

# LEUKAEMIA

The transcript of a Witness Seminar held at the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 May 2001

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

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#### Key

##### Front cover photographs, top to bottom:

Professor John Goldman (chair)  
Dr Gordon Piller (d. 2005), Sir Christopher Booth  
Professor David Galton (1922–2006), Professor Daniel Catovsky  
Professor Victor Hoffbrand, Professor Sir John Lileyman

##### Inside front cover photographs, top to bottom:

Dr Gordon Piller (d. 2005)  
Dr Colin Geary  
Sir Richard Bayliss (1917–2006)  
Dr Gordon Piller (d. 2005), Professor Ian MacLennan

##### Back cover photographs, top to bottom:

Professor Derek Crowther  
Professor Ray Powles  
Dr John Stock  
Professor Frank Hayhoe (d. 2009)

##### Inside back cover photographs, top to bottom:

Professor Humphrey Kay (1923–2009)  
Professor Sir John Lilleyman  
Dr Eve Wiltshaw  
Dr John Stock

# CONTENTS

## **Introduction**

Professor Sir David Weatherall i

## **Witness Seminars: Meetings and publications; Acknowledgements**

E M Tansey and D A Christie iii

## **Transcript**

Edited by D A Christie and E M Tansey 1

**Biographical notes** 65

**Glossary** 71

**Index** 75



# INTRODUCTION

Although the ‘Witness Seminar’ approach to the historical development of a field is looked upon with suspicion by some historians, not in the least because of their concern that scientists are unable to speak objectively about what they do, not to mention their flawed memories, nevertheless it provides a view of scientific progress that can never be obtained solely from archival material. The most successful examples of this genre usually reflect the discussion of a time of major advance or controversy in a particular field, and the survival of enough of its participants for long enough to cover the period adequately. These requirements were both met in the present Seminar.

Up to the period just after the Second World War, virtually nothing could be done for patients with leukaemia. The nitrogen mustards had been introduced as a by-product of the horrors of the First World War but, although they had some modest effect in slowing the course of lymphomas, they were not effective at all for the management of leukaemia. However, in the 1940s an increasing understanding of the mechanisms of action of certain agents required for blood production, notably folic acid, led to the development by the pharmaceutical industry of the first anti-folate drugs, notably aminopterin (page 7). This was first used to treat children with acute leukaemia by Sidney Farber in Boston, an event that opened a new era for the management of leukaemia. The elegant work of Hitchings and Elion on purine and pyrimidine metabolism led to another important therapeutic agent, 6-mercaptopurine, the first drug to have any effect on adult leukaemia (page 48). Further developments followed rapidly, notably the discovery that corticosteroids had some effect, if short lived, in controlling some types of leukaemia, and then the appearance of several completely different classes of drugs, notably derivatives of antibiotics produced by fungi, particularly daunorubicin, and the vinblastine and vincristine alkaloids derived from plants (page 15).

But although haematologists now had a series of drugs that were active against leukaemia, this was only the beginning of the story. Given alone, most of them only allowed short-term control of the disease, which nearly always regressed. There followed an active period of clinical trials using single or multiple agents in different combinations (page 53). With each successive trial, the prognosis for leukaemia, particularly the childhood leukaemias, improved, and once methods became available for destroying leukaemic cells that were hidden away in the nervous system, the dream of a genuine cure for childhood leukaemia became a reality (pages 26 and 43). Although progress was slower in acute leukaemias in adults, and in the chronic leukaemias, genuine progress was made. The way the field developed during this period was an example of collaborative clinical research at its very best. In the mid-1970s bone marrow transplantation was first introduced (page 17) and,

again, learning how to use combinations of anti-leukaemia drugs, radiotherapy, and bone marrow transplantation, further dramatic advances were made.

Most of the participants in this Witness Seminar lived through this extraordinary period of development in the leukaemia field. Its successes depended not just on the development and assessment of new drugs and their combinations, but on major improvements in diagnostic haematology and the ability to tide patients through frightful periods of bone marrow depression and the inevitable infections that followed. Although when the history of this period is examined in detail it may be concluded that the primary lead in the remarkable advances in treatment for leukaemia came from the USA, there is no doubt that the contributions which are discussed by these participants were of seminal value in many areas. Indeed, leukaemia research in the second half of the twentieth century should be viewed as a field in which international participation and collaboration worked particularly well for the benefit of patients.

*Professor Sir David Weatherall FRS  
Institute of Molecular Medicine, Oxford*

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

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

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

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

Copies of all additional correspondence received during the editorial process are deposited with the records of each meeting in Archives and Manuscripts, Wellcome Library, London.

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

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

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The Group's activities are overseen by the Programme Committee, which includes professional historians of medicine, practising scientists and clinicians. The Programme Committee during 2002–03 comprised:

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

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

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

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

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

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

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

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



# HISTORY OF TWENTIETH CENTURY MEDICINE WITNESS SEMINARS, 1993–2003

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

- 1998 **Haemophilia: recent history of clinical management**<sup>6</sup>  
Organizers: Professor Christine Lee and Dr E M Tansey
- Obstetric ultrasound: historical perspectives**<sup>7</sup>  
Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey
- Post penicillin antibiotics**<sup>8</sup>  
Organizers: Dr Robert Bud and Dr E M Tansey
- Clinical research in Britain, 1950–1980**<sup>9</sup>  
Organizers: Dr David Gordon and Dr E M Tansey
- 1999 **Intestinal absorption**<sup>10</sup>  
Organizers: Sir Christopher Booth and Dr E M Tansey
- The MRC Epidemiology Unit (South Wales)**<sup>11</sup>  
Organizers: Dr Andy Ness and Dr E M Tansey
- Neonatal intensive care**<sup>12</sup>  
Organizers: Professor Osmund Reynolds and Dr E M Tansey
- British contributions to medicine in Africa after the Second World War**<sup>13</sup>  
Organizers: Dr Mary Dobson, Dr Maureen Malowany,  
Dr Gordon Cook and Dr E M Tansey
- 2000 **Childhood asthma, and beyond**<sup>14</sup>  
Organizers: Dr Chris O’Callaghan and Dr Daphne Christie
- Peptic ulcer: rise and fall**<sup>15</sup>  
Organizers: Sir Christopher Booth, Professor Roy Pounder and Dr E M Tansey
- Maternal care**<sup>16</sup>  
Organizers: Dr Irvine Loudon and Dr Daphne Christie
- 2001 **Leukaemia**<sup>17</sup>  
Organizers: Professor Sir David Weatherall, Professor John Goldman,  
Sir Christopher Booth and Dr Daphne Christie
- The MRC Applied Psychology Unit**<sup>18</sup>  
Organizers: Dr Geoff Bunn and Dr Daphne Christie
- Genetic testing**<sup>19</sup>  
Organizers: Professor Doris Zallen and Dr Daphne Christie
- Foot And Mouth Disease: The 1967 outbreak and its aftermath**<sup>20</sup>  
Dr Abigail Woods, Dr Daphne Christie and Dr David Aickin

- 2002     **Environmental toxicology: The legacy of *Silent Spring***<sup>21</sup>  
 Organizers: Dr Robert Flanagan and Dr Daphne Christie
- Cystic fibrosis**<sup>22</sup>  
 Organizers: Dr James Littlewood and Dr Daphne Christie
- Innovation in pain management**  
 Organizers: Professor David Clark and Dr Daphne Christie
- 2003     **Thrombolysis**  
 Organizers: Mr Robert Arnott and Dr Daphne Christie
- Beyond the asylum: Anti-psychiatry and care in the community**  
 Organizers: Dr Mark Jackson and Dr Daphne Christie
- The Rhesus factor story**  
 Organizers: Professor Doris Zallen and Dr Daphne Christie

<sup>1</sup> 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.

<sup>2</sup> Hart, P D'Arcy, edited and annotated by Tansey E M. (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.

<sup>3</sup> 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.

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

<sup>5</sup> 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.

<sup>6</sup> 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.

<sup>7</sup> 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.

<sup>8</sup> 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.

<sup>9</sup> 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.

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

<sup>11</sup> Ness A R, Reynolds L A, Tansey E M. (eds) (2002) Population-based research in south Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 13. London: The Wellcome Trust Centre for the History of Medicine at UCL, 150pp.

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- <sup>12</sup> 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.
- <sup>13</sup> 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.
- <sup>14</sup> 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.
- <sup>15</sup> Christie D A, Tansey E M. (eds) (2002) Peptic ulcer: Rise and fall. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 14. London: The Wellcome Trust Centre for the History of Medicine at UCL, 143pp.
- <sup>16</sup> 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.
- <sup>17</sup> Christie D A, Tansey E M. (eds) (2003) Leukaemia. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 15. London: The Wellcome Trust Centre for the History of Medicine at UCL, 86pp.
- <sup>18</sup> Reynolds L A, Tansey E M. (eds) (2003) The MRC Applied Psychology Unit. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 16. London: The Wellcome Trust Centre for the History of Medicine at UCL, 94pp.
- <sup>19</sup> Christie D A, Tansey E M. (eds) (2003) Genetic testing. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 17. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press.
- <sup>20</sup> Reynolds L A, Tansey E M. (eds) (2003) Foot and Mouth Disease: The 1967 outbreak and its aftermath. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 18. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press.
- <sup>21</sup> Reynolds L A, Tansey E M. (eds) (2004) Environmental toxicology: The legacy of *Silent Spring*. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 19. London: The Wellcome Trust Centre for the History of Medicine, in press.
- <sup>22</sup> Christie D A, Tansey E M. (eds) (2004) Cystic fibrosis. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 20. London: The Wellcome Trust Centre for the History of Medicine, in press.

# ACKNOWLEDGEMENTS

'Leukaemia' was suggested as a suitable topic for a Witness Seminar by Sir Christopher Booth. Professor Sir David Weatherall, Professor John Goldman and Sir Christopher Booth assisted with the organization of the meeting; they provided many of the names of individuals to be invited and decided on the topics to be discussed, and we are very grateful for their input. We also thank Professor John Goldman for his excellent chairing of the occasion and for his help with the glossary. Professor John Walker-Smith and Dr Helen Dodsworth kindly read the edited transcript for general sense and understandability. We are particularly grateful to Professor Sir David Weatherall for writing such a useful introduction to these published proceedings. We thank Professors Derek Crowther, Ray Powles and Victor Hoffbrand for assistance with the glossary, Professor David Galton for additional help with the text, and Mr Richard Barnett for bibliographic research.

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

*Tilli Tansey*

*Daphne Christie*

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



## **LEUKAEMIA**

The transcript of a Witness Seminar held at the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 May 2001

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

# LEUKAEMIA

## Participants

Sir Christopher Booth

Professor Daniel Catovsky

Professor Derek Crowther

Professor David Galton

Professor John Goldman (Chair)

Dr David Grant

Professor Frank Hayhoe

Professor Victor Hoffbrand

Dr Peter Hunter

Professor Humphrey Kay

Professor Sir John Lilleyman

Professor Ian MacLennan

Dr Gordon Piller

Professor Ray Powles

Dr Rosemary Shannon

Dr John Stock

Dr Tilli Tansey

Professor John Walker-Smith

Dr Eve Wiltshaw

**Others attending the meeting:** Dr Derek Bangham, Professor Hal Cook, Dr Pete Coventry, Dr Simon Galton, Dr Colin Geary, Mr Harald Leyrer, Professor Chris O'Callaghan

**Apologies:** Dr Robert Bud, Dr Sheila Callender, Professor Judith Chessells, Dr G Crotty, Dr Bronwyn Croxson, Sir John Dacie, Dr Michael Dexter, Professor Sir Richard Doll, Dr Emil J Freireich, Professor Edward Gordon-Smith, Professor Melvyn Greaves, Dr Steve Hanney, Professor Kenneth Harrap, Professor Andrew Lister, Dr Guy Lucas, Professor Sir Michael Peckham, Professor Sir Richard Peto, Dr Howard Scarffe, Dr Donald Scott, Dr Richard Staughton, Professor Sir David Weatherall, Professor Miles Weatherall, Professor John West



**Dr Tilli Tansey:** The History of Twentieth Century Medicine Group was established by the Wellcome Trust in 1990 to bring together scientists, clinicians, and historians who have a common interest in the history of recent medicine. A particularly successful venture has been that of these Witness Seminars, where we gather together people who have been involved in particular events or discoveries, to discuss and debate amongst themselves in a chairman-led discussion about the events that they have witnessed.

This meeting on leukaemia has been organized on behalf of the Group by my two colleagues, Dr Daphne Christie and Sir Christopher Booth. We have had the detailed professional advice of Sir David Weatherall and Professor John Goldman, and we are very grateful to both of them. Unfortunately, Sir David Weatherall cannot be here today – his plane to Vienna has been rescheduled and he couldn't make it in time to be here for the first two hours of the meeting. But we are delighted to have John Goldman here; he qualified in medicine at Oxford and then in 1970, after a period in America, was enticed back to this country by David Galton, whom we are also delighted to see at this meeting, to join the newly founded Medical Research Council's Leukaemia Unit at the Hammersmith Hospital. John Goldman is now Chairman of the Department of Haematology at the Imperial College School of Medicine, based at Hammersmith Hospital, and he is also Director of the Leukaemia Research Fund's Centre for Adult Leukaemia. He has undertaken extensive research and has clinical experience in all aspects of leukaemia. We were delighted not only to have his advice during the planning of this meeting, but we are particularly grateful to him for spending the afternoon chairing this meeting. And so without further ado, I would like to hand over to the Chairman.

**Professor John Goldman:** Thank you very much, Tilli. Yes, you are right, it was indeed 1970. I was looking through some old papers recently and I came across this delightfully written and personally typed letter from David Galton, asking me if I would agree – I had already approached David Galton previously, but now he was making me a firm offer – to come to the MRC Leukaemia Unit as it was then.<sup>1</sup> He mentioned in this one paragraph that the technology that was developing – still embryonic at that time – was the use of

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<sup>1</sup> Professor John Goldman wrote: 'The Medical Research Council sought in 1966/67 to establish a specialist centre to investigate and treat acute leukaemia in adults. They approached Professor John Dacie at the Hammersmith and suggested that David Galton should be the first director. A clinical facility was then built at the Hammersmith Hospital and laboratory space was made available at the Commonwealth Building of the Royal Postgraduate Medical School. The first junior staff included Alexander Spiers, Daniel Catovsky and John Goldman.' E-mail to Dr Daphne Christie, 1 December 2002. Professor David Galton wrote: 'In those years Sir John Dacie and I had frequent meetings with Dr John Hay of the MRC (Head Office) and one, or several officers from the then Ministry of Health. Together we planned every structural detail of the new Unit, and all its fittings.' Note on draft transcript, 19 February 2003. See MRC Annual Report April 1968–March 1969, and April 1969–March 1970, pages 32 and 44 respectively.

sloppy agar to look at myelopoiesis *in vitro*.<sup>2</sup> That, of course, has become one of the major tools of the experimental haematologist since then. We made a very minor contribution in the field of experimental haematology in the 1970s.

There are a few people whom we would like to have had in this room today, who for various reasons couldn't make it, but I think the majority of people we asked and would like to have are here. Collectively there is here tremendous experience in the investigation, characterization and biology of leukaemia, and many aspects of treatment. Quite clearly, we couldn't undertake a comprehensive review of the story of leukaemia in say the last 50 years, which I think more or less would have covered everybody we invited, in one four-hour session. We had to choose things partly in accordance with the available personalities and the expertise of people who could come. I would now like to ask David Galton to say a few words about the history of leukaemia in the twentieth century.

**Professor David Galton:** It's difficult to know where to begin in a subject like this. Gordon Piller, in a few minutes' time, will say a little about the first happenings up to the early part of the last century. What I would like to do is remind you of the way certain drugs came to be developed, which were the forerunners of the whole set of drugs that we use today. I particularly want to talk about the circumstances in which three so-called biological alkylating agents were synthesized in the early 1950s at the Chester Beatty Research Institute (CBRI), which was the research arm of the then Royal Cancer Hospital,<sup>3</sup> under its Director, Alexander (later Sir Alexander) Haddow. Haddow had worked for a number of years at the old research laboratories of the Royal Cancer Hospital, under Sir Ernest Kennaway. Kennaway and his colleagues had made a fantastic contribution, by purifying the single chemicals extracted from coal tar, and finding many of these were hydrocarbons, some of which were powerfully carcinogenic and some of which were not.<sup>4</sup> Haddow became extremely interested in this very remarkable circumstance that the chemical differences between some of the hydrocarbons that were carcinogenic and those that were not, were minuscule. He saw this as a possible way of attacking, at a very basic level, the problem of how normally growing cells changed their habit and became malignant. I think that was his frame of reference throughout his years as Director of the CBRI.

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<sup>2</sup> Pike B L, Robinson W A. (1970) Human bone marrow colony growth in agar-gel. *Journal of Cell Physiology* 76: 77–84.

<sup>3</sup> The Chester Beatty Research Institute – Institute of Cancer Research, Royal Cancer Hospital. See Royal Cancer Hospital, London. (1951) *The Royal Cancer Hospital, Fulham Road, London 1851–1951: A short history of the Royal Cancer Hospital prepared for the centenary, 1951*. London: J B Shears & Sons. See also note 70.

<sup>4</sup> See Bernard J. (1934) L'érythro-leucémie expérimentale provoquée par le goudron. *Le Sang* 8: 28–38. See also Haddow A. (1974) Sir Ernest Laurence Kennaway FRS, 1881–1958: Chemical causation of cancer then and today. *Perspectives in Biology and Medicine* 17: 543–588. Waller R E. (1994) 60 years of chemical carcinogens: Sir Ernest Kennaway in retirement. *Journal of the Royal Society of Medicine* 87: 96–97.

In the 1930s he made a very important observation, which became known as the ‘Haddow’ phenomenon, and this was that some chemically induced experimental tumours could be made to regress by treating them with purified carcinogenic compounds, whereas the non-carcinogenic compounds, which were very similar, and were apparently equally toxic, did not cause regression.<sup>5</sup> He saw something very fundamental here, namely that the underlying process of carcinogenesis and this curious growth-inhibitory phenomenon were related. He also thought they were related in a Darwinian sense, namely that these compounds that proved to be carcinogenic were in fact themselves growth inhibitory, that they did something that made a cell that just did not die, survive by adopting a new habit of growth, which was malignant growth. It was not ordinary non-specific toxicity, because the non-carcinogenic compounds that were generally toxic too did not cause inhibition of growth and they did not cause cancer. That led him to a whole lot of further studies, which were the basis of the Institute’s work for the next 25 years. The fact that you could get growth inhibition of a malignant growth (an experimentally induced malignant growth), by introducing a chemical with apparently specific properties suggested to him that there was therapeutic potential here. That’s how he came to initiate a programme that went on for many years and that involved many colleagues who were biochemists, organic chemists, radiobiologists, and cytogeneticists in trying to work out a scheme for producing compounds that might be growth inhibitory in human cancer. That was the way the programme began.

I hope that John Stock, who is here, will be able to say more about this during the meeting, because it was he who synthesized the drug melphalan, one of the three drugs that are still in use today after 50 years, namely chlorambucil, melphalan and busulphan. That is actually the basis on which these compounds were studied in the first instance.

**Goldman:** I think we should stick with that note for a moment. This meeting must cover drug development to some extent, so I wonder whether John Stock would like to go on at this stage.

**Dr John Stock:** When I got the offer to participate today, and it was very kind of the Centre for the History of Medicine to invite me, I thought I would write down a few headings about the development of antitumour drugs. Then I decided I didn’t know whether this would do, because with the four or five minutes allowed it might turn out to be just a litany of drugs, so I gave up that idea and maybe, as David Galton said, we can discuss some of these things later on.

While we are talking about the old Chester Beatty, I would say how fortunate I was in 1952 to be taken on by Franz Bergel, to whom I had written. I didn’t know which way it would

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<sup>5</sup> See, for example, Haddow A, Robinson A M. (1937) Influence of various polycyclic hydrocarbons on growth rate of transplantable tumours. *Proceedings of the Royal Society of London* 122: 442–476. Professor David Galton wrote: ‘This was the “credo” of the CBRI, and we all took it for granted.’ Note on draft transcript, 29 November 2002.

go, because he had been my external examiner in my PhD, and although I got through I didn't know whether he thought much of it.<sup>6</sup> Anyway, he took me on and it was he who suggested the development. He was interested in the possibility of sticking a nitrogen mustard group onto an amino acid, and this was the origin of melphalan. We chose phenylalanine because chemically that was more suitable. Also, Walter Ross's work on nitrogen mustards was confined to the aromatic nitrogen mustards, which were rather milder in action than the aliphatic ones and HN2.<sup>7</sup>

At that time, under Alex Haddow, the Chester Beatty was a bit of a family firm really, and there were no questions of grant applications and things like that then, so we had a fairly free hand.

I went to a valedictory symposium last week in honour of Michael Jarman, who had been Head of the Chemistry section of what is now known as the Cancer Therapeutic Department, I forget its actual name now.<sup>8</sup> What interested me was that in this meeting the people who have now risen up to be directing things, the professors these days, like the policemen, get younger every year, and the place has obviously got a lot of brain power there now – and it's well funded. The chemistry we did is now rather old-hat. The new thing that has taken over [which is new to me anyway but is certainly used in industry as well as in academic situations] is called combinatorial chemistry, which means that you can produce hundreds of compounds – dozens, hundreds – at the same time, by reaction on solid support and by doing everything in one vessel. You also fish all these things out and then you screen them.

That's important, but what sort of screen? I think the initial screens will probably be enzymes, which means that one has to find enzymes that are relevant to tumour treatment. That's the big thing; it's always been the big thing I suppose, to find something that will replace the animal tumour and whether it will be found or not – the whole thing hinges on that. So what is hoped is that many lead compounds, perhaps hundreds of lead compounds will be produced and ways will be found of testing these on a very small scale; eventually the good ones can be made on a bigger scale. That seems to be the direction in which it is going. I would make that point, rather than talk about the old stuff, which would be rather a lengthy business, I think.

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<sup>6</sup> Stock J. (1952) *Experiments in the chemotherapy of tuberculosis*. PhD thesis, University of London.

<sup>7</sup> Nitrogen mustard (then known by the code name HN2). See Ross W C J. (1962) *Biological Alkylating Agents*. London: Butterworth.

<sup>8</sup> The CRC Centre for Cancer Therapeutics. Dr John Stock wrote: 'Professor Michael Jarman was Head of the Chemistry department of the Institute of Cancer Research prior to his retirement in 1950.' Note on draft transcript, 3 November 2002.

**Goldman:** Just one question for my own edification. What was the involvement of Chester Beatty himself with the Fulham Road? Why did he put his money into the Fulham Road when he did?

**Stock:** I can't remember.

**Goldman:** Because there must have been a lot of money involved by the then contemporary standards.

**Stock:** I am sorry, I have forgotten the reason. I know he came round once – Chester Beatty came round to the laboratory where I was – and he discussed painting walls.

**Professor Raymond Powles:** Just a couple of anecdotes about Alex Haddow, who was an extraordinary person. You had to meet him; he was bigger than life in every sense. He was head of the Chester Beatty when I was houseman to David Galton at the Fulham Road Marsden in 1966. Alex was admitted with a very large diabetic ulcer on his leg that he had kept secret because he thought it was cancer, which says much about the perceptions of cancer in those days. He unfortunately went blind over the following few years, but wrote two leading articles on the future of cancer research in the early 1970s.<sup>9</sup> It is a tribute not only to his knowledge of cancer but also to his wonderful gift of writing that in spite of being blind he was able to start all of 50 new paragraphs with three different words. The other nice story is that he would only ever go to the United States in a first-class suite on the Queen Elizabeth. He said if it was important enough to go to the US, then it should be on the Queen Elizabeth.

