and saw that if I could deliver a drug into babies in this way, we might be able to treat smaller children. Over the course of three years, I worked, cutting and pasting, and using sellotape, to develop some kind of a mask and thought that this was kind of relatively innovative,

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[155] For biographical details, see note 72.

until I saw in arriving here that ten years earlier a doctor in Canada, a Dr Freigang,[156] had done it all before and had developed his own large-volume spacer and his own mask. But it did mean that we could now deliver medicines to children of all ages, providing that we were convinced that they had a diagnosis of asthma. And I do say that 'providing we were convinced', because I think we have come to rely a little over much on drugs and have come to apply the diagnosis possibly in small children inappropriately.

It would not be possible to talk of the work of looking after asthma in primary care, without giving a further tribute to Greta Barnes, because the impact of nurses who are trained in asthma care and primary care has probably made the biggest single impact, even more than most drugs. It enables nurses, who are better at communicating with patients than doctors, to sit down, talk to patients, listen to them, find out what was wrong, try to develop with them an understanding of how the disease should be managed, and then teach them how to do it. In the late 1980s, enthusiasts, two of whom are here today, and again I think tribute needs to be paid to Mark Levy[157] and Sean Hilton,[158] who had the foresight to realize that if the care of asthma could be promoted among doctors in primary care, that would also have a major impact. They founded the 'GPs in Asthma Group'[159] and again that group has continued to work for the last 11 years, promoting the care of asthma in primary care. As Greta said, the initiation of government-funded asthma clinics had a major impact, although that funding is now largely withdrawn, which makes it difficult to initiate new asthma clinics.

The level of diagnosis is now good, but I do think we are in danger, as I have said, of applying the diagnosis inappropriately to young children. Fernando Martinez and his group in Tucson have pointed out that coughs and wheezes may not be asthma.[160]

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[156] Dr B Freigang wrote: 'The prototype of an inhalation device was constructed from a plastic vinegar bottle with a face mask glued to one end and on the other end, a one-way valve which replaced the MDI [metered dose inhaler] after actuation. As soon as the glue was dry the chamber was tried out on Darren [a 12-month-old boy], who was discharged home with instructions to continue on beclomethasone indefinitely. Darren's subsequent hospital admissions were few and far between. The use of "A new inhalation device" was published in the *Canadian Medical Association Journal* in 1977 [Freigang B. (1977) New method of beclomethasone aerosol administration to children under 4 years of age. *Canadian Medical Association Journal* **117**: 1308–1309]. I soon tired of gluing my fingers together...and the following year a plastics company manufactured the device for my patients. A trade mark was secured as the Aerosol Inhalation Device for Asthmatic Children (AIDAC).' Letter to Dr Chris O'Callaghan, 5 September 1997. This letter contains further details of the spacer development and it will be deposited, along with copies of all additional correspondence received during the editorial process, with the records of this meeting in Archives and Manuscripts, Wellcome Library, London.

[157] For biographical details, see note 180.

[158] Professor Sean Hilton FRCGP is Professor of General Practice and Primary Care at St George's Hospital Medical School, London, and Head of Department.

[159] Levy M. (1993) The General Practitioners in Asthma Group. *Primary Health Care Management* **3**: 10. Since its formation in 1987 its scope has broadened to become the General Practice Airways Group (GPIAG). Its membership includes nearly 1000 general practitioners with an interest in respiratory diseases common in primary care with primary care nurses and other allied healthcare professionals as associate members. See www.gpiag-asthma.org/ (visited 10 July 2001).

[160] Wright A L, Holberg C J, Morgan W J, Taussig L M, Halonen M, Martinez F D. (1996) Recurrent cough in childhood and its relation to asthma. *American Journal of Respiratory and Critical Care Medicine* **153**: 1259–1265.