**Professor Victor Hoffbrand:** The line of research at the Chester Beatty was making alkylating agents,<sup>10</sup> but meanwhile there were the antimetabolites and I just wondered if David could remind us of whether this was at the same time or earlier. I know that Sidney Farber's was the first treatment of leukaemia with aminopterin.<sup>11</sup> There were a whole

<sup>9</sup> Haddow A. (1971) Cancer research: the great debate. *New England Journal of Medicine* **285**: 24–28. *idem* (1971) Oncology: its scope and prospects. *Proceedings of the Royal Society of Medicine* **64**: 323–328.

<sup>10</sup> See, for example, Haddow A. (1973) On the biological alkylating agents. *Perspectives in Biology and Medicine* **16**: 503–524. Brookes P. (1990) The early history of the biological alkylating agents, 1918–1968. *Mutation Research* **233**: 3–14.

<sup>11</sup> The development of the folic acid conjugates led to the synthesis of aminopterin. See Farber S, Diamond L K, Mercer R D, Sylvester R F, Wolff V A. (1948) Temporary remissions in acute leukemia in children produced by folic acid antagonist 4-amethopteroylglutamic acid (aminopterin). *New England Journal of Medicine* **238**: 787–793. See also Farber S, Appleton R, Downing F H, King J, Toch R. (1954) The treatment of acute leukemia in children by folic acid antagonists, ACTH, and cortisone. A summary of five years of experience. *Proceedings of the Fourth International Congress of the International Society of Hematology*. New York: Grune and Stratton, 150.

different group of compounds that were discovered after folic acid. How did these drugs relate to each other?

**Galton:** This was a fascinating development because Sidney Farber was one of three people who had noticed a property of folic acid that had been synthesized, I think, in 1945.<sup>12</sup> Is that right? As soon as this was synthesized several people started treating patients with leukaemia with it, and three of them, independently, noticed that it had an adverse effect. One of them, who was a Dane, Jorgen Bichel, found that the leucocyte count went up after the use of folic acid. Another one was somebody you know, Victor – Frank Bethell – who made the same observation, and so did Sidney Farber.<sup>13</sup> Sidney Farber had a colleague, Dr Yella Subba Row,<sup>14</sup> a biochemist, who made conjugates of folic acid and analogues. It was soon found that some of these analogues had powerful antileukaemic properties and roughly that's how Sidney Farber got involved, I think, but Frank might correct me. In a very short time he had treated 16 infants and children with acute leukaemia, and ten of them went into very good remission.<sup>15</sup> They didn't survive long, but this was the first time anything like it had happened.

**Goldman:** This is a topic that Gordon Piller has very nicely reviewed in his publication.<sup>16</sup> Are you going to talk about methotrexate, Gordon?

**Dr Gordon Piller:** It was aminopterin, not methotrexate at first. Methotrexate was introduced a couple of years later.<sup>17</sup>

**Professor Frank Hayhoe:** While we are talking about these antimetabolites, I might just tell you a little story. In March 1956 I happened to have gone across to the US in the Queen Elizabeth. Unlike Haddow I wasn't in first-class – I was travelling steerage or something rather like that. It cost me £120 return to New York. However, I was going to a meeting that was held in Detroit at the Henry Ford Hospital. I had been invited by Joe Burchenal

<sup>12</sup> Professor David Galton wrote: 'Folic acid was synthesized in 1945 [Angiter et al. (1945) Synthesis of a compound identical with the *L. casei* factor isolated from liver. *Science* 102: 227–228].' Note on draft transcript, 29 November 2002. See also Farber S. (1949) Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer. *Blood* 4: 160–167.

<sup>13</sup> Bethell F, Bichel J, Farber S. Personal communication. op. cit. notes 12 and 67.

<sup>14</sup> Dr Y Subba Row led the group in the Research Division of the Lederle laboratories of the American Cyanamid Company, who synthesized the first folic acid antagonists and offered them for clinical trial. See Subba Row Y et al. (1946) Folic acid. *Annals of the New York Academy of Science* 48: 255–349.

<sup>15</sup> op. cit. note 11.

<sup>16</sup> See Piller G J. (2001) Historical review. Leukaemia – A brief historical review from ancient times to 1950. *British Journal of Haematology* 112: 282–292, in particular pages 289–290.

<sup>17</sup> op. cit. note 11 and page 43.

to stay in his house in Connecticut before the meeting. Anyway, we got up very early in the morning, at about half past five, to commute into New York to the Sloan Kettering Institute. This was a time when the antimetabolites were thought to be winning the battle against leukaemia. It was Burchenal's unit that had carried out clinical trials with 6-mercaptopurine (6-MP) and had published the first results in 1953.<sup>18</sup> I had also written a paper, which appeared in the *Lancet* in 1955, on the treatment of, I think, 15 patients with acute myelogenous leukaemia (AML) with 6-MP.<sup>19</sup>

To revert to the Detroit affair, when we got to this conference there were copies of a newspaper available on the table, possibly the *New York Times*, or some other widely read paper. Across a huge double-page spread was a set of chemical formulae that depicted the *de novo* synthesis of nucleic acids with about 50 different compounds en route, as it were. This was presented to the readership under a heading that said 'the one-two for leukaemia' (this is a pugilistic term indicating 'knockout', I understand). The 'one-two' for leukaemia was 6-MP and azaserine. Actually, azaserine subsequently disappeared, although azathioprine got extensively used to prevent antibody formation at a later stage.<sup>20</sup> However, I am just going to get to the story. Somebody presenting a paper at this meeting put a slide of this double-page spread from the newspaper up on the board and said:

I wonder what proportion of the population of New York who read this paper would actually be able to follow this? It reminds me of a story, of Mr Sargeant Sullivan in the law courts, presenting a case on behalf of a labourer from Killarney, Southern Ireland, who had sustained an injury of some kind, that didn't occur during his work. The judge became more and more testy and eventually said, 'But Sargeant Sullivan, surely your client must be aware that "de injuriis non in operibus, lex non curat".' Mr Sargeant Sullivan hesitated for a moment and then said, 'My lord, I understand that in Killarney they talk of little else'.

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<sup>18</sup> Burchenal J H, Murphy M L, Ellison R R, Sykes M P, Tan T C, Leone L A, Karnofsky D A, Craver L F, Dargeon H W, Rhoads C P. (1953) Clinical evaluation of a new anti-metabolite, 6-mercaptopurine, in the treatment of leukemia and allied diseases. *Blood* 8: 965–999. Burchenal J H. (1965) *Approaches to the Aetiology and Treatment of Acute Leukaemia*. London: The Queen Anne Press for the Leukaemia Research Fund. op. cit. note 143.

<sup>19</sup> Hayhoe F H J. (1955) 6-mercaptopurine in acute leukaemia. *Lancet* ii: 903–905.

<sup>20</sup> See, for example, Eridani S, Taglioretti D, Tiso R. (1965) Clinical trial of azathioprine, a new antileukaemic compound. *Panminerva Medicine* 7: 275–281. Cheng C C, Zee-Cheng K Y. (1972) Some antineoplastic antibiotics. *Journal of Pharmaceutical Sciences* 61: 485–501. Burchenal J H. (1979) Antitumor effects of azaserine and DON. *Cancer Treatment and Research* 63: 1031–1032. See also Elion G B. (1993) The George Hitchings and Gertrude Elion Lecture. The pharmacology of azathioprine. *Annals of the New York Academy of Sciences* 685: 400–407.

However, to revert very briefly to the drug development that we are discussing, before this meeting some of us were talking about John Wilkinson, who died aged 101, only a few years ago. He had worked with the original nitrogen mustard (HN2) during the wartime years and published work in 1947 on the use of this drug, not particularly in leukaemias, although I think he did use it on some chronic myeloid leukaemias (CMLs), but particularly in Hodgkin's disease.<sup>21</sup>

Similarly there were early reports from the US along the same lines, leading to the work done subsequently at the Chester Beatty on putting various attachments onto the nitrogen mustard structure. We first started using these in Cambridge in about 1956 or 1957, when we set up a clinic that we called a reticulosis clinic. One of the first drugs we used was CB1348, which subsequently became named chlorambucil.<sup>22</sup>

**Goldman:** I think, Gordon, that some of the topics we have already touched upon you have researched in detail. Would you like to continue?

**Piller:** At the beginning of the twentieth century leukaemia was generally considered to be a chronic disease, with arsenic being the only agent offering some relief.<sup>23</sup> Dr George Dock<sup>24</sup> of Ann Arbor (Michigan, USA) regularly prescribed arsenic to his patients with leukaemia and the reason for him doing that, he said, was 'that patients tended to get well, even temporarily, when it was given whereas when other remedies were prescribed they did not'. Osler, in 1914, commented that he had not seen any striking permanent improvement in patients treated with X-rays.<sup>25</sup> And, Wintrobe in 1945 stated, 'There is no specific treatment for leukaemia';<sup>26</sup> the therapeutic depression continued. Lionel Whitby's critical analysis delivered in 1951 in his presidential address to the Association of Clinical Pathologists, which was echoed in the US, was that leukaemia then was regarded as a

<sup>21</sup> Wilkinson J F, Israels M C G. (1947) Irregular response to liver extract in pernicious anaemia. *Lancet* ii: 468–469. See also Goodman L S, Wintrobe M M, Dameshek W, Goodman M J, Gilman A, McLennan M T. (1946) Nitrogen mustard therapy. *Journal of the American Medical Association* 132: 126–132. op. cit. note 33.

<sup>22</sup> Galton D A G, Israels L G, Nabarro J D N, Till M. (1955) Clinical trials of p-(di-2-chloroethylamine) phenyl butyric acid (CB1348) in malignant lymphoma. *British Medical Journal* ii: 1172–1186.

<sup>23</sup> Lissauer H. (1865) Zwei fälle von leukaemie. *Berliner Klinische Wochenschrift* 2: 403–404.

<sup>24</sup> See Davenport H W. (1982) *Doctor Dock: Teaching and learning medicine at the turn of the century*. New Brunswick: Rutgers University Press, 118.

<sup>25</sup> See Osler W. (1916) *The Principles and Practice of Medicine: Designed for the use of practitioners and students of medicine*. 8th edn. New York, London: D Appleton and Company, 746.

<sup>26</sup> Wintrobe M M. (1946) *Clinical Haematology*. 2nd edn. London: Henry Kimpton, 712. See also Gunz F W. (1980) The dread leukemias and the lymphomas: their nature and their prospects, Ch. 15, in Wintrobe M M. (ed.) *Blood, Pure and Eloquent*. New York: McGraw Hill, 511–546.



dreaded disease which few, if any, survived.<sup>27</sup> The urgent need for fresh viewpoints on the nature of leukaemia and its therapy was now acknowledged, but these were to come from a most unexpected source, chemical warfare.

The use of mustard gas by the German forces in the First World War caused the allies in the Second World War to take preventive measures in case mustard gas should be used again. Secret research, both in the USA and here in Britain, on nitrogen mustards, the nitrogen analogues of the gas, found that they produced marked changes in the haemopoietic system. It was soon realized that nitrogen mustard (then known by the code name HN2) produced an action on blood cells and bone marrow unlike any other known chemical substance. This was the advent of chemotherapy.<sup>28</sup>

In the USA Cornelius P Rhoads headed the medical division of the US Chemical Warfare Service, and recruited many investigators who, once discharged from their military duties, became a formidable group of leaders in the early development of chemotherapy. Joe Burchenal was one of them and I was very privileged, as Frank has also mentioned, to enjoy his hospitality. I asked him what was in his mind when he and his colleagues were working on nitrogen mustard. He said, 'Well, there were six of us who were working in the Army at that time on this, and we thought when we came out what we would do was to kick it around a bit.' So what he and his colleagues in New York did was seize any basement laboratory that was going and they started on the transfer of their wartime research into peaceful application. The Sloan Kettering Institute, which was opened in 1948, included an Experimental and Clinical Chemotherapy Division that all those people were a part of.<sup>29</sup> The other centres involved in America were Boston, Chicago and Salt Lake City.

As a young man I was also privileged to have a Sunday morning meeting with Sidney Farber in his laboratory in Boston. I asked him, because I was not employed by him, so it was easy to put the question to him, 'What has to be done to promote advances in the treatment of leukaemia?', knowing of his work with folic acid with Subba Row as David has pointed out.<sup>30</sup> He said it was time that patients, particularly children, with leukaemia, were 'entitled' to remission, and added that that was his mission. This gives some idea of the thoughts that were in the minds of the pioneers.

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<sup>27</sup> Whitby L. (1951) Wither clinical pathology? Trends and opportunities. *Journal of Clinical Pathology* 4: 129–136.

<sup>28</sup> See, for example, Haut A, Altman S J, Cartwright G E, Wintrobe M M. (1955) The influence of chemotherapy on survival in acute leukemia. *Blood* 10: 875–894. See also Wolff J A. (1999) Chronicle: First light on the horizon dawn of chemotherapy. *Medical and Pediatric Oncology* 33: 405–407. Mercer R D. (1999) The dawn of chemotherapy: the team. *ibid.* 33: 408–409.

<sup>29</sup> Staff included C C Stock, D Karnofsky, F Philips, J H Burchenal and their associates.

<sup>30</sup> *op. cit.* note 14.

John Wilkinson was working in Britain at this time,<sup>31</sup> and Frank Fletcher at Manchester. I met John Wilkinson after his 98th birthday at his home and I asked him various questions, mostly on leukaemia and other blood diseases. He was a bit of a character; he recognized little south of Watford Junction, but fortunately by this time I had left London. Anyhow he was very disappointed that because he was subject to the wartime Secrets Act,<sup>32</sup> he couldn't publish their findings until 1947, when, of course, there were papers published earlier on work he was involved in in Britain. He later reported on work he conducted from 1942 onwards on 18 cases, most of which were lymphomas, Hodgkin's disease and one or two leukaemias.<sup>33</sup>

Also involved in early chemotherapy were Davidson in Edinburgh and a few people elsewhere. It was Alexander Haddow who formed a major group at the CBRI in London.<sup>34</sup> The earlier pioneers were not discouraged by the initial results of this new challenge in what was essentially experimental medicine. Following this there was intensive cooperative work by investigators in Britain and the USA to find preparations that were less toxic but with a targeted effect on abnormal cells. This was achieved by chemical manipulation to improve the therapeutic efficacy of the battle against leukaemia. David Galton, who has already spoken, was one of those pioneers, leading clinical work as a member of Alexander Haddow's team; he contributed much in those early days to the success patiently achieved.

The other point I would finish on is that, although it is sometimes recognized that the Americans led the way in this, there was much effort going on in Britain too. Happily, there was a lot of cooperation.

**Goldman:** Any comments on what Frank and Gordon have said? If not, I think we will go on and ask Derek Crowther to return to the beginning, as it were.

**Professor Derek Crowther:** I was asked to give a brief summary of the history of leukaemia, which, of course, before this illustrious group I don't wish to do particularly.

<sup>31</sup> Dr John Wilkinson was then Director of the Department of Haematology, Manchester Royal Infirmary. See page 69.

<sup>32</sup> Professor David Galton wrote: 'Same restriction in the US. Rhoads could not publish work that had been started in 1941 (Gilman and Philips gave the first injection of nitrogen mustard HN2 in 1942) until 1946.' Note on draft transcript, 3 March 2002. Gilman A, Philips F S. (1946) The biological actions and therapeutic applications of the  $\beta$  chloroethylamines and sulfides. *Science* **103**: 409–415. Rhoads C P. (1946) Nitrogen mustards in the treatment of neoplastic disease. *Journal of the American Medical Association* **131**: 656–658. See also op. cit. note 16, in particular page 289.

<sup>33</sup> Wilkinson J F, Fletcher F. (1947) The effect of  $\beta$ -chloroethylamine hydrochlorides in leukaemia, Hodgkin's disease and polycythaemia vera – a report on 18 cases. *Lancet* **ii**: 540–545.

<sup>34</sup> Professor David Galton wrote: 'Sir Alexander Haddow's group at the Chester Beatty Research Institute, London, included Franz Bergel, Eric Boyland, David Galton, Peo Koller, S K Kon, Walter Ross, John Stock and Geoffrey Timmis.' Note on draft transcript, 29 November 2002. See also note 3 and page 66.

But I thought that what I would do is just make some comment, taking on board the comments that have already been made about the introduction of chemotherapy. Of course, arsenic has been mentioned. Arsenic has been used for the treatment of malignancy for 4000 years now. It was mentioned in the *Ramayana*, which is an Indian text and even Hippocrates mentioned it. It has also been mentioned off and on, throughout the ages, as being effective in the treatment of cancer. Lissauer was the first to use it in 1865 for chronic leukaemia, but it has been used since, and is currently subject to renewed interest.<sup>35</sup>

Regarding the Haddow approach during the mid part of the twentieth century, in my opinion he was the father of modern chemotherapy. He went to the Research Laboratory of the Royal Cancer Hospital in 1936, and he directed a superb team of people who were able to synthesize a whole range of different chemical substances. In fact, one of his earliest drugs was urethane (ethyl carbamate) and that was the first drug that was used in the treatment of cancer.<sup>36</sup> He went up to Manchester to liaise with Edith Paterson, who was the wife of Ralston Paterson, the Director of Radiotherapy at the Christie Hospital. I think that Edith must have contacted John Wilkinson, who was Head of the Department of Haematology at the Manchester Royal Infirmary at that time, because they both got together in the treatment of CML. Although their initial experiments with urethane weren't great, they did in fact show a reduction in white cell counts in patients with CML. In 1946 they published a paper together, showing the responses in CML.<sup>37</sup>

The real advance came with the introduction of busulphan<sup>38</sup> by that team and it was David Galton, who actually introduced that compound for the treatment of CML, where it has

<sup>35</sup> op. cit. note 23. See Chen Z, Chen G Q, Shen Z X, Sun G L, Tong J H, Wang Z Y, Chen S J. (2002) Expanding the use of arsenic trioxide: leukemias and beyond. *Seminars in Hematology* 39: 22–26. Zhu J, Chen Z, Lalemand-Breitenbach V, de Thé H. (2002) How acute promyelocytic leukaemia revived arsenic. *Nature Reviews Cancer* 2: 705–713. See also Where science and history meet. Arsenic as cancer therapy. [www.scientecmatrix.com](http://www.scientecmatrix.com) (site accessed 27 January 2003).

<sup>36</sup> op. cit. notes 37 and 63.

<sup>37</sup> Dr (later Professor) James Ralston Paterson (1897–1981) was Director of the Holt Radium Institute and then Director of Therapy. Dr Edith Paterson (1900–95) began work at the Christie Hospital in 1938. Paterson E, Haddow A, Thomas I ap, Watkinson J M. (1946) Leukaemia treated with urethane compared with deep X-ray therapy. *Lancet* i: 677–682. See also Magnello E. (2001) Ralston Paterson and the Manchester School of Radiotherapy, in *A Centenary History of the Christie Hospital, Manchester*, Ch. 4. Manchester: The Christie Hospital NHS Trust in association with the Wellcome Unit for the History of Medicine University of Manchester, 59–63.

<sup>38</sup> See Haddow A, Timmis G M. (1953) Myleran in chronic myeloid leukaemia: chemical constitution and biological action. *Lancet* i: 207–208. Galton D A G. (1953) Myleran in chronic myeloid leukaemia. Results of treatment. *ibid.* 208–213.

stood the test of time. It was the essential main base of treatment for several decades, so we have a great deal to thank David Galton for.

The 1950s showed the development of a large number of single agents in the treatment of leukaemia. We have mentioned that chlorambucil was introduced at the Chester Beatty to treat chronic lymphocytic leukaemia and, in fact, it remains one of the mainstays of treatment, even today. Melphalan was introduced, as John has mentioned, but of course that was for the treatment of myeloma by and large rather than leukaemia, although it has been used for leukaemia.

In the 1950s, the single agents that we used were busulphan, chlorambucil and 6-MP. In addition there were other drugs that were in the offing, such as the vinca alkaloids that are derived from *Vinca rosea*, the Madagascar periwinkle which is also called *Catharanthus roseus*. The vinca alkaloids were developed in the late 1950s,<sup>39</sup> so it was a great time for the synthetic chemists who prepared these derivatives from natural products.

I personally know a little bit more about the history in the early 1960s, because I was a houseman and a Wellcome Clinical Research Fellow for three years in the mid 1960s, and was supervised by Gordon Hamilton Fairley. I eventually became Senior Registrar to Sir Ronald Bodley Scott at Bart's in 1968, so I saw the development from the viewpoint of a houseman and senior registrar at that time. The major development in the treatment of acute lymphoblastic leukaemia (ALL) in my mind came from the USA. It came from St Jude Children's Research Hospital in Memphis,<sup>40</sup> with Don Pinkel introducing what he called 'Total Therapy'.<sup>41</sup> He had Total 1, Total 2, Total 3, and so on – a series of superb clinical studies. Most of them weren't randomized studies; they were just single studies of 50 patients here, 100 patients there. They would be considered to be old-fashioned now, but when he conducted those very elegant experiments during the 1960s, the principles that were applied resulted in the regular cure of more than 50 per cent of children with

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<sup>39</sup> Hodes M E, Rohn R J, Bond W H. (1960) Vincalokoblastine. I. Preliminary clinical studies. *Cancer Research* 20: 1041–1049. See also Noble R L. (1990) The discovery of the vinca alkaloids: chemotherapeutic agents against cancer. *Biochemistry and Cell Biology* 68: 1344–1351.

<sup>40</sup> See Revera G K. (1993) Treatment of acute lymphoblastic leukemia: 30 years' experience at St Jude Children's Research Hospital. *New England Journal of Medicine* 329: 1289–1295.

<sup>41</sup> See, for example, George P, Hernandez K, Hustu O, Borella L, Holton C, Pinkel D. (1968) A study of 'total therapy' of acute lymphocytic leukemia in children. *Journal of Pediatrics* 72: 399–408. Pinkel D. (1972) Total therapy of acute lymphocytic leukemia. *Journal of the American Medical Association* 222: 1170. Pinkel D, Simone J, Hustu H O, Aut R J A. (1972) Nine years' experience with 'Total Therapy' of childhood acute lymphocytic leukemia. *Pediatrics* 50: 246–251. Professor David Galton wrote: 'Donald Pinkel was a disciple of Sidney Farber, and it was Farber who emphasized "Total Care" as the ideal clinical approach to the treatment of acute leukaemia.' Note on draft transcript, 29 November 2002.

ALL. These principles were induction therapy using weekly vincristine and prednisone, a period of ‘maintenance’ chemotherapy using 6-MP and methotrexate, and then radiotherapy to the central nervous system to prevent meningeal relapse. With those treatments a tremendous increase in the survival rate of patients with ALL resulted. In fact, the treatment of adult ALL wasn’t far behind, although it took longer to develop.

The advances in the treatment of AML were slower and it was much more difficult. I attended the ASCO [American Society of Clinical Oncology] meetings in the mid-1960s, which were attended then, as I remember, by one or two hundred people. Today, the ASCO meetings are attended by many thousands of people, but in those years they were talking about single-agent therapies for AML. Cytosine arabinoside was being used with a 16 per cent complete remission rate.<sup>42</sup> Daunomycin was being used, or daunorubicin, as it was called by the French. The successful introduction of an anthracycline in the study of acute leukaemia came from Jean Bernard’s group in Paris; that was a superb team – it was well organized and they conducted some very good studies. They produced, using daunorubicin, almost a 50 per cent complete remission rate in patients with AML during the 1960s.<sup>43</sup> The unfortunate thing about it was that it was very cardiotoxic, and when I joined Bart’s as a Senior Registrar in 1968, there were patients on the ward dying with heart failure. Jim Malpas was the previous Senior Registrar, and he had treated patients with AML using daunorubicin on a five-day schedule derived from Jean Bernard’s work; there were several patients actually dying of cardiotoxicity on the ward at that time when I took over. He told me about the scheduling and said, ‘Look, don’t try to repeat the Jean Bernard stuff, because it’s very cardiotoxic – watch it’.