George Russell has also made the point.[161] I would very much echo Mike Silverman's comments in terms of 'Are we avoiding what is causing our patients' asthma?' I think with drugs freely available and encouraged by the industry, we should follow a paradigm in managing our patients, the first element of which should be avoidance. I think if we have not sought to avoid all the trigger factors that are impacting upon our children's asthma, we do them a disservice. And it is not enough to ask the parents if they smoke in the garden, because in Liverpool all parents smoke in the garden, and a study was published recently showing that cotinine levels in children whose parents smoke in the garden were exactly the same as those of parents who smoke in the house.[162] The work of nurses is critical in helping understand patients' problems taking their therapy. It isn't enough to educate, and I think only by taking into account what motivates the patient into taking their therapy, will we truly understand how to help them to manage their disease. We forget sometimes that we are making them 'able' by giving them effective treatments, but we are also reminding them of their disability by giving them treatment that they have to take on a regular basis. Device selection is critical and the British Thoracic Society (BTS) guidelines[163] in 1990 said that the commonest cause of failure in treatment in small children was in correct device selection. Device selection, I believe, does need to be tailored to patients; we do need to take them into account. The guidelines have made a major impact and drawing together wider groups into guideline formation, I think, and making them more evidence based will lead to their more successful use. One thing that struck me while I was looking at the evidence for this, for managing asthma, is that studies have been carried out on morbidity, showing that patients wake at night, in unacceptably large numbers, they miss work, they miss school, they can't do their exercise, but the figures haven't changed from 1990. So something is going wrong and I feel that in spite of all our therapies, we are still not communicating sufficiently with patients and understanding their needs, and how they wish to manage their disease. I think the way forward is not just avoidance but understanding the patient better.

Godfrey: Thank you very much. Very good. I think if the data from the Southampton study, the study and analysis of mortality trends, are correct, it shows that in the 1990s that asthma mortality is not rising, or may even be falling at 6 per cent a year, while the incidence of asthma is still apparently going up, which really implies that something is being done right. The one big thing that's happened is the education of doctors, nurses, practices and everything else, that's the new thing of the 1990s isn't it? I mean as far as steroids are concerned, you can change the molecule a little bit this way or that, or change the device, but that's not really such a big thing.

Clark: This is really an excuse for me to pay tribute to Greta Barnes, but she knows my feelings, so I won't pursue that. If I could just use this opportunity to mention a

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[161] Russell G. (1996) Childhood asthma: how best to manage the disease. *Clinical Immunotherapeutics* **5**: 96–114.

[162] Bahceciler N N, Barlan I B, Nuhoglu Y, Basaran M M. (1999) Parental smoking behaviour and the urinary cotinine levels of asthmatic children. *Journal of Asthma* **36**: 171–175.

[163] See note 150.

little bit about guidelines[164] in this historic review, as I, along with Steve [Holgate] and Martyn Partridge and others, have been involved with them, in their relatively brief lifespan.

One can argue until the cows come home as to when guidelines first appeared, and how you define what is a guideline, but they really began to appear about ten or 12 years ago. They first gained international momentum at a meeting convened by someone whom I would also like to pay tribute to, Freddy Hargreave, who convened the meeting in Canada with good old Jerry Dolovich and Mike Newhouse.[165] This was conceived as a way of trying to gather together experts from all over the world, because of the disparities in treatment that were perceived throughout the world, to see how best one could control asthma. I think 'control' was a very important word, although one can argue about whether it's the right word. In other words, there was a step change in therapeutic strategy from treating asthma symptoms, to preventing them, and to finding some way of controlling them to improve the quality of lives of individuals. Over the last decade guidelines have just blossomed and you can hardly turn without a new set of guidelines and revisions of guidelines. I would just like to make one caveat touched on by what Paul [McCarthy] was saying. There was a recent survey of asthma in the USA that revealed again the very high morbidity that still exists there.[166] The same applies here, the morbidity hasn't changed very much, but the one question that I really enjoyed most in the American survey, was a question relating to the patients' understanding of their treatment. The previous questions had established that education was very important to recognize and understand, 'preventer' treatment and 'reliever' treatment, or whatever the Americans call those treatments. And one of the questions towards the end [of the article] was 'now could you identify which is your preventive treatment?' or controller treatment, or whatever it was, and the top drug identified by patients was inhaled β-agonist, and I think that is telling us a lot.

We have grossly failed with guidelines, as we may all think we know how to treat asthma and have consensus, but we have a long way to go in conveying that where it really matters and enabling the goal of self-management to really work. In that respect Greta's activities and the work that she is doing, I think, are much more important than what a lot of other people are doing.

Godfrey: I personally think the guidelines are important for explaining to doctors and other people working with asthma, that there is a step-wise approach to asthma management. Not all asthma is the same and some patients need more treatment and

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[164] For the original guidelines, see note 150. For further revisions, see note 93.

[165] Dolovich J, Hargreave F E, Wilson W M, Greenbaum J, Powles A C P, Newhouse M T. (1982) Control of Asthma. *Canadian Medical Association Journal* **126**: 613–618.

[166] For details of the survey, see www.asthmainamerica.com/ (visited 5 July 2001). See also Rabe K F, Vermeire P A, Soriano J B, Maier W C. (2000) Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *European Respiratory Journal* **16**: 802–807.

if you need more it should be given in a logical fashion, rather than having a whole bundle of drugs dumped on the desk at the same time, used higgledy-piggledy as they are in many places. Much less here than they are across the Atlantic maybe. I would like to see some evidence-based medicine that the guidelines really do something. Personally I happen to feel that the American version, Global Initiative for Asthma (GINA) guidelines are completely impractical, because they assume that the patient is receiving no treatment whatever when he comes to see you, so then you can decide how bad he is and give him the treatment, which is ridiculous. The BTS guidelines don't assume that. They assume first of all you treat him and then you find out how bad he is by saying what step he is on, which is nice, but I mean it doesn't actually really help you. What we really need is something that gives an unbiased estimate of severity. I was joking around with Mike Silverman yesterday, saying that I would like the blood rhubarb test, by which the blood rhubarb would tell me how bad the asthmatic is, what treatment he needs, and follow him by following the levels of blood rhubarb. This would be fine, but I don't think we have it.

Warner: There is actually an evidence base on guidelines, which suggests that national and international guidelines are totally ineffective.[167]

Godfrey: Well, I was trying to be polite.

Warner: The guidelines which work are those that are developed locally with patients, and that are practical and reinforced in the clinic setting, rather than being an ivory tower-generated edict. But I just wanted to come back to what Paul [McCarthy] was saying. I neglected to say anything about epidemiology when I got up to speak, because I didn't feel that was my position to do so, but we recently have done a study to look at how many wheezing children are diagnosed as having asthma and consequently receive appropriate treatment for asthma. You can see over the last 20 years that a progressively higher percentage of recurrently wheezy children are now labeled asthmatic and a progressively higher percentage are receiving appropriate treatment for asthma. Those children left as wheezers, that are not receiving asthma treatment and don't have an asthma label, in general have very infrequent, very mild disease. Therefore there probably is no more need to drive people to make more and more diagnoses of asthma in that category of patients, because they are very mild anyway. The pressure that is being put on us to do that is creating a problem, and as other people have said, many patients are being referred as uncontrolled asthmatics, on the basis of a lot of asthma treatment, but they haven't got asthma at all.

Godfrey: I think that is a marvellous introduction for Mike Silverman to talk about what is and what isn't asthma.

Silverman: As an aside, I would just like to congratulate everybody for not trying to define asthma – well done. We've been through this repeatedly for many years.

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[167] Woolf S H, Grol R, Hutchinson A, Eccles M, Grimshaw J. (1999) Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *British Medical Journal* **318**: 527–530.