In 1968, Sir Ronald Bodley Scott, Gordon Hamilton Fairley and myself organized a combined chemotherapy with cytosine arabinoside and daunorubicin given together. At the time it was a pretty hairy prospect I can tell you for the decision to do it was considered only briefly and over coffee. I had suggested to Sir Ronald, who was running the ward rounds, that perhaps we could use a drug combination – because combinations were useful for Hodgkin’s disease and had been used for ALL – and maybe we should use a combination for AML.<sup>44</sup> He

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<sup>42</sup> Ellison R R, Holland J F, Weil M, Jacquillat C, Boiron M, Bernard J, Sawitsky A, Rosner F, Gussoff B, Silver R T, Karanas A, Cuttner J, Spurr C L, Hayes D M, Blom J, Leone L A, Haurani F, Kyle R, Hutchison J L, Forcier R J, Moon J H. (1968) Arabinosyl cytosine: a useful agent in the treatment of acute leukemia in adults. *Blood* 32: 507–523. See also Bailey C C, Geary C G, Israels M C, Whittaker J A, Brown M J, Weatherall D J. (1971) Cytosine arabinoside in the treatment of acute myeloblastic leukaemia. *Lancet* i: 1268–1271.

<sup>43</sup> Boiron M, Weil M, Jacquillat C, Tanzer J, Levy D, Sultan C, Bernard J. (1969) Daunorubicin in the treatment of acute myelocytic leukaemia. *Lancet* i: 330–333. Malpas J S, Scott R B. (1969) Daunorubicin in acute myelocytic leukaemia. *ibid.* i: 469–470.

<sup>44</sup> Nicholson W M, Beard M E, Crowther D, Stansfeld A G, Vartan C P, Malpas J S, Fairley G H, Scott R B. (1970) Combination chemotherapy in generalized Hodgkin’s disease. *British Medical Journal* 3: 7–10. See also Scott R B. (1970) Cancer chemotherapy – the first twenty-five years. *ibid.* 4: 259–265. *op. cit.* note 45.

said, ‘Go carefully because the patients are often severely pancytopenic already’. However, we did carry out myeloablative types of therapy with that combination and reported a complete remission rate of 62 per cent.<sup>45</sup> At the time, Barney Clarkson and Tim Gee in New York in the Memorial Hospital were using thioguanine and cytosine arabinoside to try to get complete remissions, and they achieved a complete response rate of about 40 per cent in 1969.<sup>46</sup> So when the 1970s broke it was decided, by a number of groups within the UK, that we should add thioguanine to cytosine arabinoside and daunorubicin. That combination proved to be quite effective in the 1970s and was, in fact, the subject of a number of MRC trials at that time.<sup>47</sup>

Another development in the 1960s that we need to remember was that an international definition of complete remission in AML was brought into play and it was generally accepted that AML could be distinguished from ALL. It seems strange at this time that we should think there was a problem with this distinction, but there was in the 1960s. For example, J Freireich<sup>48</sup> was treating all his patients with acute leukaemia in Houston with the same chemotherapy and wasn’t bothering to distinguish the type of leukaemia. The recognition that AML could be split into different groups was very important. Jean Bernard showed that acute promyelocytic leukaemia could have very long-term remissions with chemotherapy and he found that this type of acute leukaemia was very responsive, although there were difficulties in the induction phase, and this kind of leukaemia came to have long-term survival.<sup>49</sup>

Towards the end of the 1960s Georges Mathé introduced immunotherapy for the treatment of childhood ALL in complete remission,<sup>50</sup> and although some patients had apparently done quite well, later years showed that it was of little value. Subsequently, bacterial products such as BCG or *Bordetella pertussis* and irradiated leukaemia cells were used in the treatment of

<sup>45</sup> Crowther D, Bateman C J, Vartan C P, Whitehouse J M, Malpas J S, Fairley G H, Scott R B. (1970) Combination chemotherapy using L-asparaginase, daunorubicin, and cytosine arabinoside in adults with acute myelogenous leukaemia. *British Medical Journal* 4: 513–517.

<sup>46</sup> Gee T S, Yu K P, Clarkson B D. (1969) Treatment of adult acute leukemia with arabinosylcytosine and thioguanine. *Cancer* 23: 1019–1032.

<sup>47</sup> See Rees J K, Gray R G, Swirsky D, Hayhoe F G. (1986) Principal results of the Medical Research Council’s eighth acute myeloid leukaemia trial. *Lancet* ii: 1236–1241.

<sup>48</sup> See Freireich E J. (1998) Four decades of therapy for AML. *Leukemia* 12: S54–S56.

<sup>49</sup> Bernard J, Weil M, Boiron M, Jacquillat C, Flandrin G, Gemon M F. (1973) Acute promyelocytic leukemia: results of treatment by daunorubicin. *Blood* 41: 489–496. Bernard J. (1994) History of promyelocytic leukaemia. *Leukemia* 8: S1–S5.

<sup>50</sup> Mathé G, Amiel J L, Schwarzenberg L, Schneider M, Cattani A, Schlumberger J R, Hayat M, De Vassal F. (1969) Active immunotherapy for acute lymphoblastic leukaemia. *Lancet* i: 697–699. See also Mathé G, Amiel J L, Schwarzenberg L, Hayat M, Pouillart P, Schneider M, Cattani A, Jasmin C, Belpomme D, Schlumberger J R, De Vassal F, Musset M, Misset J L. (1975) Immunothérapie active des leucémies aiguës et des lymphosarcomes leucémiques. Bilan de 10 ans – étude de 200 cas. *Nouvelle Presse Médicale* 4: 1337–1342.

adult AML in remission.<sup>51</sup> Ray Powles, who is in the audience, developed this. This was a project that was organized by Peter Alexander and Gordon Hamilton Fairley, who made a very good duo in the late 1960s. Peter Alexander led the way in tumour immunotherapy and the understanding of it in the experimental sense.<sup>52</sup> In the late 1960s, he linked up with Gordon Hamilton Fairley, who gave a great thrust to the development of what was to become medical oncology. Unfortunately, Gordon Hamilton Fairley died as a result of an IRA bomb in 1975, and this took away someone who was the major influence in the development of medical oncology in the UK at that time. This was a real disaster for the speciality of medical oncology.

In the 1970s we came to the era of intensive chemotherapy. Some intensification had been provided and the treatment of AML was resulting in longer-term survival – 20 per cent were beginning to live three to five years – by the end of the 1970s, through the introduction of more intensive procedures.

But it wasn't until the introduction of bone marrow transplantation (BMT) that myeloablative chemotherapy became feasible. Razjock in 1939 was the first to give marrow to a leukaemic patient; he gave it directly into the marrow cavity.<sup>53</sup> It wasn't until 1957 that Donnall Thomas and his colleagues in Seattle showed that a large volume of marrow could be infused safely, resulting in transient engraftment.<sup>54</sup> In 1963, Georges Mathé – a horrendously hard worker, who developed many things in the 1960s – published the first report of the long-term survival of a patient with leukaemia following transplantation. He was also the first to describe graft-versus-host disease (GVHD).<sup>55</sup> It was only in the 1970s that BMT became of

<sup>51</sup> Powles R L, Russell J A, Selby P J, Prentice H G, Jones D R, McElwain T J, Alexander P. (1977) Maintenance of remission in acute myelogenous leukaemia by a mixture of BCG and irradiated leukaemia cells. *Lancet* **ii**: 1107–1110.

<sup>52</sup> See, for example, Alexander P, Fairley G H. (1967) Cellular resistance to tumours. *British Medical Bulletin* **23**: 86–92. Powles R L, Crowther D, Bateman C J, Beard M E, McElwain T J, Russell J, Lister T A, Whitehouse J M, Wrigley P F, Pike M, Alexander P, Fairley G H. (1973) Immunotherapy for acute myelogenous leukaemia. *British Journal of Cancer* **28**: 365–376.

<sup>53</sup> An account of early BMT is given in Freireich E J, Lemak N A. (eds) (1991) Supportive therapy. Bone marrow transplantation. *op. cit.* note 80, pages 107–118.

<sup>54</sup> Thomas E D, Lochte J L, Lu W C, Ferreebee J W. (1957) Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *New England Journal of Medicine* **257**: 491–496. See also Donnall Thomas E. (1994–5) History, current results, and research in marrow transplantation. *Perspectives in Biology and Medicine* **38**: 230–237. Thomas E D, Storb R, Clift R A, Fefer A, Johnson F L, Neiman P E, Lerner K G, Glucksberg H, Buckner C D. (1975) Bone-marrow transplantation. *New England Journal of Medicine* **292**: 832–843. Hamblin T J. (1991) E Donnall Thomas, MD. Nobel laureate 1990. *Leukemia Research* **15**: 71.

<sup>55</sup> See Mathé G, Amiel J L, Schwarzenberg L, Cattan A, Schneider M. (1967) Treatment of acute leukemia by allogenic bone marrow graft. *Progress in Clinical Cancer* **3**: 309–319. Mathé G, Schwarzenberg L. (1979) Bone marrow transplantation (1958–1978): conditioning and graft-versus-host disease, indications in aplasias and leukemias. *Pathologie Biologie* **27**: 337–343.

practical value; it was the Seattle group that produced extensive experience on HLA-matched allogeneic transplantation and BMT with minor mismatches, and showed that a graft-versus-leukaemia reaction had a beneficial effect.<sup>56</sup>

Three principles were proposed in the late 1970s from quite a large number of cases studied – myeloblastic therapy could minimize the leukaemic cell population; HLA-matched, or minor allogeneic mismatched BMT, could allow haematopoietic recovery, and the third, exploitation of the role of the graft-versus-leukaemia effect. Subsequently this approach has been widely used throughout the world and has been shown to improve survival in a number of haematological malignancies. Our chairman, Professor John Goldman, has been responsible for some of these rather important advances, particularly in the management of CML.

In the 1980s we come to the age of applied molecular biology and recombinant technology. The first recombinant molecule that was introduced into the clinic was recombinant alpha-interferon – in 1981, I think.<sup>57</sup> This was subsequently introduced into the treatment of CML with some effect, but the more important agents that were introduced during the mid-1980s were the recombinant haemopoietic growth factors. G-CSF [granulocyte colony-stimulating factor] had been discovered mainly following experimental work by Don Metcalf's group in Melbourne, Australia. Recombinant DNA technology allowed their pure production and, lo and behold, G-CSF was made available for patients in the mid-1980s. I wrote a protocol at that time that was sent into the Leukaemia Research Fund (LRF) for funding a student of David Weatherall's, Miguel Bronchud, who had been working in Oxford. The grant request was to conduct a phase I–II study with stem cell factor; however, stem cell factor didn't come along until much later. It was almost ten years before stem cell factor could be introduced in the clinic. It was thought that GM-CSF [granulocyte-macrophage colony-stimulating factor] was ready to go and so we wrote the grant request for GM-CSF instead. We got the clinical research fellowship from the LRF to conduct that study. Unfortunately, GM-CSF was not available either, but G-CSF had been produced by a new drug company called AMGEN, in the USA. We finally did a phase I–II study of G-CSF using intensive chemotherapy in lung cancer patients, and showed that there was an enhancement of neutrophil recovery following chemotherapy and a reduction in the incidence of infection. The paper was published in 1987 by members of the Department of Medical Oncology and Experimental Haematology in the Paterson Institute in Manchester.<sup>58</sup>

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<sup>56</sup> Thomas E D, Fefer A, Buckner C D, Storb R. (1977) Current status of bone marrow transplantation for aplastic anaemia and acute leukemia. *Blood* 49: 671–681.

<sup>57</sup> See, for example, Talpaz M. (1994) Use of interferon in the treatment of chronic myelogenous leukemia. *Seminars in Oncology* 21: 3–7.

<sup>58</sup> Bronchud M H, Scarffe J H, Thatcher N, Crowther D, Souza L M, Alton N K, Testa N G, Dexter T M. (1987) Phase I/II study of recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. *British Journal of Cancer* 56: 809–813.



Another observation in the 1980s was by Huang in China, who observed that there was a remission using all-*trans*-retinoic acid in the treatment of acute promyelocytic leukaemia (APML).<sup>59</sup> This was interesting, because molecular technology had shown that APML was a result of a translocation involving the retinoic acid receptor gene on chromosome 17 and the PML gene on chromosome 15. An explanation of the molecular mechanism of action could therefore be suggested.

The use of haemopoietic growth factors set the stage for the 1990s, when it was found that myeloablative chemotherapy could be carried out more easily and safely with haemopoietic rescue using peripheral blood stem cells collected following G-CSF treatment. The original studies were done by Sheridan in Melbourne, who used peripheral blood stem cells in conjunction with bone marrow, and showed that the recovery in granulocytes, neutrophils and in platelets was much faster than bone marrow alone.<sup>60</sup> Subsequently quite a large number of people, including ourselves in Manchester, did some work showing that you could use peripheral blood stem cells alone for haematopoietic rescue.<sup>61</sup> The technique has become widely used and is now used for lymphoblastic disease, ALL, AML and CML. The role of myeloablative procedures continues to be addressed in the new millennium.

**Goldman:** Thank you very much, Derek. That was a very beautiful overview of quite a number of things. Can I make one comment and then I am going to ask David to make a comment? After that I want to introduce a slightly new topic.

My comment is simply an anecdote that supports something you said at the beginning of your talk. I had a patient with CML who was doing rather badly, and round about 1990 she decided to go to India for therapy. She had heard of a practitioner called Dr Vadya Prakash, operating in Delhi and in Deradan. She spent about six weeks there and she came back and said it wasn't very effective. But the LRF led by Gordon Piller suggested that it would be worth looking at the particular compound that Prakash was using to treat predominantly CML. In conjunction with two other haematologists, I went to Delhi to look at this compound. There was no doubt that the compound that Prakash was making in his back garden and in his kitchen sink was controlling the leucocyte count. The leucocyte count of patients with chronic leukaemia was coming down in some cases to

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<sup>59</sup> Huang M E, Ye Y C, Chen S R, Chai J R, Lu J X, Zhao L, Gu L J, Wang Z Y. (1988) Use of all-*trans*-retinoic acid in the treatment of acute promyelocytic leukemia. *Blood* 72: 567–572.

<sup>60</sup> Sheridan W P, Morstyn G, Wolf M, Dodds A, Lusk J, Maher D, Layton J E, Green M D, Souza L, Fox R M. (1989) Granulocyte colony-stimulating factor and neutrophil recovery after high-dose chemotherapy and autologous bone marrow transplantation. *Lancet* 2: 891–895.

<sup>61</sup> Pettengell R, Morgenstern G R, Woll P J, Chang J, Rowlands M, Young R, Radford J A, Scarffe J H, Testa N G, Crowther D. (1993) Peripheral blood progenitor cell transplantation in lymphoma and leukemia using a single apheresis. *Blood* 82: 3770–3777.

normal. To the annoyance of the All-India Institute of Medical Sciences and Lady Tata Memorial Hospital, he was building up a considerable practice in his own private office in Delhi. He didn't know what was in the compound, or he told us it was a mixture of things he made in his back garden. I guess many people will have got an idea where we are heading; we brought the compound back to London for analysis and, of course, it contained between 15 and 25 per cent arsenic. We wrote about this, as it was a partly modified ayurvedic medicine.<sup>62</sup> This was before the time that arsenic underwent the renaissance to which you referred a few moments ago, Derek, but I suppose the moral of the story is, (a) to keep an open mind, and (b) note that some of the old remedies may actually recur on one. David, you were going to say something?

**Galton:** I wanted to comment on three of the things that we have heard this afternoon. The first one is again arsenic. You would hardly believe it, but arsenic was still being used in Switzerland in the 1950s. I had a patient referred by a very, very distinguished Swiss haematologist, Karl Rohr, whose name many of you will know, because he had heard of busulphan. This patient had been treated with arsenic and I discovered that it was quite commonly used in Switzerland at that time.

The second point that I wanted to make was to go back to Alex Haddow and urethane, because Haddow had a remarkable brain – he kept his eyes open and picked on things of interest from every sphere. He met up with a plant pathologist whose name was Sexton, who had found that if he germinated cereals and onions, the mitosis in the root tips could be arrested by urethane, or one of its analogues. Haddow, of course, immediately got onto it and found that it was a very good inhibitor of some of his experimental tumours,<sup>63</sup> and that's how it worked its way into clinical practice. He had collaborated with Ralston Paterson [of the Christie Hospital in Manchester], who was a fellow Scot, and that's how Paterson got onto it.

Now an interesting little side story about this is that at the time that Edith Paterson was studying urethane, so was a young clinician at the Royal Cancer Hospital. Because of Edith's radiotherapy training, she had regular blood counts done on her patients treated with urethane and it was she who noticed the fall in the blood count in patients without leukaemia but with malignant diseases.<sup>64</sup> Haddow was a bit cross about this because it had

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<sup>62</sup> Treleaven J, Meller S, Farmer P, Birchall D, Goldman J, Piller G. (1993) Arsenic and ayurveda. *Leukemia and Lymphoma* 16: 189–190.

<sup>63</sup> Haddow A, Sexton W A. (1946) Influence of carbamic esters (urethanes) on experimental animal tumours. *Nature* 157: 500–503.

<sup>64</sup> See note 37.

been totally missed by the young lady who was studying this compound at the Royal Cancer Hospital. Anyhow, an amusing thing is that one of the people who received urethane to test, from Alex Haddow, was Harold Himsworth, who was then Professor of Medicine at University College Hospital. At UCH this drug was known as the 'Manchester drug' because the finding of a depressed leucocyte count came from Manchester.<sup>65</sup>

Another interesting point about urethane is that it made patients dreadfully sick and it was very difficult to get them to tolerate it. One of the people who had received urethane in the USA was Wayne Rundles at Duke University in North Carolina. He was a physician, a haematologist, and he could do what he liked in treating patients. This wouldn't have been possible in this country with say myelomatosis, because myeloma was treated by radiotherapy. In the 1950s radiotherapists were, let's put it in a general way, the custodians, if you like, of the knowledge, the science, of malignant disease. They were the ones who kept registers, they were the ones who knew how long people survived, and they knew the natural history of the disease better than anyone else. So they had, rightly I think, a rather lordly attitude to radiotherapy in relation to the new-fangled drugs. They were highly suspicious of them and I think they were probably correct. But with myeloma they went too far, because they used to treat this disease, which mainly produced terrible bone pains in different parts of the body, by irradiating one painful site after another. They went on doing this until the patients were in severe renal failure on the one hand, or bone marrow failure on the other. At that stage they were handed over to people who were trying chemotherapy drugs and, of course, all that the drugs did was kill the patients, because they were now in total renal failure, and/or pancytopenia. Wayne Rundles wasn't under any such constraints and he treated myeloma patients with urethane with great success.<sup>66</sup> Furthermore, he developed a way of giving it by suppository and this reduced a good deal of the nausea and vomiting. I must say that this raises a general problem about the introduction of these agents in the UK, because I think it wasn't only the radiotherapists who were highly sceptical. Most physicians were very reluctant to handle these drugs, and it was a hard core of wonderful people who saw their potential and their future, and it was they who gave us a lot of support.

Derek told us about Ronald Bodley Scott; he was at the forefront of those who supported the new studies. At Hammersmith there was John McMichael and Russell Fraser, who gave the opportunity for using these drugs at a time when most physicians were not at all friendly to them; there was also Percy Thompson Hancock and John Harman, who gave encouragement at the Royal Marsden Hospital.

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<sup>65</sup> op. cit. note 37.

<sup>66</sup> Loge J P, Rundles R W. (1949) Urethane (ethyl carbamate) therapy in multiple myeloma. *Blood* 4: 201–216.

Incidentally, somebody mentioned aminopterin. Here's another little story. Sidney Farber had just done the first studies on childhood leukaemia with aminopterin.<sup>67</sup> I think it was February 1948 when a well-known poet, who was also an amateur mountaineer and a school teacher, had been on holiday in Switzerland mountaineering, and to his horror found that he was getting breathless when he got beyond a certain height. He was worried about this and on his return his wife, who was a Scottish girl and also a poet, persuaded him to seek medical advice. He was diagnosed as having acute leukaemia and was referred to John McMichael at Hammersmith. But his wife was a Scot who knew Alex Haddow, and she asked Alex if there was anything that could be done to treat this awful disease, because she had heard that it was incurable. Haddow said there was probably nothing, but a colleague of his, Professor Eric Boyland, had just received a supply of a new drug which had come from America and that was doing unexpectedly good things in the treatment of childhood leukaemia; he asked if she would be prepared to let her husband receive this drug. Of course she was only too delighted and I took over Eric Boyland's aminopterin. This would be impossible today – you would have to fill in all kinds of forms and it just couldn't be done – but I took this stuff over, and John Dacie and I studied the blood of this patient. He had a horrible form of leukaemia that would now be called M5 – acute monocytic leukaemia. John McMichael's team treated this patient with the drug. He went into a complete remission, something amazing, because nowadays none of the folate antagonists is used in the treatment of this disease. He had three months of good life and then he relapsed with multiple skin nodules, came back to Hammersmith, had more aminopterin, but it did no good and he died. His wife went to see Alex Haddow afterwards and he was deeply apologetic for having inflicted what proved to be a useless treatment on her husband; he felt that it shouldn't have been done, but the wife said, 'On the contrary, these three months were almost the best three months of our lives. Every day of good health was appreciated and it was wonderful, thank you very much.' That was the second thing I wanted to touch on.

The third was that Derek spoke about the advent of BMT. I think one of the first bone marrow transplants ever given in the UK was – don't laugh – by Humphrey Kay. I had a patient who had CML, who unfortunately had received busulphan for two weeks longer than she should have. I was very foolish; she was going on holiday and I gave her a supply two weeks beyond her next appointment. She didn't keep the appointment; she went on taking the drug, became pancytopenic, and arrived back in this terrible state. Humphrey said, 'Why don't we try to get some bone marrow from a donor that could be easily obtained by asking Mr Barrett (who was one of the surgeons at the Brompton Hospital next door), if he would agree to cut out a few ribs next time he was doing a thoracotomy – and could

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<sup>67</sup> Farber S, Diamond L K, Mercer R D, Sylvester R F, Wolff J A. (1948) Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroylglutamic acid (aminopterin). *New England Journal of Medicine* 238: 787–793.

we please have the marrow? That's exactly what he did. Humphrey filtered it off to get rid of the fat, and of course in those days (1953), nobody knew anything about histocompatibility groups at all. Anyway she had the marrow but I am afraid she died.

**Goldman:** Can I just ask you to comment briefly on one of your earlier points? You said that radiotherapists and some other physicians were not very well disposed to the use of chemotherapeutic agents to treat malignant disease. What was the response of the radiotherapy community to your publication on busulphan versus radiotherapy in CML?<sup>68</sup>

**Galton:** By that time they had become extremely cooperative. The point is that they raised no objections whatever – in fact they were fully supportive when the Medical Research Council Working Party wanted to put on this trial of radiotherapy versus busulphan,<sup>69</sup> and we had nothing but cooperation from them.

**Goldman:** That was not because they expected radiotherapy to be better, but because they were genuinely interested.

**Galton:** They wanted to find out which was better. The other thing was after a few years of, I suppose, hostility, radiotherapists welcomed the advent of chemotherapy. In fact, at the Royal Marsden Hospital, David Smithers, who was Head of Radiotherapy, arranged for a joint consultation clinic between Elspeth Ledlie, who was one of his radiotherapists, and myself to see patients with malignant lymphoma once a week. Constance Wood, at Hammersmith Hospital, slightly reluctantly I think, arranged for me to have a joint clinic once a week with Leon Szur, one of her radiotherapists who dealt mainly with lymphoid neoplasms and so on. These were very valuable.

**Dr Eve Wiltshaw:** I would like to confirm what David [Galton] and others have said about the Institute of Cancer Research when Haddow led it. I think it was the golden age for the Institute of Cancer Research<sup>70</sup> and I was very glad to be part of it. I came to the Institute from Boston at a time when [Maxwell] Wintrobe was around. The Boston haematologist, William Dameshek, was showing off every week with his foreign patients and the children's

<sup>68</sup> Report of the Medical Research Council's Working Party for Therapeutic Trials in Leukaemia. (1968) Chronic granulocytic leukaemia: comparison of radiotherapy and busulphan therapy. *British Medical Journal* **i**: 201–208.