I think there is an interesting story here, because attitudes to asthma and wheezing in paediatrics have changed noticeably over the last 30 or 40 years, and it's more than simply terminology. The story relates to wheezing diseases in childhood, because attitudes have changed considerably. In the 1960s there was a distinction, and the Aberdeen cohort that has been referred to is the embodiment of this[168] – a distinction between wheezy bronchitis and asthma in Aberdeen, not just in pre-school children. There was an acceptance that amongst the wheezing disorders of childhood, there were different types of disease. There was something called wheezy bronchitis, which was generally wheezing and coughing (a wet cough) associated with acute infections, and there was asthma, which we all recognize as being generally an atopic disorder. But then in the 1970s (and I think this is interesting and more than a coincidence), with the development of effective therapy we were urged to call all wheezing asthma, not to split, but to lump the whole lot together. And that is probably because there was effective therapy for the first time and it was realized that using antibiotics and other therapies for wheezy bronchitics wasn't the appropriate thing to do. Therefore we were urged to make the diagnosis of asthma more actively, and the diagnosis was accepted because there was a form of therapy and treatment with effective drugs. There was also, and there has been increasingly, an increase in the promotion of drugs and awareness of asthma and diagnosis of asthma by all organizations with an interest, whether commercial or noncommercial. And whether by coincidence or not, the epidemic of asthma really started in the late 1960s and 1970s and it became obvious that there was an increasing amount of it. So in the 1970s it became unfashionable to think of different subclasses of asthma and we all had to call everything that wheezed in childhood, asthma, and that I think was a mistake. But it may have been an inevitable consequence of the new drugs. We have talked a lot this afternoon about how drug development has influenced the way in which we have all behaved and practised medicine, and I think this is another example.

In the 1980s there was an increase in recognition that what had become known as phenotypes of asthma, different types of wheezing disorders, were detectable in the population of wheezing children. And I will say as an aside that I think this is now feeding through into adult practice (and it is one of a number of examples I could give you of attitudes in paediatrics that have begun to have an effect on chest physicians, too), and allow them to begin to think of asthma phenotypes or different varieties of asthma in adults. Obviously there are some leaders in this field like Donald Lane here, who have always been aware that there were different forms of asthma, as he hinted earlier, but among the majority that hasn't been the case. Evidence accumulated in the 1980s with epidemiological studies,[169] with studies looking at the outcome of wheezy bronchitis, as opposed to atopic asthma and I think with the important publication by Nicola Wilson who isn't here today, in 1989, which raised the question: 'Should we really be thinking

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[168] Dawson B, Illsley R, Horobin G, Mitchell R. (1969) A survey of childhood asthma in Aberdeen. *Lancet* **i**: 827–830.

[169] See, for example, Sporik R, Holgate S T, Cogswell J J. (1991) Natural history of asthma in childhood – a birth cohort study. *Archives of Disease in Childhood* **66**: 1050–1053.

about a separate disorder and not lumping this particular variety of wheeze together with the rest of asthma?'[170] In the 1990s there was increasing awareness of the benefits of splitting wheezing disorders in childhood into subsets to begin to look, as Donald [Lane] said earlier, at the possibility that they have different mechanisms requiring different forms of therapy. There is evidence from clinical trials in very young children that, of course, wheezing in young children doesn't respond to standard therapy as effectively as in older subjects. There must be reasons behind that which need more research. There have been increasing doubts about the role of atopy – house-dust mite sensitivity or bronchial responsiveness – in wheezing in very young children, unlike older asthmatics. There are lots of reasons for splitting and evidence that there are different subsets.

Cough has been mentioned, and I am not going to go into that, but again that has suffered the same sort of fate. In the 1980s we had 'cough variant asthma' and we were urged to treat children who coughed at night with antiasthma therapy. It has become obvious from more detailed studies in the 1990s that children who cough without wheezing don't generally have asthma; it's a different disorder. So there again I think we have moved on from the stage in the 1970s which was driven by the new therapies, to be free to begin to think about the different mechanisms of disease – different subclasses, different phenotypes, different genetic variants – which are contributing to asthma. I would suggest that this has fed through into adult practice too. Perhaps not as far as it might (I am not just thinking of chronic bronchitis but of other disorders too) to free people up and to allow them to begin to explore subsets of asthma and not to think of it as a single disease, but as a syndrome, the word Donald [Lane] used earlier.

Godfrey: Thank you very much. I would just like to add a little bit to what Mike Silverman has said and particularly to pay tribute again to outstanding work done, epidemiological work in this country, by various people, particularly the study from Newcastle by Edmund Hey. This was highly original and extremely important. This was a specific group of babies who had had proven respiratory syncytial virus bronchiolitis. A marvellous study with a matched control group followed for years. These little babies looked like little asthmatics, little wheezers, they wheezed their poor little guts out and they looked just like any other asthmatics, but he showed clearly that they were not. They had a virus-induced disease that was not asthma, because what happened was the wheezing gradually petered out over a few months, or a year or two, and when you looked at these children, I think it was ten years later, they were quite different from what we normally recognize in asthma. There were very small differences, if any, between the control group and the asthmatic groups several years down the line. I think that probably predated Martinez by a long time.[171]

From the floor: Can I quote you data from the 1960s showing the same thing. John Fry in 1961 conducted two very carefully carried out studies showing that wheezing

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[170] Wilson N M. (1989) Wheezy bronchitis revisited. *Archives of Diseases in Childhood* **64**: 1194–1199.

[171] Pullan C R, Hey E N. (1982) Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *British Medical Journal* **284**: 1665–1669.

in early infancy is a self-limiting disorder.[172] There is nothing original about that.

Godfrey: Well, Boesen said that in the 1950s actually,[173] if we really are going to go into a 'my reference is earlier than your reference' kind of thing. And it always takes the Americans a little bit longer to wake up, and basically Martinez is saying the same sort of thing. Now I know you think that it isn't specific to respiratory syncytial virus (RSV), you think it is other viruses do it, and I can't argue with that, I haven't got the information, but we certainly see now a lot of little babies who are wheezy who do not have asthma, but we do see some little wheezy babies who do have asthma. Now we have an infant lung function laboratory, we developed the technology here, originally at the Brompton and then the Hammersmith. We have the technology for looking at lung function in small infants and for looking at their response to medication and we see a small proportion of the wheezy babies behave like asthmatics and I think this is fair, they are asthmatics. In Israel about 10 per cent of children have asthma, rather less perhaps than here, so I don't expect more than 10 per cent of wheezy babies to have asthma. The others don't have asthma, they have these virus-associated diseases and they don't respond to antiasthmatic medication, which is the important thing. They don't respond to anything else either, by the way.

I would like for us just to remember one other very special person in the history of childhood asthma in this country and that's Dick Jones from Liverpool,[174] who was undoubtedly the father of modern exercise-induced asthma, even though Sir John Floyer described exercise-induced asthma 300 years ago. Dick Jones did some very beautiful, simple clinical studies, showing that asthmatic children wheezed when they exercised and he did a lot of studies on the physiology and treatment, and he used exercise to try to diagnose asthma and to grade its severity. Although Mike [Silverman] and I and many of us have worked for years and years doing research on exercise-induced asthma, I really honestly think that we've just kind of dotted 'i's and crossed 't's and added very, very little to what came out of those studies published in the early 1960s from Liverpool.

Silverman: I would reinforce that, but I would also like to say that I think Simon [Godfrey] is being a little bit modest, because he picked up Dick Jones's idea and ran with it. I think that you [Simon Godfrey] were actually responsible for developing the

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[172] Dr John Fry CBE FRCS FRCGP (1922–1994) was in general practice in Beckenham, Kent, from 1947 to 1992, single-handed until 1960. He was a founder member of the Royal College of General Practitioners and a member of its council for over 30 years.

[173] Boesen I. (1953) Asthmatic bronchitis in children. Prognosis for 162 cases, observed 6–11 years. *Acta Paediatrica* **42**: 87–96.