<sup>69</sup> *op. cit.* note 68. See Burchenal J H. (1968) Chemotherapy and radiotherapy – competitors or partners? *Cancer* **22**: 790–795. Henk J M. (1996) A brief history of British radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* **36**: 213–218, in particular page 214.

<sup>70</sup> See Brunning D A, Dukes C E. (1965) The origin and early history of the Institute of Cancer Research of the Royal Cancer Hospital. *Proceedings of the Royal Society of Medicine* **58**: 33–36. Haddow A. (1961) The Chester Beatty Research Institute (of the Institute of Cancer Research: Royal Cancer Hospital). *Nature* **191**: 430–432. See also Thomson A L. (1987) *Half a Century of Medical Research*. Vol. 1: *Origins and Policy of the Medical Research Council (UK)*. London: Medical Research Council, 156–159.

hospital [under Sidney Farber] was starting its treatments for acute leukaemia and later for other tumours. I had gone to Boston because I knew that nobody in London would take me on, having come from a university called the University of Wales. I was quite right in that and after two years I came to London and saw Haddow, because I had a letter of introduction from my own haematologist. Haddow and David told me, 'Go and see John Dacie about your future'. So, with two years of clinical haematology behind me, treating leukaemia and lymphomas, both laboratory-wise and in the clinic, Dacie said to me, 'But Eve, you are not considered a proper doctor. In the UK you are not a proper physician because you have been in the lab, and you are not a haematologist because you have been treating patients. Go back to America.' I didn't want to go back to America, because I didn't like the way they lived. The fact was that this country then had haematologists who worked in laboratories and doctors who didn't know anything about haematology, treating patients with haematological disorders and nobody was prepared to make the obvious change.

You have all been talking about various innovations, new drugs, new methods, and new ideas, but there wasn't, apart from Haddow and his colleagues, a single UK advance. I am not taking this up to the present, but I am talking about the 1950s and 1960s. We had got some drugs from the Institute of Cancer Research, and we had got a lot of different ideas, which mainly came from America, based on the fact that they were willing to take risks. There were no risk takers here. There was no medical oncology – there wasn't much medical oncology in the USA, but there was none here. I remember trying to get jobs. The only doctor who was interested in me having a job outside the Marsden and the Institute was David Weatherall; otherwise people said, 'What do you mean? There is no subject. Why don't you do radiotherapy?' [From the floor: What year was that?] When I started looking for a job? Oh, the mid-1960s, and even now, we are short of medical oncologists.

**Goldman:** What about David Galton, he didn't get appointed? I don't think he was a consultant for many years.

**Wiltshaw:** David is too nice to everybody, even now. They kept him out of a position of responsibility and the ability to do anything for a long time, and it was because they used the clash between the Institute and the Hospital to do that. I suspect that's one of the reasons why David left in 1969 to go to the Hammersmith Hospital full time.

**Professor Daniel Catovsky:** I just want to put the record straight, at least on the late 1960s and early 1970s, about Sir John Dacie and the Hammersmith and David Galton, because they started the first leukaemia unit in the UK. Maybe I don't know where we learnt great advances, but Sir John Dacie was instrumental later on, maybe not in the 1950s, in changing the philosophy of haematology through bridging the gulf between the laboratory and clinical branches. He had very good clinicians in his group, like Michael Brain and Ted Gordon Smith.

When I was about to go back to Argentina in 1970, David encouraged me to stay in the UK and work with him. Then John Goldman and Alexander Spiers came to join us in forming the first Leukaemia Unit. Although the MRC provided financial backing and David Galton directed the Unit, it was Sir John who was responsible for its formation, so it is he who changed the early philosophy and eventually the direction of haematology in the UK.

**Sir Christopher Booth:** I just wanted to support that view. I became Professor of Medicine in succession to John McMichael at the Hammersmith in 1966. The chairman of the board at that time who promoted my appointment to that post was John Dacie. I had worked in his department as a haematologist before I became a gastroenterologist and he was particularly involved in this question over the clinic and the laboratory at that time. After I was appointed, my first senior registrar was Michael Brain, who had a joint appointment in my department in medicine and with John Dacie in haematology. Within two years of my appointment John Dacie was making rounds in the American way of seeing patients. I do know that he was deeply committed to clinical haematology, which led to his promotion of the Leukaemia Unit at the Hammersmith, which has been so successful.

**Powles:** Following on from Derek's [Crowther] nice summary about the Bart's side of things reminds me of exactly what it was like for the patients being treated in the early 1960s. I was a student on Bodley Scott's firm in 1962 and a houseman on the same unit for a year in 1965. There were up to 40 in-patients at a time with leukaemia and many others scattered in other wards throughout the hospital. Most had acute leukaemia and the median survival from diagnosis was about 12 weeks. Probably 1000 went through Bart's in this period and I don't think there was a single long-term survivor.

As a houseman, the dominant duty was putting up intravenous drips in the morning using Guest cannulae and taking them down again in the evenings. We might be putting up 30 or 40 drips per day and preserving the veins was all that was keeping these patients alive.<sup>71</sup> Young patients when first admitted would start in a bed at the far end of the ward and would work their way up to the two single rooms that were at the entrance to each ward, where two or three of them would die every day – of course, some of the patients didn't even know they had leukaemia in those days, which was the standard practice of those days.

Now, just following on from Derek about the drugs – vinblastine was interesting. We gave vinblastine daily and this often led to devastating paralytic colitis requiring the raising of a caecostomy – it was only the colon that was paralysed, not the small bowel. We learnt quite

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<sup>71</sup> Professor Raymond Powles wrote: 'We became lifelong experts at finding a suitable vein for intravenous work, which still keeps me in good stead today. The wards were very much "Nightingale" in their format, with open fires at the end and prayers dominating the ethos of the unit. The sisters wore high starched hats and were sacrosanct. The consultant asked her permission to come into the ward.' E-mail to Dr Daphne Christie, 8 January 2003.



quickly to give the drug weekly. At that time Hamilton Fairley and John Matthias were the senior registrars followed by Jim Malpas and subsequently Derek Crowther. Daunorubicin was also introduced at this time and given in very high doses; consequently I saw more cardiomyopathy in this period than in my entire subsequent career. Leukaemia drugs were not yet being used in combination and platelet transfusions were only just becoming available following the extraordinary vision of Isaac Djerassi in Philadelphia.<sup>72</sup>

In 1968 I joined Peter Alexander and Hamilton Fairley at the Royal Marsden Hospital in Sutton, Surrey, where they set up a Tumour Immunology Research Programme looking at the possibility of undertaking immunotherapy as treatment for leukaemia following the pioneering work of Georges Mathé at Villejuif in Paris.<sup>73</sup> I spent four months with Georges learning all about BCG. In Sutton, Humphrey Kay already had a most imaginative state-of-the-art leukaemia unit treating children in plastic bubbles that could be made germ free. The ‘Concord trial’ started at this time under the auspices of the MRC<sup>74</sup> to see if BCG versus nothing could be tested for the maintenance of remission of children with leukaemia. These children did not have any CNS prophylaxis and I think the median survival was 32 weeks. It was at this time that it was shown at St Jude’s Hospital in Memphis, Tennessee that CNS prophylaxis actually produced cures.<sup>75</sup>

**Goldman:** I want to move on to morphology in one moment, but before that I just want to take up your last point, Ray, which is the word cure. I would like somebody, maybe Humphrey, to comment on the transition in concept from the idea that children could never be cured of their leukaemia to the idea that cure could become a reality. I don’t want to trespass on what John Lilleyman might be saying in a few moments. Humphrey, do you want to comment on the notion of cure?

**Professor Humphrey Kay:** The first cases we were interested in were Joe Burchenal’s cases, weren’t they? He had two or three who appeared to be totally cured and all the haematologists thought he had got the diagnosis wrong – they must have been cases of infectious mononucleosis.

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<sup>72</sup> Djerassi I, Farber S. (1965) Conference on obstacles to the control of acute leukemia. Control and prevention of hemorrhage: platelet transfusion. *Cancer Research* 25: 1499–1503. See also Djerassi I. (1972) Platelet transfusions and supportive care. A requirement for currently effective chemotherapy. *Journal of the American Medical Association* 222: 1172–1173. Roy A J, Jaffe N, Djerassi I. (1973) Prophylactic platelet transfusions in children with acute leukemia: a dose response study. *Transfusion* 13: 283–290.

<sup>73</sup> op. cit. note 50, and page 16. See also, Freireich E J, Lemak N A. (eds) (1991) op. cit note 80, pages 120–122.

<sup>74</sup> Professor David Galton wrote: ‘The MRC leukaemia trials began in 1959 under the chairmanship of Professor L J Witts, and I was the Secretary.’ Note on draft transcript, 3 March 2002. op. cit. note 149.

<sup>75</sup> Pochedly C. (1979) Prophylactic CNS therapy in childhood acute leukemia: review of methods used. *American Journal of Pediatric Hematology/Oncology* 1: 119–126. See also note 40.



**Goldman:** If the patient survived then the diagnosis had been wrong?

**Kay:** Yes. But gradually we had to revise that.

**Galton:** One point, when Derek was talking, he was speaking about technical advances and how they influenced the development of treatments.<sup>76</sup> This is supposed to be a historical meeting. Ray spoke about platelet transfusion. I think very few people below a certain age can remember our working conditions in the early 1950s. For example, nowadays people use butterfly cannulas for intravenous transfusions and they can do all kinds of things with them.<sup>77</sup> In our day we had dreadful glass syringes; they had a central nozzle and there was no way you could get into a small vein – we always had to use the cubital fossa veins. If we wanted to put up a drip, for example, we had to rummage about in a great cardboard box where there were lots of rubber tubings of different sizes, and we had to fit these up and stick them into a glass rod that fitted into a hole in a cork in a bottle – we didn't have any plastic transfusion equipment.<sup>78</sup> All this took a great deal of time. There were no platelet transfusions. I felt that we could stop our acute leukaemia patients from dying a miserable haemorrhagic death if we could get very fresh blood into them. Where were we going to get fresh blood? Very fresh. We had a system whereby we would invite two or three donors – do you remember that, Eve? Then one of us would bleed the first donor; the other one would put up a drip into the patient, and the idea was to get this blood in while it was still warm. Of course we had the cross-matching business, and it took a very long time to get three units of blood taken in such a way that they were really fresh and went in 'hot'. We did find that the patients stopped bleeding for several days, [to Eve Wiltshaw] wasn't it? But this was a terrible palaver and I think at about the same time Gordon Wetherley-Mein wrote about it.<sup>79</sup> I think anyone from St Thomas's can tell me when that happened. He was trying

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<sup>76</sup> See pages 12–19.

<sup>77</sup> Professor David Galton wrote: 'Butterflies are small-bore needles with flat metal wings for taping to the skin and immobilizing the needle. The proximal end of the needle continues in a thin plastic tube ending in a receiver for the nozzle of the syringe or intravenous drip set. The butterflies are useful for injecting several drugs in succession, through already filled syringes, and also for infusing drugs from a "drip" set over a period of minutes or hours.' Note on draft transcript, 29 November 2002. See also Tansey E M, Christie D A. (eds) (1999) *op. cit.* note 82, 29–30.

<sup>78</sup> Prior to 1954, blood transfusions were performed with rubber tubes and plastic bottles [See Kliman A, Gaydos L A, Schroeder L R, Freireich E J. (1961) Division of Biologics Standards and the National Cancer Institute, National Institutes of Health, Bethesda, MD]. Diamond L K. (1980) A history of blood transfusion, Ch. 19, in Wintrobe M M. (ed.) *Blood, Pure and Eloquent*. New York: McGraw Hill, 659–683. See also Freireich E J. (1998) Four decades of therapy for AML. *Leukemia* 12: S54–S56. *op. cit.* notes 81 and 84.

<sup>79</sup> Wetherley-Mein G. (1981) Haematology at St Thomas's 1818–1983. *St Thomas's Hospital Gazette* 82: 5–12.

to get very fresh blood to get platelets in quickly. So we forget nowadays what a palaver these things were and the sheer time wasted in doing these things was quite extraordinary.

**Dr Peter Hunter:** Just a very quick question. What is the date of the first very fresh blood platelet transfusion?

**Powles:** Platelet transfusions were about 1968–69. That's when they were certainly being effectively used. I don't know about fresh blood.<sup>80</sup>

**Hayhoe:** Regarding fresh blood, I think Whitby was certainly using it at the Middlesex before the war and you remember he very largely organized the blood transfusion services during the war – during the Second World War.<sup>81</sup>

**Goldman:** No, I think it goes back further than that.

**Crowther:** I think it was carried out on a man who lost his leg in the First World War. It was tried several times in the First World War and sometimes it was useful and sometimes it wasn't. They didn't understand about compatibility. I heard that in the trenches direct blood transfusions were given but several soldiers died from incompatibility. I think they used animal blood in the nineteenth century.<sup>82</sup>

**Goldman:** Animal blood was certainly used experimentally. It would be difficult to get it through your research ethics committee today, though. What about prophylactic antibiotics?

**Powles:** In 1965 we were using oral chloramphenicol and erythromycin as the main treatment of infection; they were given in combination and this was considered extremely innovative and against the standard accepted wisdom for using antibiotics.<sup>83</sup>

<sup>80</sup> The first case of transfusion of the blood of a patient with leukaemia was carried out by George Callender in 1873 at St Bartholomew's Hospital in London. See *British Medical Journal* Editorial. Transfusion of blood. *British Medical Journal* i: 593. See also Piller G J. (2001) Historical review. Leukaemia – a brief historical review from ancient times to 1950. *British Journal of Haematology* 112: 282–292, in particular page 287. An account of blood platelet transfusion is given in a letter from Dr Peter Hunter to Dr Daphne Christie, 1 February 2003, which will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London. See also Freireich E J, Lemak N A. (eds) (1991) Platelet transfusion, in *Milestones in Leukemia Research and Therapy*. Baltimore, London: The Johns Hopkins University Press, 91–95.

<sup>81</sup> See Dodsworth H. (1996) Blood transfusion services in the UK. *Journal of the Royal College of Physicians of London* 30: 457–464. Gunson H H, Dodsworth H. (1996) 50 years of blood transfusion. *Transfusion Medicine* 6: 1–88.

<sup>82</sup> See, for example, Ponfick E. (1875) Experimentelle beitrage zur lehre von der transfusion. *Virchows Archiv* 62: 273–335. Zimmerman L M, Howell K M. (1932) History of blood transfusion. *Annals of Medicine and History* 4: 415–433. See also 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, 13.

<sup>83</sup> See Spencer D H, Algire D H, Smith N G. (1965) Cancer chemotherapy: A bibliography of agents, 1955–1959. *Cancer Research* 25: 1–436. See also 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.

**Piller:** Exchange blood transfusion was started first at Bart's Hospital in the middle of the nineteenth century and also at Great Ormond Street Hospital for Sick Children.<sup>84</sup> In one case the blood that was administered was from an animal and in the other from a human, both without success. As far as I know, the first complete blood exsanguination transfusion, born of desperation, was given in a case of leukaemia by Jean Bernard and Marcel Bessis in 1947.<sup>85</sup> The result was a temporary remission of a few months – when a remission in cases of acute leukaemia was almost unknown at that time.

**Goldman:** I think the issue of 'first' is often very difficult to work out because it depends on how you define the blood transfusion or indeed the bone marrow transplant as we mentioned already. I would like to raise just one question. Does anybody here have some experience of blood transfusion inducing remission of acute leukaemia?

**Hayhoe:** I had extensive experience of this in the early 1950s, when I went as an Elmore research student to join Lionel Whitby's unit in Cambridge. There initially the only form of treatment was blood transfusion and prayer for acute leukaemias; we didn't yet have 6-MP. The folic acid antagonists were just beginning to be used, and of course prednisolone, cortisone and adrenocorticotrophic hormone (ACTH) were also just beginning to appear. Most of our patients were given blood transfusions, preferably very fresh, and a proportion of them undoubtedly went into full, though relatively short-term, remission. If you look at the *British Journal of Haematology*, volume one, page one, you will find a paper by Lionel Whitby and myself, in 1955, describing our experience, which included maybe a dozen or 20 patients.<sup>86</sup> It was also actively practised in Paris, and Bessis particularly used exsanguination transfusions to produce remissions in ALL in children, and produced a high proportion of them. Whether this was due to a steroid effect or what really mediated it, I am not sure.

**Galton:** Just a very quick point. I very well remember receiving that very first paper from Frank and Lionel Whitby. John Dacie gave it to me. It was the first paper for the new *British Journal of Haematology* that I edited in 1955. Lovely.

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<sup>84</sup> See, for example, Prevost J L, Dumas J B. (1821) Quoted by Maluf N S R. (1954) History of blood transfusion. *Journal of the History of Medicine* 9: 59–107. Waller C. (1959) On the transfusion of blood: its history and application in cases of severe haemorrhage. *Transactions of the Obstetrical Society of London* 1: 61–74. See also Diamond L K. (1980) op. cit. note 78.

<sup>85</sup> Bessis M, Bernard J. (1947) Remarquables resultats du traitement d'un cas de leucemie aigue par l'exsanguino-transfusion. *Bulletins et Memoires de la Societe Medicale des Hospitaux de Paris*, seance du 4 Novembre, 63: 871.

<sup>86</sup> Hayhoe F G J, Whitby L. (1955) The management of acute leukaemia in adults. *British Journal of Haematology* 1: 1–19.

**Goldman:** I think we should change topic now, quite radically, and talk about morphology. Maybe Frank, you could start briefly and we will go on to Danny, and David, in that order.

**Hayhoe:** I think that to approach the subject of morphology, I have got to divide it into about four main sections, with a couple of subsidiary sections. I was asked to do it in five minutes, and I shall try to do something of that sort.

The first is the use of panoptic staining, introduced by Paul Ehrlich in 1877 or thereabouts but still substantially used today.<sup>87</sup> The Romanowsky dyes, basically eosin and methylene blue mixtures in methanol, which were long used in this country in the form of either May–Grünwald–Giemsa or Leishmann stains, in the USA as Wright stain, and more recently in this country as Heyl stain or some other purified form of azure B and eosin Y.<sup>88</sup> These panoptic stains produce a very effective delineation of the morphological structure of leukaemic cells. The problem was that although haematologists recognized the differences between almost as many classes as we recognize today – if you look at Forkner’s 1938 Textbook on *Leukemia and Allied Disorders*,<sup>89</sup> you will find that he subdivides the leukaemias into virtually as many categories as we include today, various myeloid groups, monocytic, lymphoblastic, those with erythroid components, those with megakaryocytic or megakaryoblastic components, eosinophilic predominance and so forth – it was all there at that time. There was a powerful difficulty about the use of these stains. Although every skilled haematologist reckoned that he could subdivide the leukaemias accurately, in point of fact there was very wide disagreement. If you look at the recorded figures from different areas of the USA, as to the proportion of lymphoid to myeloid leukaemias for example, they vary enormously, despite the fact that the most disparate figures often came from neighbouring regions in the USA. When in the early 1950s, the new forms of treatment which we have been discussing earlier, became available for the leukaemias, the Medical Research Council set up Working Parties on the treatment and, as a preliminary, on the typing of leukaemia. With Leslie Witts as chairman, a small working group was designed to see to what extent we could agree on our classifications. I was the secretary of this group and we arranged for a number of centres to send slides from every new case of leukaemia to me in Cambridge. The participants in this study included Leslie Witts himself and Sheila Callender from Oxford, John Dacie from the Hammersmith, David Galton then at the Marsden, Gordon Wetherly-Mein from St Thomas’s, Ronald Bodley Scott from Bart’s, Roger

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<sup>87</sup> Ehrlich P. (1877) Beitrag zur kenntnis der anilinfärbungen unter ihrer verwendung in der mikroskopischen technik. *Archives Mikrochirurgie Anatomischer* 13: 263–277.

<sup>88</sup> Wittekind D. (1979) On the nature of Romanowsky dyes and the Romanowsky–Giemsa effect. *Clinical and Laboratory Haematology* 1: 247–262.

<sup>89</sup> Forkner C E. (1938) *Leukemia and Allied Disorders*. New York: Macmillan.

Hardisty from Great Ormond Street and Bill Davidson from King's. In addition, we brought in Eric Easson, James Fountain, C A Holman, Eddie Blackburn from Sheffield and R B Thompson from Newcastle. That made 13 people altogether, to whom we circulated the slides with their identity and origin masked. We circulated 100 slides. About 50 of them were of chronic leukaemias, chronic myeloid or chronic lymphocytic, and the 13 people by and large agreed on these. The other half of the cases were acute leukaemias. We had not specified the labels that should be put on the acute leukaemias, and left it to each individual to put their own label on it. Of the acute leukaemias sent round to these 13 observers, not one single case had an agreed diagnosis; some cases had eight or nine different diagnoses from the same slide. So at this stage, I played an unpleasant trick, and took six of the cases that had shown the most disparate diagnoses, relabelled them and circulated them again as fresh slides. We didn't get any better agreement the second time round, but many of the observers gave a different diagnosis on their second reading from what they had given at the first.

It was as a result of that study, and partly because in 1951 I had presented an MD dissertation at Cambridge on the use of cytochemistry in haematology,<sup>90</sup> that I thought it was a good idea to apply cytochemical techniques more widely. I am not going to discuss this second major morphological contribution in detail now, but simply to say that as a result of the study of another 140 cases, using particularly the Sudan black and PAS [periodic acid–Schiff] reactions, as well as peroxidase, we were able to establish a reasonably satisfactory pattern of diagnosis that became generally used subsequently in later MRC trials.<sup>91</sup>

I have to move on quickly from the use of panoptic and cytochemical staining, which still continues today, to the next supplement following cytochemistry, which was cytogenetics. This, of course, is another component of morphology. Remember that when we were starting this work, the human chromosome number was not known – it was generally thought to be 48.<sup>92</sup> In fact Tjio and Levan showed the number to be 46 in 1956.<sup>93</sup>

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<sup>90</sup> Hayhoe F G J. (1951) The value of cytochemical methods in haematology. MD thesis. Cambridge University.

<sup>91</sup> Hayhoe F G J, Quaglino D, Doll R. (1964) *The Cytology and Cytochemistry of Acute Leukaemias: A study of 140 cases*. London: HMSO. See also Catovsky D. (1982) Symposium: classification of leukemia. 1. The classification of acute leukemia. *Pathology* 14: 277–281. Lilleyman J S, Britton J A, Anderson L M, Richards S M, Bailey C C, Chessels J M. (1994) Periodic acid–Schiff reaction in childhood lymphoblastic leukaemia. The Medical Research Council Working Party on Childhood Leukaemia. *Journal of Clinical Pathology* 47: 689–692. Hayhoe F G J, Flemans R J. (1969) *An Atlas of Haematological Cytology*. London: Wolfe. Hayhoe F G J, Quaglino D. (1980) *Haematological Cytochemistry*. Edinburgh, London: Churchill Livingstone.

<sup>92</sup> See, for example, Darlington C D. (1931) Meiosis. *Biological Reviews* 6: 221–264. Hsu T C. (1952) Mammalian chromosomes in vitro. I. The karyotype of man. *Journal of Heredity* 43: 167–172.

<sup>93</sup> Longo L D. (1978) Classic papers in obstetrics and gynecology. The chromosome number in man. Joe Hin Tjio and Albert Levan. *Hereditas* 42: 1–6 (1956). *American Journal of Obstetrics and Gynecology* 130: 722. Tjio J H. (1978) The chromosome number in man. *ibid.* 130: 723–724.

The first paper that I remember which showed that the chromosome pattern might be abnormal in acute leukaemias came from Ford, Jacobs and Lajtha in 1958.<sup>94</sup> From that time everybody got pitched into a study of chromosomes in acute leukaemias. I did, among others. Dennis Quaglino, who was then working with me, and I went down to St George's [London], where Stafford and Kemp had started to get satisfactory metaphase spreads, to learn their technique.<sup>95</sup> We started using it in Cambridge and by 1964 we were able to report on something like 20 or 30 cases and find another 200 or 300 in the literature.<sup>96</sup> But at that stage, all that the early morphological chromosome studies were doing was spotting numerical and structural defects among which the Ph chromosome of CML was the most important.<sup>97</sup> There weren't the techniques available yet to distinguish the different chromosomes, other than very crudely by their size, and you couldn't separate the 6–12 group anyway. In 1970 Caspersson introduced quinacrine banding, Q banding and Giemsa banding quickly followed.<sup>98</sup> With the use of high-resolution Giemsa-banded chromosomes, you could identify individual chromosomes and start to find specific translocations. It was with Giemsa banding that people both in Scandinavia, this country and also in the USA, particularly Janet Rowley's unit, began to find and report the now well-known translocations that occur in acute leukaemia.<sup>99</sup> Following that, with the subsequent development of molecular biological studies, which followed 10 or 15 years later, it became possible to produce highly specific probes for individual chromosomes. Using techniques such as fluorescence *in situ* hybridization (FISH), localized translocations and defects of one kind or another were much more widely explored and defined. I see that nowadays multiple

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<sup>94</sup> Ford C E, Jacobs P A, Lajtha L G. (1958) Human somatic chromosomes. *Nature* **181**: 1565–1568.

<sup>95</sup> Stafford J L, Kemp N H, Tanner R. (1963) The cytogenetics of human leukaemia and allied states. *41st Annual Report of the British Empire Cancer Campaign*. London: The Campaign, 306–307.

<sup>96</sup> Hayhoe F G J, Hammouda F. (1965) Cytogenetic and metabolic observations in leukaemias and allied states, in Hayhoe F G J. (ed.) *Current Research in Leukaemia*. Cambridge: University Press.

<sup>97</sup> Nowell P C, Hungerford D A. (1960) A minute chromosome in human granulocytic leukemia. *Science* **132**: 1497. *idem* (1960) Chromosome studies on normal and leukemic human leukocytes. *Journal of the National Cancer Institute* **25**: 85–109.

<sup>98</sup> Caspersson T, Zech L, Johansson C, Modest E J. (1970) Identification of human chromosomes by DNA-binding fluorescent agents. *Chromosoma* **30**: 215–227. Caspersson T, Gahrton G, Lindsten J, Zech L. (1970) Identification of the Philadelphia chromosome as a number 22 by quinacrine mustard fluorescence analysis. *Experimental Cell Research* **63**: 238–240. Caspersson T, Lindsten J, Zech L, Buckton K E, Price W H. (1972) Four patients with trisomy 8 identified by the fluorescence and Giemsa banding technique. *Journal of Medical Genetics* **9**: 1–7.

<sup>99</sup> Rowley J D. (1973) Identification of a translocation with quinacrine fluorescence in a patient with acute leukemia. *Annales de Genetique* **16**: 109–112. See also Lindgren V, Rowley J D. (1977) Comparable complex rearrangements involving 8;21 and 9;22 translocations in leukaemia. *Nature* **266**: 744–745.

staining methods are available, with multiple FISH techniques that enable you to paint every individual chromosome a different colour and spot whether bits of it have gone here or there. This is the expanding contribution of cytogenetics to morphology.

Finally, the contribution of immunology to morphology followed when cytochemical immunological techniques became available to demonstrate the presence of particular surface antigens. The beginning of this was Mel Greaves's discovery of an antibody reacting with the common ALL surface antigen,<sup>100</sup> but of course in 1975 when César Milstein and Georges Köhler published their techniques for producing specific monoclonal antibodies, we then got a fantastic development.<sup>101</sup> I don't know how many monoclonals there are on the list at the moment, it must be at least 150 or 200 and many of these, perhaps 30 or so, are of importance to haematologists. With their use, demonstrable morphologically by techniques like the avidin–biotin peroxidase methods and the APAAP (alkaline phosphatase anti-alkaline phosphatase) technique, you can demonstrate what particular surface antigens there are in leukaemia cells.<sup>102</sup> Those are the main techniques in leukaemia morphology: panoptic staining, cytochemistry, cytogenetics and immunocytochemistry.

I'd like just briefly to mention and then to dismiss two other morphological techniques that have contributed in our lifetime. The first is phase contrast. I had a go at this in the late 1950s. The particular exponent of phase-contrast study of leukaemic cells in this country was Pulvertaft,<sup>103</sup> who was Professor of Pathology at the Westminster [Hospital, London]. In France, Dausset was working similarly on the subject and in Switzerland, Moeschlin. I looked at their analyses of case series studied by phase-contrast microscopy to see what proportion of monocytic cases they had found, which Pulvertaft had demonstrated to me

<sup>100</sup> See Brown G, Capellaro D, Greaves M. (1975) Leukemia-associated antigens in man. *National Cancer Institute* 55: 1281–1289. Brown G, Hogg N, Greaves M. (1975) Candidate leukaemia-specific antigen in man. *Nature* 258: 454–456. Greaves M F. (1979) Cell surface characteristics of human leukaemic cells. *Essays in Biochemistry* 15: 78–124. Ritz J, Pesando J M, Notis-McConarty J, Lazarus H, Schlossman S F. (1980) A monoclonal antibody to human acute lymphoblastic leukaemia antigen. *Nature* 283: 583–585.

<sup>101</sup> Köhler G, Milstein C. (1975) Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256: 495–497. See also Tansey E M, Catterall P P. (eds) (1997) Technology transfer in Britain: The case of monoclonal antibodies, in *Wellcome Witnesses to Twentieth Century Medicine*, vol. 1. London: The Wellcome Trust, 1–34.

<sup>102</sup> See, for example, Chechik B E, Rao J, Greaves M F, Hoffbrand A V. (1980) Human thymus/leukaemia-associated antigen (a low molecular weight form of adenosine diaminase) and the phenotype of leukaemic cells. *Leukemia Research* 4: 343–349. Newman R A, Sutherland R, Greaves M F. (1981) The biochemical characterization of a cell surface antigen associated with acute lymphoblastic leukemia and lymphocyte precursors. *Journal of Immunology* 126: 2024–2030.

<sup>103</sup> Pulvertaft R J V, Humble J C. (1956) Culture de moelle osseuse sur lames tournantes. *Revue d'Hématologie* 11: 349–377.

in his lab very beautifully. Dausset didn't find any among his analysed set, Moeschlin found 6 per cent, and Pulvertaft found 60 per cent, so it didn't look as though one was getting very much agreement on phase contrast.<sup>104</sup>

Finally, on to electron microscopy; a number of books have been written on the subject, particularly by Tanaka and Goodman, by Bessis and by John Cawley, and me.<sup>105</sup> Although electron microscopy has contributed in a valuable way to learning about the nature of the inclusions in leukaemic cells, I don't think it has been of very much importance in terms of classification.

**Goldman:** Thank you very much indeed, Frank; that has been very interesting. I think it leads almost straight on, because you dwelt for a while on monoclonal antibodies and other techniques that Danny Catovsky has exploited, so I think if we could hear Danny and then we will go on to David.

**Catovsky:** Thank you. Just an anecdote as it is an anecdotal day. I am a younger witness and I remember attending a meeting in Argentina on leukaemia, where Professor Hayhoe was speaking; I became a very great admirer of British haematology and that led me to come to this country. I was also a great admirer of his early book on leukaemia,<sup>106</sup> which I thought was a masterpiece with its illustrations, especially the cytochemistry. I think the greater masterpiece was his monograph that he quoted, resulting from the study from the Medical Research Council on classifying the acute leukaemias by cytochemistry. It was a small monograph, published by Her Majesty's Stationery Office in 1964.<sup>107</sup> I still regard it as a masterpiece on the way the things were analysed, and on the material from the UK trials. From that time on I became a very enthusiastic supporter of the value of morphology and the cytochemistry of leukaemia and was lucky to have landed at the Hammersmith when David Galton was there. In those days he also had a great interest in chronic lymphocytic leukaemia, which being a form of chronic leukaemia is substantially different from acute leukaemia.

At that time, John Dacie asked me to look at the myeloma cells that were in the same sort

<sup>104</sup> Dausset J. (1950) Essai de différenciation des diverses variétés de leucémies aignès par l'examen du sang et de la moelle à l'état frais. *Sang* 21: 610–622. Moeschlin S. (1957) Phase-contrast microscopy of leukocytes, in Rebeck J W, Bethell F H, Monto R W. (eds) *The Leukaemias, Aetiology, Pathophysiology and Treatment*. Henry Ford Hospital International Symposium. New York: Academic Books Ltd., 37–53.

<sup>105</sup> See Tanaka Y, Goodman J R. (1972) *Electron Microscopy of Human Blood Cells*. New York: Harper & Row. Bessis M. (1973) *Living Blood Cells and their Ultrastructure*. Berlin, Heidelberg, New York: Springer Verlag. Cawley J C, Hayhoe F G J. (1973) *Ultrastructure of Haemic Cells: A cytological atlas of normal and leukaemic blood and bone marrow*. London: W B Saunders.

<sup>106</sup> Hayhoe F G J. (1960) *Leukaemia: Research and Clinical Practice*. London: J & A Churchill Ltd. *idem* (1965) op. cit. note 96.

<sup>107</sup> Hayhoe F G J, Quagliano D, Doll R. (1964) op. cit. note 91.



of immunological pathway; David Galton had started an MRC trial in myeloma,<sup>108</sup> and a lot of slides and other material were coming through. That led me to study the immunological aspects. The best initial development on the lymphoid leukaemias was the distinction between malignant B- and T-cells [I think the first report in the *Lancet* was by Nossal, from Australia, who published a report showing that one type of lymphocyte had immunoglobulin on the surface.<sup>109</sup>] Then almost at the same time, or very shortly afterwards, people realized that another type of lymphocyte was forming rosettes with sheep erythrocytes.<sup>110</sup> Then we had to face up to the question of B- and T-cell malignancies. In effect this marked the beginning of the immunological definition of the lymphoid leukaemias, which was developed subsequently, as already mentioned, in the UK by Mel Greaves and George Janossy, and by other people in the USA. Sen and Borella published the first study recognizing T lymphoblastic leukaemia;<sup>111</sup> it's a very distinct form of childhood leukaemia in which the blast cells form rosettes with sheep erythrocytes. They realized that these leukaemias did not start in the marrow, because in these patients the blood counts, the haemoglobin and platelet counts were normal, and very often they had a mediastinal mass. Clearly it was with a sort of leukaemia/lymphoma starting in the thymus and apart from that the cells had very distinct characteristics. We became very excited at the time, and started looking at patients with high white counts with ALL. I remember going to see one of our immunologists at the Hammersmith at the time, but he was reluctant to embark on what he regarded as rather applied research. We managed to publish in the *British Medical Journal* on T lymphoblastic leukaemia; there were about four or five patients presenting with very high white counts.<sup>112</sup> I think one of them that I remember well was a young boy, one of your patients, David. We also realized that these patients were mainly teenagers who had developed the malignancy from their still present thymus. In the UK, the topic was further developed by Mel Greaves and George Janossy. They examined terminal transferase, the discovery of which was another major advance. In fact, McCaffrey discovered it and I think that Victor Hoffbrand got involved in the early demonstration of

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<sup>108</sup> Galton D A, Peto R. (1968) A progress report on the Medical Research Council's therapeutic trial in myelomatosis. *British Journal of Haematology* 15: 319–320. Galton D A. (1971) Treatment of myelomatosis – MRC trial. *British Medical Journal* ii: 323–324.

<sup>109</sup> Wilson J D, Nossal G J. (1971) Identification of human T and B lymphocytes in normal peripheral blood and in chronic lymphocytic leukaemia. *Lancet* ii: 788–791.

<sup>110</sup> See, for example, Stathopoulos G, Elliott E V. (1974) Formation of mouse or sheep red-blood-cell rosettes by lymphocytes from normal and leukaemic individuals. *Lancet* i: 600–601.

<sup>111</sup> Sen L, Borella L. (1975) Clinical importance of lymphoblasts with T markers in childhood acute leukemia. *New England Journal of Medicine* 292: 828–832.

<sup>112</sup> Catovsky D, Goldman J M, Okos A, Frisch B, Galton D A. (1974) T-lymphoblastic leukaemia: a distinct variant of acute leukaemia. *British Medical Journal* ii: 643–646.

the enzyme's existence in the thymus gland. After that one could recognize lymphoblastic leukaemia, where TdT or terminal transferase is positive and the myeloid leukaemias, where terminal transferase is negative.<sup>113</sup> That complemented the cytochemistry that was done earlier, because cytochemistry was very good in deciding which of the leukaemias were myeloid. The classification of the lymphoid leukaemias was not so specific at the time, but then the sheep erythrocyte rosettes, terminal transferase staining and the common ALL antigen allowed better classification of lymphoid leukaemias.

The other point that I want to mention is that, even with those advances with the B- and T-cell definitions and with cytochemistry, the classification of acute leukaemia was still very confusing. Each group had its own nomenclature and it became a problem of trying to reproduce a reliable classification of leukaemia as what would happen later in the field of lymphoma.

One anecdote. In 1975, I had a fortuitous meeting with David Galton and Claude Sultan, from Paris, and one of our American colleagues, John Bennett. It was decided to have a small group that would permanently or regularly meet to review the morphology of acute leukaemia. That group was the FAB (French–American–British) group. There were three French, Claude Sultan, George Flandrin and Marie-Thérèse Daniel, two Americans, John Bennett and Harvey Galnick, and two British, David Galton and myself. We started meetings where we just spent a week looking at slides down the microscope and discussing. The idea was not to change things, but gradually to try to move things forward. Although the FAB group did not change what the things were named, it defined them better and over the years people gradually adopted the FAB-proposed nomenclature.<sup>114</sup> This at least put a stop to the problem of calling the same thing by different names. One of the major achievements of the FAB group was that from 1976 onward they published about 12 papers; one of them became a citation classic,<sup>115</sup> because everybody quotes it. I think even now that this classification will be superseded by the new WHO classification.

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<sup>113</sup> Kung P C, Long J C, McCaffrey R P, Ratliff R L, Harrison T A, Baltimore D. (1978) Terminal deoxynucleotidyl transferase in the diagnosis of leukemia and malignant lymphoma. *American Journal of Medicine* 64: 788–794. Janossy G, Hoffbrand A V, Greaves M F, Ganeshaguru K, Pain C, Bradstock K F, Prentice H G, Kay J E, Lister T A. (1980) op. cit. note 118. Janossy G, Tidman N, Bradstock K F, Hoffbrand A V, Bollum F J. (1982) Terminal transferase positive cells in the human bone marrow and thymus. *Advances in Experimental Medicine and Biology* 145: 161–176.

<sup>114</sup> Bennett J M, Catovsky D, Daniel M T, Flandrin G, Galton D A, Galnick H R, Sultan C. (1976) Proposals for the classification of the acute leukaemias. French–American–British (FAB) Co-operative group. *British Journal of Haematology* 33: 451–458.

<sup>115</sup> op. cit. note 114. See also Bennett J M, Catovsky D, Daniel M T, Flandrin G, Galton A G, Galnick H R, Sultan C. (1981) French–American–British (FAB) Co-operative Group: The morphologic classification of acute lymphoblastic leukaemia: Concordance among observers and clinical correlations. *British Journal of Haematology* 47: 553–561.

**Goldman:** Just one question. What other diseases has the FAB group concentrated on apart from the acute leukaemias?

**Catovsky:** Acute leukaemias first and then later on in, I think, the 1980s, it produced a classification of the chronic lymphoid leukaemias,<sup>116</sup> and myelodysplasia as well. Just as the group was fading away, one of the latest papers was on the CMLs. One of the major achievements, and I have to agree here with Frank Hayhoe, was that the cytogenetics came in more or less as these things were developing and then we, the FAB group, started having meetings with cytogeneticists. I remember attending several of the chromosome workshops again in the 1970s with cytogeneticists, who were correlating cases and karyotypes, meanwhile we morphologists were looking at the slides without knowing the karyotype. It became apparent in some of these early studies that some of the leukaemias had very distinct chromosome abnormalities. Promyelocytic leukaemia was very clearly shown to have the t(15;17) translocation and so on. The rest is recent history.

**Hoffbrand:** Since 1972 we had been measuring the immediate DNA precursors, the deoxynucleotide triphosphates, in human blood and bone marrow cells. We set up the assays at the Hammersmith Hospital in order to explore the DNA defect in megaloblastic anaemia.<sup>117</sup> We realized, after the publications of Fred Bollum, Mary Coleman and John Hutton, that we could adapt the assay to measure terminal deoxynucleotidyl transferase (TdT). Dr K Ganeshaguru established the TdT assay at the Royal Free Hospital in 1974. Fairly soon after that Professor George Janossy joined the Department.<sup>118</sup> We realized that with a combination of different immunological markers and the TdT biochemical assay, we could further characterize the acute leukaemias.<sup>119</sup> The combination of these tests with measurement of the transcobalamins, and Danny Catovsky's cytochemical and lysozyme

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<sup>116</sup> Bennett J M, Catovsky D, Daniel M T, Flandrin G, Galton D A, Gralnick H R, Sultan C. (1989) Proposals for the classification of chronic (mature) B and T lymphoid leukaemias. French–American–British (FAB) Cooperative Group. *Journal of Clinical Pathology* 42: 567–584.

<sup>117</sup> Hoffbrand A V, Ganeshaguru K, Lavoie A, Tattersall M H N, Tripp E. (1974) Thymidylate concentration in megaloblastic anaemia. *Nature* 248: 602–604.

<sup>118</sup> Professor Victor Hoffbrand wrote: 'He had worked with Mel Greaves on characterization of leukaemic cells by immunological markers.' Note on draft transcript, 27 February 2002. See, for example, Janossy G, Hoffbrand A V, Greaves M F, Ganeshaguru K, Pain C, Bradstock K, Prentice H G, Kay H E M, Lister A. (1980) Terminal transferase enzyme assay and immunological membrane markers in the diagnosis of leukaemia – a multi-parameter analysis of 300 cases. *British Journal of Haematology* 44: 221–234.

<sup>119</sup> Hoffbrand A V, Ganeshaguru K, Janossy G, Greaves M F, Catovsky D, Woodruff R K. (1977) Terminal deoxynucleotidyl-transferase levels and membrane phenotypes in diagnosis of acute leukaemia. *Lancet* ii: 520–523.

assays also enabled characterization of the myeloproliferative diseases.<sup>120</sup> These studies, together with those of other groups, led to an increased understanding of the origin and nature of the leukaemic cell. One study showed close similarities between leukaemic cells and normal cells at similar stages of development.<sup>121</sup> They also showed subtle variations between leukaemic and normal cells, for example, cross-expression of myeloid and lymphoid markers. They also revealed the ontogeny of leukaemia cells and the cell from which each type of leukaemia appeared to arise. The combined tests revealed new subtypes of acute and chronic leukaemia. The use of combinations of markers also provided the first accurate tests for minimal residual disease (MRD) in patients in remission.<sup>122</sup> With Ken Bradstock, work was done which made possible the detection of a single residual leukaemia cell, for example, a bone marrow cell expressing both CD3 and TdT when the patient was in clinical and morphological remission of T-ALL.<sup>123</sup> This association with Mel, Danny, and George Janossy was extremely productive.

**Galton:** May I just follow on from Daniel, to pay tribute to the late Claude Sultan, whom he mentioned, because it was Claude who persuaded us of the necessity for having a group that turned out to be the FAB group?<sup>124</sup> The point is that Claude had travelled and spent

<sup>120</sup> See Catovsky D, De Salvo Cardullo L, O'Brien M, Morilla R, Costello C, Galton D, Ganeshaguru K, Hoffbrand V. (1981) Cytochemical markers of differentiation in acute leukaemia. *Cancer Research* 41: 4824–4832. Professor Victor Hoffbrand wrote: 'George Janossy and Ken Bradstock then introduced the immunological detection of TdT. This made detection of nuclear TdT in conjunction with cytoplasmic and membrane immunological tests effective for single cell analysis.' Note on draft transcript, 27 February 2002.

<sup>121</sup> Bradstock K F, Janossy G, Pizzolo G, Hoffbrand A V, McMichael A, Pilch J R, Milstein C, Beverley P, Bollum F J. (1980) Subpopulations of normal and leukaemic human thymocytes: An analysis with the use of monoclonal antibodies. *Journal of the National Cancer Institute* 65: 33–42.

<sup>122</sup> Bradstock K F, Pizzolo G, Papageorgiou E S, Cetto G L, Prentice H G, Ganeshaguru K, Prentice A G, Smith A, Chilosi M, Ambrosetti A, Hoffbrand V. (1981) Terminal transferase expression in relapsed acute myeloid leukaemia. *British Journal of Haematology* 49: 621–627. Freireich E J, Cork A, Stass S A, McCredie K B, Keating M J, Estey E H, Kantarjian H M, Trujillo J M. (1992) Cytogenetics for detection of minimal residual disease in acute myeloblastic leukemia. *Leukemia* 6: 500–506.

<sup>123</sup> See, for example, Bradstock K F, Papageorgiou E S, Janossy G, Hoffbrand A V, Willoughby M L, Roberts P, Bollum F J. (1980) Detection of leukaemic lymphoblasts in CSF by immunofluorescence for terminal transferase. *Lancet* i: 1144. Professor Victor Hoffbrand wrote: 'These were, therefore, the first tests which could detect disease at levels as low as 1 in 10<sup>3</sup> or 1 in 10<sup>4</sup> normal cells. There was a good correlation between a positive test for MRD in the bone marrow and subsequent relapse and negative test and continuing remission. These new tests also could reveal extramedullary disease when morphology alone failed to distinguish a malignant cell from a normal lymphocyte. For instance, the presence of a cell expressing TdT in cerebrospinal fluid could be definitely identified as leukaemic in a patient with ALL.' Note to Dr Daphne Christie, 27 February 2002.

<sup>124</sup> Professor David Galton wrote: 'The FAB group's first work was on the acute leukaemias, and the classification the group proposed for the acute myeloid leukaemias was based on that adopted for the analysis of the patients admitted to MRC Trials 4 and 5, and was devised by J V Dacie and D A G Galton.' Note on draft transcript, 29 November 2002. op. cit. note 114.

several months in various institutions in the USA and, of course, at the Hammersmith. He spent quite a lot of time with us at Hammersmith, and he was struck by the fact that we were all seeing the same cells but naming them in a different way. Frank pointed out that there were many differences, even in neighbouring states in the USA, in the way they were naming cells. Claude was particularly worried about the definition of a blast, because blast cells were defined in totally different ways in the USA, in France, and in the UK,<sup>125</sup> and he asked, ‘What’s the use of trying to compare the results of treatment in various series, from different countries, when you don’t know what they are treating?’ It was as simple as that. That persuaded the FAB group to get on with it, and I think that Claude played an enormously important part there.

Another point. Daniel was talking about the Sternberg lymphoma, the T lymphoblastic disease beginning in the thymus that used to be the province of radiotherapists, because radiotherapy worked like magic – after a few hundred rads the tumour disappeared, you see, but after a few months these young people always came back with a leukaemia. At that stage they were sent to us, and we tried to persuade the radiotherapists that they shouldn’t start with radiotherapy, because while they were irradiating the chest the cells were spreading to the bone marrow and so on. I don’t know quite how we persuaded them to let us have a new patient or two, but in the end we found that with chemotherapy you could get better results, although of course they weren’t all that good.