[174] Dr Dick Jones was a paediatric cardiologist and respiratory physiologist at the Institute of Child Health, University of Liverpool, and Alder Hey Children's Hospital, Liverpool, in the 1960s and 1970s. See Jones R S, Buston M H, Wharton M J. (1962) The effect of exercise on ventilatory function in the child with asthma. *British Journal of Diseases of the Chest* **56**: 78–86. Jones R S, Wharton M F, Buston M H. (1963) The place of physical exercise and bronchodilator drugs in the assessment of the asthmatic child. *Archives of Disease in Childhood* **38**: 539–545.

real scientific physiology, the exploration of exercise-induced asthma.[175] The initial work took place in the labs at the Brompton Hospital at what was the Cardiothoracic Institute about 1970 and led to Sandy Anderson's subsequent work and famous dispute or duel, with Regis McFadden in the United States about the mechanism of exercise-induced asthma.[176] So I think you are being somewhat modest. I would like also to say that your comment that I think is also somewhat modest about infant lung physiology, was another important milestone.[177] Another related development at the Brompton in 1970 was your development and encouragement of measurement of infant lung physiology using the body box that was derived from work from Kenneth Cross at the London Hospital,[178] and, if I remember, computer programming work in FORTRAN[179] at the Imperial College, but which you developed and which led to a lot of clinical applications and investigations of pulmonary physiology, and its applications in infants. I would like you to reflect on what you have been saying about others, I think you have had an important impact in a number of areas, and those are just two examples.

Godfrey: I am glad now that I arranged for you to have a free lunch!

Silverman: I will do anything for a free lunch!

Dr Mark Levy:[180] Just two anecdotes and a comment related to general practice. I think it is fair to say that there has been a major change in general practice management of asthma in the last 20 years and while I accept the criticism that we may be over-diagnosing asthma, I remember there were two things that patients said when I first went into practice in the late 1970s, early 1980s. One was that a parent had contacted the local council to complain and to try to find out why there was an epidemic of asthma in Northolt, where I was working. I was looking after three streets of people and there happened to be quite a lot of people in those streets who were suddenly getting asthma. If you remember the prevalence of asthma at that time was about 3 per cent and in my practice it was about 11 or 12 per cent, which is a figure

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[175] See note 90.

[176] Anderson S D. (1984) Is there a unifying hypothesis for exercise-induced asthma? *Journal of Allergy and Clinical Immunology* 73: 660–665. Anderson S D, Daviskas E, Smith C M. (1989) Exercise-induced asthma: a difference in opinion regarding the stimulus. *Allergy Proceedings* **10**: 215–226. Anderson S D, Daviskas E. (1992) The airway microvasculature and exercise-induced asthma. *Thorax* **47**: 748–752.

[177] Godfrey S. (1972) The study of physiological responses to exercise in children. MD thesis, University of London.

[178] Cross K W. (1949) The respiratory rate and ventilation in the newborn baby. *Journal of Physiology* **109**: 459–474. Godfrey S, Mearns M, Howlett G. (1978) Serial lung function studies in cystic fibrosis in the first five years of life. *Archives of Disease in Childhood* **53**: 83–85.

[179] FORTRAN is an acronym for FORmula TRANslation, the first high-level computer programming language developed by IBM in the 1950s.

[180] Dr Mark Levy FRCGP (b. 1948) has been in general practice since 1977, three-quarter time since March 2001. He has published original research papers and three books on asthma and in 2000 was appointed Senior Lecturer (part-time), Department of General Practice and Primary Care, Aberdeen University. He has edited the *Primary Care Respiratory Journal* since 1996 and has been Secretary of the General Practice and Primary Care Group of the European Respiratory Society since 2000. See www.kbmc.org.uk (visited 10 July 2001).

that Nigel Speight had come out with.[181] But the other comment that a patient made then was, one of my receptionists overheard a patient saying in the waiting room, 'Whatever you do, don't tell him that you have got a cough'. Nowadays patients come in clutching their printouts from the Internet saying, 'Has my child got asthma?' So things have changed a hell of a lot in the last 20 years.

Godfrey: Thank you very much.

O'Callaghan: As well as thanking Simon [Godfrey] for being an excellent chairman, I would like to thank you all for coming and contributing. I have thoroughly enjoyed myself, limericks and all, and I hope you have.

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[181] Speight A N, Lee D A, Hey E N. (1983) Underdiagnosis and undertreatment of asthma in childhood. *British Medical Journal* **286**: 1253–1256.

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