The last point relates to Frank’s mention of cytogenetics. I wonder whether people realize just how the Philadelphia chromosome was discovered and why it was called Philadelphia chromosome. There was a very busy MRC Cytogenetics Group in Edinburgh, headed by Bill Court Brown. One of the people he had working there was Patricia Jacobs. At that time the Unit as a whole was studying inherited conditions with chromosome abnormalities. That was all in the air, but they had also been looking at some malignant cases, and she was studying CML. She had six cases, in which she had noticed a tiny chromosome looking something like the Y, and she realized these needed careful study, but there was immense pressure at that time for the Unit to publish work on the inherited chromosome abnormalities. So she put the slides in a drawer, meaning to get on with it in about six months’ time. Unfortunately, a short paper from Nowell and Hungerford [from Philadelphia], describing this chromosome, appeared in *Science* before she had time to look at them again.<sup>126</sup> Patricia was immediately

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<sup>125</sup> Professor David Galton wrote: ‘It was hoped that if the recommendations were generally accepted and the published definitions were used, there would be uniformity in the diagnosis of the different diseases instead of the chaotic muddle prevailing. It wasn’t a question of “right or wrong” but just a way of ensuring that we were all describing what we say in the same way.’ Note on draft transcript, 29 November 2002.

<sup>126</sup> Nowell P C, Hungerford D A. (1960) op. cit. note 97.

able to correct one of their findings, because they only had two cases, both males, and they thought it was an abnormal Y, but she had some males and females in her collection, and she knew it couldn't be a Y. She gave them the credit for the first description by naming it Philadelphia chromosome.<sup>127</sup>

**Goldman:** It was, in fact, named Ph<sup>1</sup> in recognition of the probability, the thought that there would be further specific abnormalities.

**Galton:** She thought this would be the first of many.

**Goldman:** Let me give you a personal point of view about the topic that I know too well, perhaps, and others in the room, but not everybody, also know very well and that is to take up the story of the Philadelphia chromosome and end with STI571 (imatinib), which was licensed for clinical use on Thursday of last week.<sup>128</sup>

The story for me starts, I think it was 1974, when I was attending a meeting in Poitiers on the involvement of chromosomes 9 and 22 in leukaemia.<sup>129</sup> The stars present were, of course, Janet Rowley, Joseph Tanzer and Sven-Åge Kilmann. I remember very well Sven-Åge Kilmann saying to Janet Rowley deliberately, directly to her, 'You are going nowhere, you are just stamp collectors', a famous statement directed at the cytogeneticists in those days, but of course she wasn't just stamp collecting at all.

I think the next important development in that story was the publication in 1984 of a paper from Grosveld's group in Rotterdam on the BCR [breakpoint cluster region], which was the clustered breakpoint in 19 different patients with CML.<sup>130</sup> He, Groffen and Heisterkamp showed very elegantly that the breakpoint on the Philadelphia chromosome in different patients with CML was clustered in the 5.8 kb region.

The next five years was a period of very exciting and rapid development that David and others will remember well, with the characterization of first the juxtaposition of the ABL protooncogene with the BCR sequences and then the characterization of the BCR gene.

<sup>127</sup> Tough I M, Court Brown W M, Baikie A G, Buckton K E, Harnden D G, Jacobs P A, King M J, McBride J A. (1961) Cytogenetic studies in chronic myeloid leukaemia associated with mongolism. *Lancet* i: 411–417.

<sup>128</sup> Gleevec (imatinib mesylate), formerly known as STI571, was approved by the FDA in May 2001. Further details can be found at [www.centerwatch.com/patient/drugs/dru699.html](http://www.centerwatch.com/patient/drugs/dru699.html) (site accessed 29 October 2002). See also Habeck M. (2002) FDA licences imatinib mesylate for CML. *Lancet Oncology* 3: 6. Radford I R. (2002) Imatinib. Novartis. *Current Opinion in Investigational Drugs* 3: 492–499.

<sup>129</sup> See Van den Berghe H. (1973) The Ph1-chromosome: translocation to chromosome 9. *Lancet* ii: 1030–1031. Nowell P C, Jensen J, Gardner E. (1975) Two complex translocations in chronic granulocytic leukemia involving chromosomes 22, 9, and a third chromosome. *Humangenetik* 30: 13–21.

<sup>130</sup> Groffen J, Stephenson J R, Heisterkamp N, de Klein A, Bartram C R, Grosveld G. (1984) Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. *Cell* 36: 93–99.

In 1986 I spent a period in the Whitehead Institute for Biomedical Research that is attached to Massachusetts Institute of Technology in Cambridge, Massachusetts. There was a young PhD student who was an extremely enthusiastic student of David Baltimore's, and his project, which seemed at the time ambitious but still completable, was to put the BCR-ABL fusion gene into murine haemopoietic stem cells, murine progenitor cells, and so to simulate CML in mice. George Daley's paper, as some will know, was published in *Science* in 1990,<sup>131</sup> and I think for almost everybody, it set the seal on the belief, or the conviction, that the BCR-ABL fusion gene was the proximate cause, the major cause, of the chronic phase of CML.

A lot of 'i's were dotted and 't's were crossed in the next ten years and it is certainly not appropriate to go through all the many pieces of additional data that accumulated, but round about 1995, an ex-colleague of mine, whom Ray Powles will probably remember, John Ford, called me up to say they had a new compound that was active in blocking the kinase activity of the ABL protooncogene and, 'Was I interested in studying it?' I said, 'Yes', without any hesitation. Meanwhile, Brian Druker in Oregon had worked together with the chemists at Ciba Geigy to develop this compound and published in 1996 that it was very good at suppressing the survival of CML cell lines and CML progenitor cells *in vitro*.<sup>132</sup> In 1998 this compound entered clinical practice in the USA as treatment for CML. Initially, I think many people, including Brian Druker, were highly dubious as to whether it would have any effect. In the event, it has proved over the last 18 months that the administration to patients of this compound that was made by Ciba Geigy in the early 1990s is highly effective, given by mouth, at inducing haematological control in patients with CML and in more than 50 per cent it induces a major or complete chromosome remission.<sup>133</sup> It is much better than alpha-interferon in those regards and, of course, it's much less toxic.

The new pharmaceutical company, Novartis,<sup>134</sup> submitted papers for registration in the USA to the FDA in February of this year; they submitted to the European authorities at the

<sup>131</sup> Daley G Q, Van Etten R A, Baltimore D. (1990) Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. *Science* 16: 824-830.

<sup>132</sup> Druker B J, Tamura S, Buchdunger E, Ohno S, Segal G M, Fanning S, Zimmermann J, Lydon N B. (1996) Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nature Medicine* 2: 561-566.

<sup>133</sup> Druker B J, Talpaz M, Resta D J, Peng B, Buchdunger E, Ford J M, Lydon N B, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers C L. (2001) Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *New England Journal of Medicine* 344: 1031-1037.

<sup>134</sup> Novartis was created in 1996 from the merger of Ciba and Sandoz. See [www.novartis.com](http://www.novartis.com) (site accessed 7 February 2003). See also Lee K, Spufford N G. (1993) *Portrait of a foundation: a brief history of the Ciba Foundation and its environment*. London: Ciba Foundation.



same time, and about four days ago, Thursday of last week, the FDA formally announced that it had approved the use of STI571 [signal transduction inhibitor] for treatment of CML.<sup>135</sup> This is thought to be the most rapid licensing of any drug in oncology by the FDA within the last 25 years. ASCO, which is usually a moderately boring meeting, today was apparently transformed by the news of the STI licensing. So what's the moral of the story? The moral of the story simply is that here is a very elegant example of the translation of our understanding of what is literally the molecular biology of a form of leukaemia into therapy. There are other examples I know, such as the use of all-*trans*-retinoic acid for treatment of M3 acute leukaemia, the targeting of other kinases and I think there are other good examples, but possibly none as elegant as the one I have just recounted. I think there is little doubt in my mind, let me rephrase that, I very much hope that as we enter the twenty first century, we will see the end of the era of non-specific cytotoxic drugs designed to cure leukaemia – and they have undoubtedly been effective to some degree in that regard – and we will see the innovation, the instigation, of the era of so-called targeted molecular therapy for leukaemia. That was just a sort of personal reminiscence really. I have had the privilege of being a close observer and have been involved to a minor extent in this story, and it's been great fun. I don't think that needs a discussion unless anybody else has something to add particularly on that topic. It's not even proper history – it's recent history rather than distant history.

**Hunter:** Just one very small ethical note to say about that. Novartis has announced that the drug is called Gleevec or Glivec,<sup>136</sup> according to which side of the Atlantic you are on, and they are going to market it, pricing it according to the financial means of the patient being treated.

**Goldman:** We want to switch our attention now. We have talked a little bit about children, but I want to return to ALL in children. I am going to ask John Lilleyman to open and then I think Humphrey Kay would like to make some comments.

**Professor Sir John Lilleyman:** Thank you very much, John. I have to say it's an increasingly rare pleasure for me to attend any meeting where I don't skew the average age upwards, and I do feel a very junior witness here since I have only been in this game for just over 30 years, and therefore you will have to forgive me. Talking about the history of childhood leukaemia and the treatment of it means that we have to look back over 50 years. So for the first two decades of this, I am going to have to ask Humphrey, who is my mentor, to mark me out of ten and correct me where I go wrong. I am not going to talk about it very much because I hope he's going to fill in the gaps. We are talking about the history of the treatment of childhood leukaemia in the UK. We have first of all to be clear that we are talking about

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<sup>135</sup> op. cit. note 128.

<sup>136</sup> The drug is marketed as Gleevec (imatinib mesylate) in the USA, and Glivec (imatinib) outside the USA.



the treatment of ALL, a rather irritating tautology, since there's no chronic lymphoblastic leukaemia, but by common practice and usage that's what we call it. This, of course, accounts for some 80 per cent of all childhood leukaemias and is the most common malignant disease in children between the ages of 1 and 10. It's an extraordinary story, the treatment of childhood ALL, and it begins with the seminal publication we have already discussed by Farber and colleagues on the use of aminopterin in 1948.<sup>137</sup> The year 1948 was also important in this country, because it marked the establishment of the National Health Service, which also has had an influence on the development in this country of treatment of malignant disease in general, and childhood leukaemia in particular. If we take the five decades, these are quite useful chunks of time for us to look at the various stages of the evolution of the treatment of childhood leukaemia. We have to start by saying that before 1948 there was little treatment, I won't say nothing, in the way of treatment, because of course there were always transfusions and antibiotics available at least from the mid-1930s onwards.<sup>138</sup> To find what actually happens to children when you do absolutely nothing, you have to go further back than that, and the earliest case report that I have found is in the *Lancet* in 1884.<sup>139</sup> I presume that case reports in the *Lancet* even in those days were fairly unusual cases, so this must have been fairly remarkable for its time. It describes a five-and-a-half-year-old boy who's admitted with fever and pallor, and tachypnoea. He didn't have organomegaly that they could discover and his history was of gradual onset over six weeks. He survived for only 11 days following his admission into hospital and he got increasingly unwell with pallor and tachypnoea. The fascinating thing about this is that his blood was examined three days before he died, and the only comment in this case report is that there were three white corpuscles for every one red corpuscle. Just to save you the agonizing mental arithmetic, I looked at this and of course you don't know what his white count is, but assuming it was, say, as high as a million, that would mean that his haemoglobin would be of the order of 1g/dL when he actually perished. That's what happens if you do nothing. Children die within a few weeks. They die in about three months if you support them with transfusions and antibiotics and, of course, now we have reached the stage where if you take all children with ALL, the long-term event-free survival for the whole group, would be of the order of 70 per cent.<sup>140</sup> We have gone from that to that in 50 years. The original paper by Farber actually studied 16 children, and it must have been remarkable at the time to be around to see

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<sup>137</sup> *op. cit.* note 11.

<sup>138</sup> Tivey H. (1954) The natural history of untreated acute leukemia. *Annals of the New York Academy of Sciences* 60: 322–358.

<sup>139</sup> A Mirror of Hospital Practice, British and Foreign. (1884) St George's Hospital. Case of leucocythaemia in a child aged five years and a half. *Lancet* i: 158–159. See also Piller G J. (1992) *The history and presentation of leukaemia, 1845–1960*. PhD thesis. Open University.

<sup>140</sup> 70 per cent with probable full-life expectancy.

the effect that it had, where it describes moribund individuals going into complete remission. STI571, as we have just heard, is pretty dramatic, but this must have been even more dramatic. Yet doctors were severely criticized for meddling with children who would all relapse and die eventually and so the ethical debate went on for quite a long time. Paediatricians are a fairly conservative bunch generally, particularly in the UK, and they were fairly slow to take up the challenge to treat children with this condition, particularly when the word ‘cure’ hadn’t come into the debate, and didn’t come into the debate for some years after that.

There were one or two interesting diversions and I don’t know whether they were British or not, but I came across an interesting article that, of course, is historical for me; it may actually be contemporary for others, certainly David Galton perhaps, as I think he was in the original group.<sup>141</sup> There was an MRC group that looked at the use of ACTH and cortisone in various blood diseases. I think they took 88 patients with a miscellany of blood disorders that were taken at random out of any haematology textbook and gave them ACTH or cortisone, of whom 20 were children with acute leukaemia. Of those I think four were noted to have some response, and I think that might have been one of the very earliest descriptions of the response of childhood leukaemia to steroids.<sup>142</sup>

The next most seminal publication after the 1948 Farber paper was probably the 1953 Burchenal paper, looking at 6-MP, which had been developed by Gertrude Elion and George Hitchings, and for which they got a Nobel Prize.<sup>143</sup> That, of course, gave us three very useful drugs: the folic acid antagonists, the purine analogues and steroids. Then the vinca alkaloids came in towards the end of the 1950s. The interesting thing about the vinca alkaloids was that they came in around the time that there was this huge burst of scientific clinical activity at the National Cancer Institute, where they noted that if you gave

<sup>141</sup> Professor David Galton wrote: ‘No, I was not, but I remember the work well.’ Note on draft transcript, 3 March 2002.

<sup>142</sup> Pearson O H, Eliel L P, Rawson R W, Dobriner K, Rhoads C P. (1949) ACTH- and cortisone-induced regression of lymphoid tumors in man. A preliminary report. *Cancer* 2: 943–945. Farber S, Schwachman H, Toch R. (1950) The effect of ACTH in acute leukemia in childhood, in Mote J R. (ed.) *Proceedings of the First Clinical ACTH Conference*. Philadelphia: Blakiston, 328–330. See also Pearson O H, Eliel L P. (1950) Use of primary adrenocorticotrophic hormone (ACTH) and cortisone in lymphomas and leukemias. *Journal of the American Medical Association* 144: 1349–1353.

<sup>143</sup> Elion G B, Hitchings G H, van der Werff H. (1951) Antagonists of nucleic acid derivatives. VI. Purines. *Journal of Biological Chemistry* 192: 505. Elion G B, Burgi E, Hitchings G H. (1952) Studies on condensed pyrimidine systems. IX. The synthesis of some 6-substituted purines. *Journal of the American Chemical Society* 74: 411–414. op. cit. note 18. Burchenal J H, Ellison R R, Murphy M C, Karnofsky D A, Sykes M P, Tan T C, Mermann A C, Yuceoglu M, Myers W P L, Krakoff I, et al. (1954) Clinical Studies on 6-mercaptopurine. *Annals of the New York Academy of Sciences* 60: 359–368. *idem* (1954) Clinical evaluation of 6-mercaptopurine in treatment of leukemia. *American Journal of the Medical Sciences* 228: 371–377.

vincristine with the myelotoxic drugs that we had been using so far, you didn't get synergistic myelotoxicity, but you did get synergistic tumour toxicity. This was the birth of combination chemotherapy.<sup>144</sup> The history of the treatment of childhood leukaemia is written large in the annals of oncology in general.

Of course, platelets came in towards the end of the first decade. If we are talking about 1950–1960, the very first reports of platelet transfusion did creep in at the end of that time.<sup>145</sup>

I think the position of the UK in the first decade was mostly to watch the Americans, and not doing much, but there were one or two children who were treated with the single agents around at that time who are long-term survivors to this day. Most units that dabbled in this have got such patients, although, as we have heard earlier, the diagnosis might have been wrong. In fact, where you can go back and look at this, the diagnosis was usually right. There have been one or two patients who have had very late relapses, where the disease is clearly the same as it was at diagnosis. I do remember one of the first patients that I became involved with, who had been looked after by Professor Ronald Illingworth, a paediatrician of some renown in his day. He treated this boy with daily oral methotrexate for about ten years, because no one knew when to stop – there were no guidelines. Eventually he did stop, the boy was well and his leukaemia never came back, but he eventually died in his early 20s of oesophageal bleeding from fibrosis of the liver, probably induced by the methotrexate, so that was a bitter–sweet story.

Going into the 1960s and 1970s, the next major milestone as we have already heard was the St Jude's story: Don Pinkel's vision to come up with this idea of total therapy by looking at all the nooks and crannies, getting the disease to go away, consolidating it, and then the inspirational stroke of giving maintenance chemotherapy.<sup>146</sup> Maintenance chemotherapy is a peculiar notion; it flies in the face of all basic oncological principles and the strange thing about the commonest type of lymphoblastic leukaemia is that for some reason it needs a long prolonged phase of this basically immunosuppressive chemotherapy. Nobody quite understands what this therapy is doing, but Pinkel's original rationale was based on the observation of tuberculosis and the idea that the cycling time of the leukaemic blast cell was roughly analogous to the tubercle bacillus, and so the notion of giving maintenance chemotherapy was based entirely on this idea of long-term chemotherapy for

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<sup>144</sup> See, for example, Keating P, Cambrosio A. (2002) From Screening to clinical research: The cure of leukemia and the early development of the cooperative oncology groups, 1955–1966. *Bulletin of the History of Medicine* 76: 299–334.

<sup>145</sup> op. cit. note 72.

<sup>146</sup> See Pratt C B, James D H, Holton C B, Pinkel D. (1968) Combination therapy including vincristine (NSC67574) for malignant solid tumours in children. *Cancer Chemotherapy Report* 52: 489–495. Pinkel D. (1987) Curing children of leukemia. *Cancer* 59: 1683–1691.

tuberculosis.<sup>147</sup> Whatever his reasoning, he did the right thing at the right time, and as I say, childhood ALL to this day remains the only human malignancy that I am aware of where this type of therapy is not only effective but essential. I think it was dear old Tim McElwain<sup>148</sup> who said that the worst way to treat cancer is to dribble in little bits of chemotherapy over a long period of time, which is precisely what you do when you treat childhood ALL with maintenance treatment. So what that's doing, we really don't know.

We started at this time to have some ideas of our own in the UK and we have heard about the Concord trial that was a joint Anglo–French venture run by the increasingly popular MRC-based UK group and the French.<sup>149</sup> This was slightly less successful, perhaps, than the aeroplane, with which it was co-named, because that was being designed at about the same time. Humphrey will correct me if I am wrong, but it did one very useful thing. It highlighted something that hadn't been focused on, and that is maintenance treatment; because it was a three-way randomization for immunization versus nothing, versus maintenance, it was possible to show that it was, above all, maintenance that made a lot of difference and improved things. Giving immunotherapy and giving nothing was about the same. There are very few randomized trials that actually show the effect of maintenance treatment. The only other data on this came from the West German group much later on, where they tried to drop maintenance. Most of the children relapsed, and as they were perhaps ashamed of it, they never actually published it. But that's another story.<sup>150</sup>

That takes us to the 1970s and 1980s, and I am getting onto slightly more comfortable ground here, because I am talking more from personal experience now, so Humphrey can relax a little bit. This was the sort of zenith, I suppose, of the MRC working party that was very much led by Humphrey as Secretary, although he never chaired it, as far as I recollect. There was Professor Hutchinson first of all; then there was Roger Hardisty, and then I think Tim McElwain after Roger. Humphrey was the driving force behind it and under his stewardship we launched the series of UKALL trials.<sup>151</sup> They were based on the St Jude template and they were trying the

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<sup>147</sup> Pinkel D. (1971) Five year follow up of 'total therapy' of childhood lymphocytic leukemia. *Journal of the American Medical Association* 216: 648–652.

<sup>148</sup> Professor Sir John Lilleyman wrote: 'Tim McElwain was latterly Professor of Medical Oncology at the Royal Marsden Hospital.' Note on draft transcript, 26 November 2002.

<sup>149</sup> Leukaemia Committee and the Working Party on Leukaemia in Childhood. (1971) Treatment of acute lymphoblastic leukaemia. Comparison of immunotherapy (BCG), intermittent methotrexate, and no therapy after a five-month intensive cytotoxic regimen (Concord Trial). Preliminary report to the Medical Research Council. *British Medical Journal* 281: 189–194. See also page 58.

<sup>150</sup> Jorg Ritter. (1993) Personal communication. See Schellong G, Creutzig U, Ritter J. (1985) Treatment of acute myelogenous leukemia in children. *Medical Oncology and Tumor Pharmacotherapy* 2: 17–25.

<sup>151</sup> Professor Sir John Lilleyman wrote: 'This series of trials was published under the authorship of the Medical Research Council Childhood Leukaemia Working Party from 1970 to 1990.' Note on draft transcript, 26 November 2002.

addition of this, or the subtraction of that, but during the 1970s we had UKALL I, II, III, IV intensive, V, and VII.<sup>152</sup> We had quite a lot of trials, but not huge numbers of patients, and we learnt quite a lot about how best to give maintenance therapy. We learnt that alkylating agents didn't seem to offer very much in routine therapy. We did notice that boys didn't do as well as girls, which sent us off down a blind alley for a long time, thinking that the testis was a sanctuary site and we had to do something with it, like irradiate it. But I digress.

Taking us to the 1980s very quickly. What was happening at this time was that whilst we were getting organized and getting children into centralized randomized clinical trials in the best traditions of the MRC, the results that we were getting weren't quite matching up to those that were being obtained overseas by apparently similar protocols. This puzzled and worried us. So what we did in 1980 was to take a Children's Cancer Group (CCG) protocol from the USA, word for word, comma for comma, and applied it in the UK simultaneously, with the cooperation of the CCG. The first thing that we noticed was that it was much, much more toxic than anything we had used before, despite the fact that on paper it looked very similar. The reason was that the protocol was much more prescriptive and did not allow the clinician the freedom to stop treatment when children got a little bit poorly. We pressed on and I have to say that we did lose some children, because we weren't aware of the toxic side effects of this treatment, but once we got the hang of it, we produced the biggest single increase in overall event-free survival in this country. It was about a 20 per cent jump from the previous cohort studies to this one, UKALL VIII, that ran from 1980–1985.<sup>153</sup> We have never explained the reason for that jump, but we suspect it's something to do with physician compliance with the protocol and sustained chemotherapy, both in the consolidation phases and the maintenance phases, but that's still an open question. The West Germans were producing much better results than we were, although they weren't doing it on a randomized trial basis – they were just doing cohort studies and producing better overall survival figures than anybody else, and in the sort of Teutonic way that they have, were saying, 'This is how you should all do it'. Eventually they persuaded people, their theories were put to the test of the randomized trial by both by the Americans and us, and we confirmed that what they said was correct while they just sat there with their arms folded and said, 'Well, we told you so'.

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<sup>152</sup> Report to the Council by the Working Party on Leukaemia in Childhood. (1986) Improvement in treatment for children with acute lymphoblastic leukaemia: the Medical Research Council UKALL Trial, 1972–1984. *Lancet* i: 408–411.

<sup>153</sup> Eden O B, Lilleyman J S, Richards S, Shaw M P, Peto J. (1987) Medical Research Council Childhood Leukaemia Trial VIII compared with trials II–VII: lessons for future management. *Hamatologie und Bluttransfusion* 30: 448–455. *idem* (1991) Results of Medical Research Council Childhood Leukaemia Trial UKALL VIII (report to the Medical Research Council on behalf of the Working Party on Leukaemia in Childhood). *British Journal of Haematology* 78: 187–196.

But now what's happening since the results of treatment of all groups are improving, is that it's getting increasingly difficult to be confident about a real improvement in outcome, and so the randomized trial is actually having a renaissance and, not only that, we are having to look to international collaboration to get the numbers of patients to achieve the statistical power to answer the current questions that remain. We have still got a long way to go, but, as I say, overall survival ever since chemotherapy began has never been zero, but 5, 10 per cent, even, with single-agent therapy, 20 per cent with the early combined therapies, through 30, 40, 50 per cent, and we are now somewhere up at 60–70 per cent. We have caught up with the rest of the world in terms of our results in the UK. We are not ahead of the game, as we are with childhood AML, but that's another story that I haven't got time to go into. For childhood ALL, we are now all at the same level, looking to international collaboration. The MRC Childhood Leukaemia Working Party played a very pivotal part in that and pivotal to that working party was Humphrey Kay, who will now comment.

**Goldman:** Before we go to Humphrey I have one question. Peter Hunter, do you want to comment on 6-MP, because John did mention it briefly?

**Hunter:** Briefly, I feel the intellectual background behind the discovery of the antileukaemic action of 6-MP in 1952, should be mentioned. In 1940, two ground-breaking papers by British experimental pathologists appeared and established that the antibacterial action of sulphanilamide was due to a blocking effect on bacterial multiplication, caused by competition with 'an essential growth factor', para-amino benzoic acid (PABA). Sulphanilamide and PABA had closely similar but subtly different structures, i.e. they were analogues. Paul Fildes suggested that the drug might occupy the substrate binding site on an enzyme and prevent the enzyme from functioning. The Woods and Fildes's hypothesis suggested that a rational approach for research in chemotherapy would be to synthesize analogues to specifically targeted molecules. This idea was taken up in 1942 at Burroughs Wellcome in Tuckahoe by George Hitchings. His remarkable research strategy used the Woods and Fildes's hypothesis but focused it on analogues of the purine and pyrimidine constituents of DNA. The system that he chose to detect biological effects of these analogues, was a culture of *Lactobacillus casei*. By 1951 his colleague Dr Trudy Elion had synthesized and tested over 100 purine analogues. This led them to try 6-MP as an appropriate animal disease model at the Sloan Kettering Institute, where they had been cooperating with Rhoads since 1947. 6-MP was found to be of high efficacy and relatively low toxicity. Regarding the financial mechanisms that facilitated 6-MP's discovery, it is interesting that their laboratory was for many years partly financed by the Sloan Kettering Institute, despite the fact that it was in Burroughs Wellcome American research headquarters.<sup>153a</sup>

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<sup>153a</sup> Much of this work is described in detail with references in a letter from Dr Peter Hunter to Dr Daphne Christie, dated 31 January 2003, which will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

**Goldman:** Now we rely on the reverse – drug companies funding hospitals. Humphrey, let's return to children's ALL.

**Kay:** Can we start at the late 1960s, when we had created, at the newly built Marsden Hospital at Sutton, a new unit where it was possible to give intensive treatment and hope that the patients wouldn't get infected, and we could give them platelets and so on? At that point, we were visited by Leslie Witts, who had been in charge of the MRC trials, and had despaired of getting a childhood leukaemia trial going. The reason for that, looking back, was very clear. It was a subject that was one of rapid progress and unless you had a lot of patients in your intake, you couldn't complete a sufficient number before people wanted to do something different, as indicated elsewhere. In order to get a sufficient number of patients, we more or less had to cover the whole of the UK, and it was quite easy as a matter of fact, through persuasion and diplomacy, to induce most of the major centres throughout England, Wales, Scotland and Northern Ireland to put their patients into an established protocol. There were various ideas at that time. Intensive therapy with combinations such as VAMP [vincristine, amethopterin (methotrexate), 6-MP, prednisolone] were on the market, but we were most attracted by Georges Mathé's claim for immunotherapy. Had we looked a bit more carefully, we would never have done this trial at all. He had claims for eight long-term remission patients. However, if you look at it, first of all there was no record of what previous chemotherapy any of those patients had had. The immunotherapy they had consisted of either Pasteur BCG, irradiated leukaemic cells, or both BCG and cells, so there were three different treatments, resulting in long-term remission. We thought we ought to try some sort of immunotherapy, and we asked Colindale<sup>154</sup> about the Pasteur BCG, which they said was an inconsistent product, sometimes contained other microorganisms as well, and it was doubtful that they would be able to supply enough. We went for what we could get as a standard product, the Glaxo BCG, and as John Lilleyman has said, it did have this one valuable result that showed that if you continued your maintenance treatment, patients did better than if they had no further treatment or immunotherapy. We had, in a sense, a positive result, but we quickly abandoned immunotherapy at that time, and started on a series of UKALL trials comparing various regimens, length of treatment, CNS prophylaxis and so on. I don't think we were ever very innovative, and from that point of view I have to say that the stimulus came from Donald Pinkel in Memphis and later from Riehm in Germany, who had more intensive treatment. I think at the beginning we couldn't have had those intensive treatments, because I don't think there was either the expertise or the facility in all the centres throughout Britain to do that. We would have lost some children as a result

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<sup>154</sup> The Public Health Laboratory Service which was based at Colindale. See Williams R E O. (1985) *Microbiology for the Public Health. The evolution of the Public Health Laboratory Service 1939–1980*. London: Public Health Laboratory Service.



of the treatment. Nevertheless, we had these comparisons and I think, in some ways, the most valuable part of it was that there was a discussion of the protocol before and during, and people learned from others what the snags were and how you should manage the patient at each point in the regimen. That was one valuable thing.

The next valuable thing was that we were able to provide Mel Greaves with a large supply of leukaemic blood cells, so that he could do his characterization and distinguish common ALL, B-cell and T-cell diseases.

Later on still the cytogeneticists came in and there is now this wonderful monograph by Lorna Secker-Walker on the chromosomes of ALL,<sup>155</sup> which I think would have been much more difficult to compile if we hadn't had trials going throughout the 1970s and 1980s. Anyway we did manage to get acceptable forms of treatment.

We did find a few snags and another value of the trial was to pick out toxicity. A particular one was methotrexate neurotoxicity. That came up in the course of a conversation one day, when one haematologist had a patient in his centre with neurotoxicity and another clinician said he also had one, and somebody else said that they had one as well. In no time there were seven cases that we could write up. It was because you had a group discussing the whole thing that it was possible to identify that complication.

One other thing, which I am sorry we never emphasized because we were rather under the control of the statisticians, who wouldn't accept anything unless it was significant at a particular level, is that those weren't necessarily the most interesting comparisons. The thing I noticed at one stage was that the two Scottish centres, Edinburgh and Glasgow, were getting the best results of the lot. When you looked at the case records, it was because they were seeing their patients more often. Whereas in England, for example, they were seen every fortnight, in Edinburgh and Glasgow it would be every week, and later every fortnight in Scotland and every four weeks in England. I am sure that had two effects. It enabled them to regulate the dosage better, keep it up to the maximum tolerated and probably also induced a better measure of compliance by the parents, because I am sure, in the early stages at least, compliance failed here and there. Now how did they do it? Well I became aware in the 1980s that the Scottish Health Service, is a lot better funded than the English Health Service. I actually had a figure last week and they are 23 per cent better funded than we are in England, and I am sorry that we didn't make the point when we published some of these results. There was another example at the same time, which was that when we were doing transplants and we wanted cytomegalovirus-free blood, the Scottish transfusion centres could provide it and all the English centres said they couldn't afford to do so. I do think that

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<sup>155</sup> Secker-Walker L. M. (1997) *Chromosomes and Genes in Acute Lymphoblastic Leukaemia*. London: Landes Bioscience.



that should have been published. If you believe, as I do, that our health service is structurally very good, but has been seriously underfunded for 30 years, it would be very nice to find other examples and publish them.

**Goldman:** Humphrey, that's very interesting, especially your emphasis on the impoverished nature of England compared with Scotland.

**Professor John Walker-Smith:** I came to Bart's in the role of a general paediatrician in early 1973. I remember very vividly coming to that dynamic unit with Gordon Hamilton Fairley and Jim Malpas. There was one great difficulty for the compliance with these very tough regimens, and this was the conservative view of some of the nursing staff, who made it particularly difficult for the consultants.

You mentioned the UKALL trials. I think these trials helped enormously in many ways. Once these trials were underway it enabled the consultants to encourage the nursing staff that it was absolutely vital to stick to the protocols as a great way of improving care. Prior to the introduction there was tremendous pressure on the consultants at times to moderate the regimens on an individual needs basis. The UKALL trials led to much better nursing compliance.

**Goldman:** That's a very good point. These last few minutes were meant to be on ALL, and we have merged it with MRC clinical trials, to which we are coming in more detail. Is there anything that people would like to raise on ALL, the treatment of ALL specifically in relation to what John and Humphrey have been talking about?

**Dr Rosemary Shannon:** I think quite rightly we have put a lot of emphasis on the drug treatment of leukaemia, but I think there are other factors that have also contributed and certainly made life easier for the patients, like the introduction of central venous lines that I think we haven't mentioned, and the use of prophylactic Septrin (co-trimoxazole) and better antibiotics and blood products. Certainly I think one should pay tribute to the introduction of specialized nursing, because that's revolutionized the lives of some of the patients, actually.

**Goldman:** You make some very good points. Supportive care and specialized nursing, and specialized medical practitioners. Remember, if you go back enough years, Bodley Scott was an example of a superb general physician who had a major interest in haematology, but as far as I know he was never trained as a haematologist. I think he was trained as a general practitioner. Isn't that right, Ray? In other words he trained himself, and of course to a large extent David and others did.

**Powles:** Bodley was indeed the finest general physician I ever met; one of his patients was, of course, the Queen.

**Crowther:** I understood that he did his MD thesis in the 1930s, on the role of bone marrow examination as a useful tool in haematology.<sup>156</sup>

**Goldman:** I think we slightly more modern haematologists sometimes forget that examination of the bone marrow by aspirate came in only in the 1930s. Is that right, David?

**Booth:** Let me just quote John Dacie, with whom I had tea on Tuesday, saying he introduced aspiration biopsy to Manchester, when he worked with Wilkinson in 1936.

**Shannon:** One thing I didn't mention was the introduction of the measles vaccine. I can remember being taught in my early career as a paediatrician that measles was an important cause of death in children on chemotherapy. In my entire career as a consultant I have yet to see a child with measles, so I think there were other factors that were running in parallel in the general health of children at the time.

**Galton:** I just have two points to make. One is that a little earlier on, one of you, and I have forgotten who, referred to the problem that arose in the 1950s and 1960s when children were being treated with some modest success, and a few of them appeared not to be relapsing.<sup>157</sup> How long did you go on with their maintenance therapy? This used to be a topic in which at international conferences interested haematologists would meet privately and discuss how many patients they had who had been on either long-term methotrexate, or 6-MP, five or even ten years. Was it safe to stop? Nobody knew.

Then in 1970 or 1971, I visited Mila Pearce, who was head of the Leukemia Group A, I think, in the USA, and whom I had met many years earlier, when she was at Great Ormond Street. She pointed out that they had made very careful observations in Leukaemia Group A studies and they were pretty convinced that you needn't go on beyond five years. I don't know whether that was ever published, but she was very certain about that. So I was able to take off a number of patients who had had their five years, and as far as I know very few later relapsed.

**Goldman:** But you wouldn't treat for five years today would you John?

**Lilleyman:** No, we still don't know what the optimum time is for maintenance therapy, despite having done several randomized trials to try to find out, and even a meta-analysis. In general it seems that the longer this treatment goes on, the less likely patients are to relapse and the more likely they are to die of treatment. When those risks balance each other is very difficult to define, but presently, just to be logical about it, we are treating the boys for three years and the girls for two years.

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<sup>156</sup> At St Bartholomew's Hospital, London, Sir Ronald Bodley Scott learned the newly developed technique of bone marrow aspiration; an account of its use formed the basis of his thesis for a doctorate of medicine at Oxford University in 1937.

<sup>157</sup> See page 14.

**Galton:** A second point about poor funding from the NHS. Now that may be true in a major sense, but the authorities weren't oblivious to this. For a good many years the then Department of Health and Social Security (DHSS) used to send a representative to all our MRC steering committee and working party meetings, and there came a point where it was quite obvious that some of the centres couldn't possibly give the intensive – well, it was intensive for those days – treatment that they were supposed to in the protocol, without more nurses. The person who came from the DHSS reported this when he got back to headquarters, and in fact for a number of years centres that needed extra nurses, if they had enough patients, could get financial support. I can't remember how long this went on for, but it was certainly helpful to the trials.

**Goldman:** I don't know if it still goes on. In a few moments we are going to ask David Grant to comment on funding leukaemia research and leukaemia therapy in this country. But before we do that I think we should address specifically the issue of other MRC trials, and I think the main person I am going to ask is Ian MacLennan, but also I think David might like to comment and Humphrey might like to comment afterwards. Ian, would you like to open the topic of MRC clinical trials?

**Professor Ian MacLennan:** The MRC trials, particularly those on the acute leukaemias, have been extraordinarily successful. The proportion of patients with any type of cancer that get into trials is usually well under 10 per cent and often only 1 or 2 per cent of patients with certain cancers get into trials. This contrasts with the majority of people with acute leukaemia in this country getting into an MRC trial; in some cases this is the overwhelming majority of patients. I do not think one can underestimate the educational role that the MRC's trials have had in increasing the standards of the treatment in the UK and bringing forward new treatments. The MRC has largely conducted randomized control trials. Often these have not been large enough, but sometimes they have. I would like to highlight one or two examples where they have been successful and informative.

When I first came into the working party on leukaemia in adults in 1971, the results of the latest AML trial showed a median survival of six weeks. Derek Crowther has been telling us about the Bart's experience. This inspired the MRC to carry out a phase III immunotherapy trial; John [Goldman], you will remember that, in the early 1970s. At that stage different centres were getting remarkably different remission rates using what was then called the Bart's 3 regimen, which was DAT 1 plus 5.<sup>158</sup>

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<sup>158</sup> Rees J L, Hayhoe F G. (1978) DAT (daunorubicin, cytarabine, 6-thioguanine) in acute myeloid leukaemia. *Lancet* i: 1360–1361. Rees J K, Sandler R M, Challener J, Hayhoe F G. (1977) Treatment of acute myeloid leukaemia with a triple cytotoxic regime: DAT. *British Journal of Cancer* 36: 770–776. See also Rees J K, Gray R G, Swirsky D, Hayhoe F G. (1986) op. cit. note 47.

The differences in remission rates between the centres was almost entirely due to differences in supportive care. Frank Hayhoe and John Rees introduced the escalation of that DAT regime, going from 1 plus 5 to 2 plus 7 and then 3 plus 10.<sup>159</sup> They produced one of the most startling results from any controlled trial. Provided the platelet transfusions and the antimicrobial treatment that were available by that stage were used, patients spent a shorter period in hospital, if they had the more intensive chemotherapy. In addition, remission rates were better.<sup>160</sup> This was a really important result and it was hard evidence that allowed one to bring forward intensive chemotherapy in subsequent studies. I think it's also worth remembering in relation to AML that in the early 1970s there was a strong debate as to whether it was ethical to treat people with AML at all.<sup>161</sup>

If I can go back on to the childhood leukaemia trials. There was an unfortunate policy for which I was not entirely blameless, in which there was an aim to try to minimise treatment-associated toxicity in childhood leukaemia. We identified where during treatment patients were getting measles, encephalitis and interstitial pneumonias. These previously had been rare diseases in children. The treatments were modified to reduce toxicity at the time of maximum risk of these complications developing. This unfortunately also reduced the anti-leukaemic efficiency of the treatment. Eventually it became clear that the gentle approach treatment was giving sub-optimal results. More intensive therapy was given and physicians learned how to manage toxicity.

Intensification doesn't always work and I am going to give another trial example illustrating this. In the MRC first myeloma trial<sup>162</sup> it was realized that many patients with multiple myeloma were dying from renal failure. At least one-third of the patients in this trial presented with renal failure that persisted despite an initial period of hydration. The conclusion was that the light chains of T-cells were causing the renal failure and that, of course, is correct. This conclusion was used as a rationale, in the third trial, to test whether

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<sup>159</sup> DAT 1 + 5: daunorubicin for 1 day with cytarabine and 6-thioguanine for 5 days; DAT 3 + 10: same dose drugs for 3 + 10 days, respectively. Professor David Galton wrote: 'The MRC Leukaemia Unit's experience with 3 + 10, which may have preceded the work at Bart's was also influential in leading the MRC Steering Committee and Working Party on Leukaemia in adults to accept this regimen in the next AML trial.' Note on draft transcript, 29 November 2002.

<sup>160</sup> See, for example, Rees J K, Gray R. (1987) Comparison of 1 + 5 DAT and 3 + 10 DAT followed by COAP or MAZE consolidation therapy in the treatment of acute myeloid leukaemia: MRC ninth AML trial. *Seminars in Oncology* 14: 32–36.

<sup>161</sup> See, for example, Burge P S, Prankerd T A, Richards J D, Sare M, Thompson D S, Wright P. (1975) Quality and quantity of survival in acute myeloid leukaemia. *Lancet* ii: 621–624.

<sup>162</sup> Report of the MRC's Working Party for Therapeutic Trials in Leukaemia. (1973) Report on the first myelomatosis trial. I. Analysis of presenting features of prognostic importance. *British Journal of Haematology* 24: 123–139.

the renal failure could be reversed by removing the light chains by giving intensive chemotherapy. This approach was associated with early mortality in most patients given the intensive therapy. Analysis of the pathogenesis of renal failure in multiple myeloma showed that in most instances it was secondary to a selective proximal renal tubular defect caused by the presence of light chains. This caused fluid loss, which predisposed the patients to renal failure. The selective nature of the defect was shown by patients still able to reabsorb glucose and some low-molecular weight proteins from the glomerular filtrate. Based on these studies a regimen using a sustained high fluid intake was introduced for managing and preventing renal failure in patients with multiple myeloma. This has been successful in a high proportion of patients. Using this approach the median survival in the third trial of 37 days for patients presenting with creatinine levels of about 200  $\mu\text{m/L}$ , was extended to more than 18 months in the fourth trial. Relatively few patients with multiple myeloma now die of renal failure.

Those are just one or two examples that illustrate the success of the MRC trials. Again I want to emphasise their important educational role. The new cooperation with the cancer funders and the Health Service, and the formation of the National Cancer Research Institute, offer a very real possibility of getting high numbers of patients with other neoplasms into trials. It is important that good phase I and phase II trials are run by specialist centres and groups, for these feed the multi-centre phase III trials. The leukaemia trials have worked well because there have been strong centres doing phase II trials.

**Galton:** The MRC trials were brought up at a meeting of the MRC Cancer Committee in 1957, at that time under the chairmanship of Lord Cohen. It was recommended that a working party should be set up to start trials as soon as it was practicable, and the next move we have already heard about from Frank, was the setting up of this typing committee to show how impossible it was at that time to try to allocate treatment according to the type of leukaemia, because we didn't diagnose them properly. When the Working Party was set up it was not specifically for adults or children, but it was, I think, mainly for adults at that time. That working party began its work in 1959.

The first trials were extraordinarily primitive, and the results rather difficult to interpret. They weren't very good, but they did show just about a glimmer of hope and that led to their continuation. I must say that the most significant point about the early trials was the way in which the statisticians were involved. The first meetings were attended by Sir Austin Bradford Hill and Sir Richard Doll; it's a great, great pity that he and Richard Peto aren't here today, because they helped to provide a proper framework in which these trials could be designed and statistically analysed. I know that Humphrey was a little bit disparaging about their role in some of the children's trials when he spoke a few minutes ago. I didn't have much to do with the children's trials; all I can say is that the statisticians have been and still are an absolutely amazingly efficient group of people. The trouble they take is immense, their efficiency is terrific, and I was tremendously impressed from the start by the trouble the young disciples

of Richard Doll and later Richard Peto were prepared to take, to understand something about the disease. I remember Richard Peto came in 1964, when we had the first myeloma trial, and I showed him X-rays of myeloma patients, case histories, told him about immunoglobulins and showed him slides; he got to know a lot about myeloma. The same was true of the statisticians who became involved with the leukaemias too – they were absolutely essential and I think everybody concerned with today’s trials will confirm what I have said.

The other point that I would like to make very briefly, is that several people have already referred to the first group of trials in AML, and I can say that the major trials that have yielded results were those that were started in 1970. Before that, rather feeble combinations of drugs were used, but 1970 was the first of a series on multiple-drug therapy. One of the good things about the early trials was that one arm was kept from one trial to the next, and in fact the one that survived the longest was the one we have heard about; it was devised at Bart’s and became known as Bart’s 3.<sup>163</sup> The point of great interest was that in successive trials the Bart’s 3 regimen results got better and better and this, Richard Peto always said, was the best evidence necessary to show that randomized trials were the way to find out how things worked. Historical controls were useless, because you would have the Bart’s 3 effect claiming successive new treatments to be better, which were not better at all. It was probably because of the improved experience of the physicians involved and their increased confidence in giving the regimens exactly as specified. Unfortunately, J Freireich<sup>164</sup> is not able to be here this afternoon. He, of course, never did controlled trials, he didn’t believe in them at all, so it would have been nice to hear what he would have said.

**Goldman:** Freireich would certainly have given you a spirited rebuttal at that last point. Derek, do you want to comment on Bart’s 3 at all?

**Crowther:** Not really, apart from saying that all the Bart’s studies were small, with relatively small numbers of patients. I think that we treated about 70 patients with AML on the original five-day regimen, before moving on to Bart’s 4, and so on. The previous results in our own practice using single agents were terrible. They all died and I don’t think we had anybody who went into complete remission. However, I do remember that we had one patient at Bart’s who had been treated in the 1950s with continuous 6-MP, for just a three-month period. This patient went into complete remission, and stayed in remission as far as I can remember, for about 20 years. The pathology was looked at again and the diagnosis was confirmed. With the new combination chemotherapy the whole team could see that the

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<sup>163</sup> op. cit. note 158.

<sup>164</sup> Some of his work is described in Carbone P P. (1997) Drug development in solid tumors: personal perspective of Dr Emil J Freireich’s contributions. *Clinics in Cancer Research* 3: 2614–2622. Freireich E J. (2001) Emil J Freireich: a pioneer of modern oncology (interview by Sue Silver). *Lancet Oncology* 2: 459. See also page 66.

majority of patients were returning to normal health. If J Freireich had been here he would have pointed out that when he came to London in the early 1970s, he said that he thought that ‘remission induction’<sup>165</sup> for patients with AML was no longer a problem, but we had to learn how to treat patients in remission and how to keep them in remission. We did terribly badly with that and nearly all the AML patients I treated at Bart’s eventually died. We had very few long-term survivors in those early trials, although we did have a high complete remission rate.

**Goldman:** Humphrey, would you like to comment on clinical trials from what you have heard?

**Kay:** I am very sorry Richard Peto isn’t here. He and I had fairly profound differences, and I have been looking back at an article I wrote in 1983 and I think that most of the points I made are still valid.<sup>166</sup> The question is whether you need total randomization throughout all multicentre trials. The fact is we have had a number of trials in which there has only been partial randomization, the polycythemia trial is one and UKL 6 and 7; testicular irradiation was one some centres went in for and others didn’t. I think you can get away without total randomization throughout the whole time.

Then there is the question of whether you are comparing results of treatment, or treatment policies, because what the statisticians tended to say was that you can only compare treatment policies; if you can’t continue with a treatment, that’s a failure. Now I think that is a mistake. There are instances, the one I took was the myeloma 3 trial, in which you had either cyclophosphamide, relatively non-toxic, or melphalan plus prednisolone, and the difference between the two in aggregate was not significant. However, if you looked at the results, you could see that in the ones on melphalan plus prednisolone, some patients developed severe myelotoxicity; clearly that was an inappropriate treatment for them, but for those who could tolerate it, they did better than the cyclophosphamide patients. You mustn’t just compare treatment policies – you must compare tolerated treatments – and that’s something that doesn’t appear in any of their articles. David said something about comparison with the previous best or a standard treatment and, of course, that can work both ways; but one way it can work is that if you know all the snags in an existing treatment, your patients may do better, because you know how to avoid those – you don’t know how to avoid the snags of the new treatment.

Finally, there’s the question of measurable and unmeasurable. You can measure lots of things like duration of remission, mortality and so on; what you can’t measure is the quality of life

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<sup>165</sup> That is inducing a ‘remission’ of the disease.

<sup>166</sup> Kay H E M. (1983) Planning and comparisons in clinical trials. *British Journal of Cancer* 47: 315–318.

during these treatments and a whole lot of other things that should influence you in relation to the treatment you are comparing, but they don't enter the statisticians' textbook.

**Catovsky:** I am not going to defend the statisticians, but I think they have changed over the years since you left, Humphrey, because certainly quality of life is now part of all the studies. Now the studies are so large, with thousands of patients, that they allow for many different randomizations; so they can ask many questions – like we have seen yesterday in the MRC review meeting [the annual review of the MRC Leukaemia Trials] – two or three or four questions in the various trials, which are only possible because of the large number of patients entering. I certainly do not necessarily always agree with the statisticians, but they have improved. I also have to say that Richard Peto hasn't been part of the MRC trials for a long time. He now has a number of people who have been following the trials; some do have a more open mind perhaps, more than they had early on.

**Goldman:** Ray, we are interested in your personal reminiscences of the allogeneic stem cell transplant development over probably 25 years. If I may introduce the subject by referring to a conversation I had in a bar with Ray Powles at the King David Hotel in Jerusalem in 1977, we both thought that the time had come to start formal allogeneic BMT for AML patients in remission. Ray got it off the ground and I did not.

**Powles:** The UK has a long track record of innovative work in haemato-oncology. In my own working lifetime, it has been interesting to see how my research started with an immunotherapy slant, became very chemotherapy orientated, then BMT dominated the picture, which has brought the whole circle once again, back to immunotherapy.

First of all I can't stress how important the initial Bart's trials were, not only in devising biological treatments but also in introducing the discipline of randomized trials in haemato-oncology, and how important Derek was in bringing this discipline to our field. The statistician involved was Malcolm Pike, who was very receptive to the nuances of leukaemia and was also a wonderful character.

An anecdote from this period was the naming of the 'Concord' trial. It had no 'e' as compensation for having lost the battle for the naming of the aeroplane that did have an 'e'. Although this trial showed slight benefit, almost all the patients were dead in a year, which were much worse results than for comparable patients who were also receiving CNS cranial irradiation as prophylaxis.<sup>167</sup> A disappointment with the Concord trial is that we did not exactly repeat the method of immunotherapy used by Mathé; he used BCG

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<sup>167</sup> See, for example, George P, Pinkel D. (1965) CNS radiation in children with acute lymphocytic leukemia in remission. *Proceedings of the American Association for Cancer Research* 12: 22. Aur R J, Simone J, Hustu H O, Walters T, Borella L, Pratt C, Pinkel D. (1971) *Central nervous system therapy and combination chemotherapy of childhood lymphocytic leukemia*. *Blood* 37: 272–281. op. cit. note 75.



scarification<sup>168</sup> whereas in our trial, the BCG was given using a Heaf gun. We will never know whether this explained the failure of this trial but the lesson to learn is, if you wish to repeat a study which has shown efficacy, then it must be repeated exactly.

In my time with Mathé in Paris, at the end of 1968, I was very impressed with the fact that he was already using intensive treatment, including BMT. He was an inspirational leader and his haemato-oncology meetings in Paris every summer were legendary. Every day lunch would be in the very smart Lebanese club; the menu was from a different region of France and done with such exquisite style.

We undertook four immunotherapy trials including the randomized study at Bart's. There were three other immunotherapy studies done worldwide in AML and all showed a trend for benefit, particularly for survival after patients had relapsed.<sup>169</sup>

**Goldman:** But I think you were the first person to start routine allografting for leukaemia, were you not?

**Powles:** In 1973 Professor Don Thomas in Seattle invited me to give a lecture on immunotherapy because, at that time, they had already undertaken 100 matched sibling allogeneic transplants, but only 11 patients had survived, with a large proportion of patients dying because of recurrent disease, or due to the procedure. The recurrent disease was in many respects because these were drug-resistant, heavily pre-treated relapsed patients. Don had the vision to spot that an allogeneic transplant may be the perfect springboard for post-transplant immunotherapy, an area that is very topical at the moment. Don, of course, won the Nobel prize for his work. I was very impressed with the discipline of the Seattle unit and, particularly, by the input of Rainer Storb. Rainer's mother lived in Germany, so we highjacked him into coming to our Sutton unit and transplanting one of our patients with aplastic anaemia on one of his visits to his mother. We thus had our first success in 1973 followed in 1975 by our first successful transplant for acute leukaemia.<sup>170</sup>

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<sup>168</sup> Mathé G. (1971) Active immunotherapy. *Advances in Cancer Research* 14: 1–36. Mathé G, Weiner R, Pouillart P, Schwarzenberg L, Jasmin C, Schneider M, Hayat M, Amiel J L, de Vassal F, Rosenfeld C. (1973) BCG in cancer immunotherapy: experimental and clinical trials of its use in treatment of leukemia minimal and or residual disease. *National Cancer Institute Monographs* 39: 165–175. Mathé G, Facy F, Hatton F, Halle-Pannenko O. (1974) BCG vaccination and acute leukaemia. *Biomedicine* 21: 132–134.

<sup>169</sup> Professor Ray Powles wrote: 'However, other treatments, particularly with chemotherapy and bone marrow transplantation, were just beginning to give true cure expectations and so superceded further research into immunotherapy.' E-mail to Dr Daphne Christie, 8 January 2003.

<sup>170</sup> Thomas E D, Storb R, Fefer A, Slichter S J, Bryant J I, Buckner C D, Neiman P E, Clift R A, Funk D D, Lerner K E. (1972) Aplastic anaemia treated by marrow transplantation. *Lancet* i: 284–289. See also Terasaki P L. (ed.) (1991) *History of Transplantation: Thirty-five recollections*. Los Angeles: UCLA Tissue Typing Laboratory.

At that time blood cell separators also became available.<sup>171</sup> Hamilton Fairley, through the MRC, purchased the fourth separator in the world, the first in the UK, which we started using for collecting leukaemia cells for use in immunotherapy at Sutton. It cost £30 000 then, which in today's terms would probably be ten times this amount.

Now let us go on to allografting. Cyclosporin has been an enormous benefit for preventing GVHD following BMT and we at the Marsden were the first to develop its use. Although it had shown considerable potential for use in kidney transplantation, it was not possible for Professor Sir Roy Calne to use it for kidney patients because of its known nephrotoxicity.<sup>172</sup> As a consequence we were able to first use it for patients receiving bone marrow transplants, and show that its nephrotoxicity was reversible and could thus be used safely for kidney transplants.<sup>173</sup> We also showed that for BMT it could be used optimally in combination with methotrexate and also in a mismatch transplant. To this end, using these methods, we even managed to undertake a bone marrow transplant from father into leukaemic son and then, after he was cured, the father developed leukaemia and we were able to transfer the son's marrow (now the surrogate father's) back into the father. Both are cured 15 years later.<sup>174</sup>

Immunotherapy has become topical again following the observation of John Goldman that patients with CML, who after allogeneic BMT developed GVHD have less relapses than those who do not have GVHD. We saw a similar observation in AML.

<sup>171</sup> Professor Ray Powles wrote: 'Blood cell separators, which are now a standard requirement for allogeneic transplantation, and it is of interest that they were also first developed very early on in the mid-1960s for leucapheresis for patients with high white blood counts, and for plasma exchange...30 years later these machines have been instrumental in allowing for the development, over the last few years, of the ability to collect bone marrow stem cells from the peripheral blood for use in transplants. Once again a full turn of the circle.' E-mail to Dr Daphne Christie, 8 January 2003.

<sup>172</sup> Calne R Y, Rolles K, White D J G, Thiru S, Evans D B, McMaster P, Dunn D C, Craddock G N, Henderson R G, Aziz S, Lewis P. (1979) Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* **ii**: 1033–1036. *idem* (1981) Cyclosporin A in organ transplantation. *Advances in Nephrology from the Necker Hospital* **10**: 335–347. Tilney N L. (1989) The early course of a patient with a kidney transplant. Cyclosporin A nephrotoxicity, in Morris P J. (ed.) *Kidney Transplantation. Principles and Practice*. Philadelphia: W B Saunders Company, 275–278. See also 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, 58–59.

<sup>173</sup> Powles R L, Barrett A J, Clink H, Kay H E, Sloane J, McElwain T J. (1978) Cyclosporin A for the treatment of graft-versus-host disease in man. *Lancet* **ii**: 1327–1331.

<sup>174</sup> Powles R L, Parikh P M, Helenglass G, Aboud H H, Smith C L, Mrazek I A, Shepherd V, Milliken S T, Treleaven J, Sharrock C, et al. (1990) Bone-marrow transplant from father to son and subsequent graft from son to father. *Lancet* **335**: 999–1000.

Concerning aciclovir. We were lucky to be able to have access to this drug to assess its potential in treating herpes viruses at the end of the 1970s, quite a long time before it became available in the USA. There was a problem with FDA approval, since it is a drug that interferes with DNA and they were concerned that it might do more harm than good.<sup>175</sup>

**Goldman:** I think we now should address the last issue of the day that is very important and, of course, I refer to money. I think we have been lucky and I personally have been lucky in having been associated with the LRF for almost the whole time that I was at the Hammersmith. Gordon Piller was the brains behind the instigation of the LRF, but David Grant is now very much in charge, and we have asked David to talk about funding of leukaemia research in general and leukaemia therapy. As I have said already, much of what we have talked about today wouldn't have been possible without funding in general, and I guess the LRF in particular. David, would you like to comment?

**Dr David Grant:** Thank you for the invitation. I am sure my illustrious predecessor, Gordon, could speak far better than I on the first 30 years of the Fund, but I will be pleased to comment on the last 11 years, while I have been associated with it. Out of interest, in 1961 the annual income of the LRF was £8000 and the research spend was £5000. In 2001 the income was £19 800 000 and the research spend was £21 100 000. We are the third-largest national cancer charity. Obviously, leukaemia research is the paradigm for cancer research, because the disease is so accessible; it's so easy, well, straightforward to diagnose. Response to treatment can be monitored fairly easily, and the paradigm of leukaemia research, of course, is childhood leukaemia, as you have alluded to, in the spectacular success of the MRC leukaemia trials. Therein, I think, lies the issue and the challenge for the future. It was William Osler who said, 'It's much more important to treat the disease that the patient has, rather than the patient with the disease',<sup>176</sup> and that we must aim to transfer all the very intellectually clever and powerful science in the laboratory into clinical benefit.

I want to touch on two issues. The first is the support from translational research, as it is called now, and how we can achieve this. The second is the career structure in the UK that at the moment is causing great concern for clinical scientists. As I said, obviously childhood

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<sup>175</sup> Professor Ray Powles wrote: 'We were able to publish from the Marsden Hospital, the first definitive report of benefit [Perren T J, Powles R L, Easton D, Stolle K, Selby P J. (1988) Prevention of herpes zoster in patients by long-term oral aciclovir after allogeneic bone marrow transplantation. *American Journal of Medicine* 85: 99–101].' E-mail to Dr Daphne Christie, 8 January 2003.

<sup>176</sup> Osler W. (1919) *A Way of Life*. An address delivered to Yale students on the evening of 20 April 1913. Springfield, Illinois: C C Thomas.

leukaemia is the paradigm for leukaemia research and for cancer research to some extent; all cancer charities unashamedly use that as the success story, and of course we are seduced by the spectacular success of the leukaemia trials. In fact, it was the trials and not laboratory research that achieved that success. The overall survival rate hit 70 per cent in 1990, and to my knowledge in the last ten years that I have been with the Fund, it has probably crept up to 75 per cent. The last 25 per cent stubbornly refuse to be cured, and there are all sorts of reasons for that, which we are starting to unravel now. It's vital, I think, that one crucial role for the Fund is to integrate laboratory research with the clinical trials that you have been discussing for the last half an hour or so, because there's so much information that can be gleaned from primary material that can then be fed back into designing much more informed and directed trials and then to start to stratify patients. Again from childhood leukaemia, the example is monitoring minimal residual disease by molecular means, so that you can monitor tumour load in response to therapy, monitor clearance kinetics and start to identify the good performers from the poor performers. The spectacular success of cytogenetics that was commented on earlier in terms of patient stratification, understanding the molecular basis of the way the drugs work and the basis of relapse, is linked to genetic polymorphisms. All this is coming through now and should be integrated into future trials.

The other problem though, of course, is that you need the people to do that, and there has been a concern in the last five years, in particular, with the introduction of new specialist haematology training structures, that the clinical scientists of the future are not coming through. I think it is one of the tasks of the Fund to put in a structured career path in the UK for the outstanding young haematologists and oncologists who grow up with this culture of bringing the laboratory-based knowledge through to well-designed and informed clinical trials.

**Goldman:** David, you certainly strike a very popular cord, because I feel that this is a major problem that has developed over the last ten years. The training of clinical scientists that seems to have been neglected by the National Health Service and Calman<sup>177</sup> has also unfortunately been neglected through the university grant mechanisms. Something needs to be done, otherwise we will fall very far behind our colleagues in the developed world. Gordon, do you want to comment particularly on the early days of the LRF on funding for leukaemia research?

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<sup>177</sup> See Anderson J M. (1999) The effect of Calman reforms on recruitment training and service provision. *Archives of Disease in Childhood* **80**: 485–487. See also 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.

**Piller:** Yes, the LRF was set up in response to calls for what more could be done; this was not a criticism of what was being done, but we established the Fund to be partners with the clinicians and the scientists. To go back to what [Sir Lionel] Whitby was saying: when the LRF was set up we instituted two rules. First, that you backed research on a pound-for-pound basis, that means to say that you could then engage in long-term grant giving, simply because you preserve your resources. Secondly we insisted that we would not succumb to popular feelings at the time, the press etc., but that the Fund would be governed and controlled. We then set up a Medical and Scientific Advisory Committee, which is still in place today and it has been chaired by many famous people, including Sir John Dacie. It started working with the professions and listening to what needed to be done, and then in collaboration achieving their wish for better treatments and scientific approaches. The result was, I think, that we set up our first professor when the LRF was just eight years old. He's a very distinguished gentleman who's sitting just in front of me now [Frank Hayhoe]. We also decided to support research in depth and to do two things: first to support clinical research and set up clinical fellowships, and second to install units where they were required and to support them. We came back to the best way to do this, by sticking to our principle of financing research on a pound-for-pound basis, and with all legacies we adopted the commonsense rule: if aunties or uncles were going to leave you something in the will, you were not expected to go out and blow it. We had a strict rule that every legacy was invested, and the Fund today has some £70 million to back Virchow's wish in 1858 that, 'I hope that this disease, leukaemia, would eventually succumb and be cured',<sup>178</sup> and that's our aim.

**Goldman:** We are certainly moving in that direction, thanks in large part in this country to the LRF. David, what about national policies for clinical care of patients with leukaemia? Are we as a haematology community doing enough to encourage funding for clinical care in the ward?

**Grant:** As it happens, I hope that the National Cancer Research Network will certainly focus minds. It is very interesting that the emphasis since I have been here has been very much on the success of trials, the importance of trials and the continuity of trials – that it is crucial that one trial leads on to another trial. Even in the haematology community,

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<sup>178</sup> Rudolf Virchow (1821–1902) described his first case of chronic myeloid leukaemia in 1845 [Virchow R. (1845) *Weisses Blut. Froriep's Notizen* 36: 151–156]. See also *idem* (1849) *Zur pathologischen des blutes. IV. Farblose, pigmentierte und geschwante nicht spezifische zellen im blut. Archives of Pathology, Anatomy and Physiology* 2: 587–598. *idem* (1856) *Gesammelte Abhandlungen zur Wissenschaftlichen Medicin*. Frankfurt: Merdinger Sohn & Co. *idem* (1858) *Cellular Pathologie*, 170. Berlin. See also Ackerknecht E H. (1953) *Rudolf Virchow: Doctor, Statesman, Anthropologist*. Madison: University of Wisconsin Press. Further details are given in a letter from Dr Gordon Piller to Dr Daphne Christie, dated 3 April 2002, and will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

enough adult patients are still not entering trials, and that is a crucial omission and something that certainly needs to be encouraged.

**Booth:** I wonder if I can comment on a point that Gordon Piller made earlier. I think I understood you to say that legacies were invariably invested and not spent. Is that correct? I am very intrigued by that, because you must have had to deal with the charity commissioners. As I have found in charitable foundations that I have been involved with, charity commissioners insist that you spend your money and you don't save it. How did you get away with that?

**Piller:** Well, be tough with the charity commissioners! The answer is that all medical research is there for the long term until other circumstances pertain. We would take the view, and do take the view, that we need money year by year to cover all our present and forward commitments; for all the grants from the LRF, once they are made, we have the commitment to honour them. So we go back to the charity commissioners, who are not experts in medical research, and argue our case. [**Booth:** I quite agree with that]. So that is how we store it up. The subsidiary rule to investing money for charity is a very simple one – your capital is only worth the income it produces – so you then have to work on the income from that and from other fundraising to balance the books, but remembering that if new approaches in medical and scientific research arise, we have the financial reserve to respond and quickly. That's the answer that we would give to the charity commissioners.

**Booth:** Obviously a very good policy. Well done.

**Goldman:** Any other points that people would like to bring up before we close? I think Tilli would like to speak on behalf of the Wellcome Trust, but I would like to thank the people who were invited to speak, those who have spoken, and the audience generally for being very, very valuable and productive.

**Tansey:** Can I just echo those sentiments and thank you all very much for contributing to this afternoon. Let me warn you that your endeavours are not over; we will be in touch with you later, as we edit the transcript for publication. We will want more details from you all, so you will be hearing from us quite a bit in the future. I would particularly like to thank John Goldman for his excellent chairing this afternoon. It's been a splendid occasion and I hope you will now all join us in a glass of wine next door.

**Piller:** On behalf of all of us here, may I thank the organizers, the Wellcome Trust and contributors for providing such a splendid afternoon.

## Biographical notes

### Sir Christopher Booth

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

### Professor Eric (Dick) Boyland

(b. 1905) was Professor of Biochemistry, University of London, at the Chester Beatty Research Institute, Institute of Cancer Research, Royal Marsden Hospital, from 1948 to 1970, now Emeritus, and Visiting Professor in Environmental Toxicology at the London School of Hygiene and Tropical Medicine from 1970 to 1976.

### Professor Daniel Catovsky

FRCP FRCPATH FMedSci (b. 1937) graduated in 1961 in Buenos Aires and then moved to London to work with David Galton and John Dacie at the Royal Postgraduate Medical School (RPMS). He was a founder member of the first MRC Leukaemia Unit at the RPMS, created in 1970, and was appointed Professor of Haematology at the Royal Marsden Hospital and Institute of Cancer Research in 1988, and Honorary Consultant at the Royal Marsden Hospital. His main area of research is in lymphoid leukaemias. See Catovsky D, Foa R. (1990) *The Lymphoid Leukaemias*. London: Butterworth.

### Professor Derek Crowther

FRCP FRCR (b. 1937) qualified in medicine in 1963 from St Bartholomew's Hospital, London, and was appointed as the first Professor of Medical Oncology at the Christie Cancer Centre [formerly the Christie Hospital], University of Manchester in 1973. He retired as Director of the Department of Medical Oncology in Manchester in 1997. He is currently Chairman of the Leukaemia Research Fund Clinical Trials Advisory Panel, President of the Association of Cancer Physicians, and Foundation Scholar at Clare College, Cambridge. A copy of his notes and correspondence will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

### Sir John Dacie

Kt FRS FRCP (b. 1912) was Professor of Haematology at the Royal Postgraduate Medical School of London, University of London, from 1957 to 1977, now Emeritus. He was Chairman of the Medical and Scientific Advisory Panel, Leukaemia Research Fund, from 1975 to 1985.

### Gertrude Elion

FRS (1918–99) was Head of the Department of Experimental Therapy, at the Burroughs Wellcome Co. Laboratories from 1967–83, Scientist Emeritus from 1983. Her work with George Hitchings on enzymes in nucleotide metabolism and development of drugs (e.g. azathioprine) earned them the Nobel Prize for Physiology or Medicine in 1988. See Colvin M. (1999) Gertrude Belle Elion. *Science* 284: 1480. op. cit. note 143.

### Dr Sidney Farber

(1903–73) was appointed resident pathologist at the Children's Hospital and assistant in pathology at Harvard Medical School in 1928. For a

discussion of treatment of leukaemia with aminopterin, see page 5, op. cit. note 11. See Craig J. (1996) Sidney Farber (1903–73). *Journal of Pediatrics* 128: 160–162. Vawter G F, Cohen J. (1988) Founders of pediatric pathology: Sidney Farber 1903–1973. *Perspectives in Pediatric Pathology* 12: 1–9.

#### **Dr Emil J Freireich**

was Director of the Adult Leukemia Research Program, University of Texas, MD Anderson Cancer Center, Houston, Texas. Much of his research was on human leukaemia cells *in vitro*. See Freireich E J. (1998) Four decades of therapy for AML. *Leukemia* 12: S54–S56. op. cit. note 164.

#### **Professor David Galton**

CBE MA MD FRCP (b. 1922) graduated in 1946 from Cambridge and carried out the first clinical trials from 1948, later with Dr Morwenna Till and Dr Eve Wiltshaw, of promising cytotoxic drugs synthesized at the Chester Beatty Research Institute. Three – busulfan, chlorambucil, and melphalan – are still used (see pages 4–6). He was Secretary of the MRC Working Party on Leukaemia from its inception in 1959, and later Chairman of the Working Party on Leukaemia in Adults, and of the Steering Committee on Leukaemia. He was Honorary Director of the MRC Leukaemia Unit and Leukaemia Research Fund, Professor of Haemato-Oncology in the University of London at the Royal Postgraduate Medical School and is Honorary Consultant Physician at the Hammersmith Hospital, London. A collection of his papers and correspondence will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

#### **Professor John Goldman**

DM FRCP FRCPPath FMedSci (b. 1938) worked at the MRC Leukaemia Unit from 1970 to 1992, was Professor of Leukaemia Biology and Therapy at Imperial College School of Medicine, London,

since 1987, and Chairman of the Department of Haematology, Imperial School of Medicine/Hammersmith Hospital, since 1994. He has been Director of the Leukaemia Research Fund Centre for Adult Leukaemia since 1992.

#### **Dr David Grant**

(b. 1949) is a graduate in Physiology and Biochemistry from the University of Southampton and completed his PhD at the Royal London Hospital Medical School. After a research fellowship in Uppsala, Sweden, he returned to St George's Hospital Medical School, first as a Lecturer and subsequently a Senior Lecturer in biochemistry. He was appointed Scientific Director of the Leukaemia Research Fund in 1990.

#### **Professor Mel Greaves**

FMedSci (b. 1941) worked at the Karolinska Institute, Stockholm, and the National Institute for Medical Research before joining the Imperial Cancer Research Fund, heading up an immunology laboratory in 1976. In 1984 he was appointed Director of the Leukaemia Research Fund's first specialist centre, at the Institute of Cancer Research, London.

#### **Professor Sir Alexander Haddow**

Kt FRS FRSE (1907–76) was Professor of Experimental Pathology at the University of London, from 1946 to 1972, later Emeritus. He was Director of the Chester Beatty Research Institute, Institute of Cancer Research, Royal Cancer Hospital, London, from 1946 to 1969, and President of the Section of Oncology, of the Royal Society of Medicine, from 1970 to 1971. See Bergel F. (1977) Alexander Haddow. *Biographical Memoirs of Fellows of the Royal Society* 23: 133–191.

#### **Professor Gordon Hamilton-Fairley**

FRCP (1930–75) joined in 1965 the staff of St Bartholomew's Hospital, London, and moved to



the Royal Marsden Hospital in 1967. In 1970 he was appointed Director of St Bartholomew's Research Unit in Medical Oncology and offered the Chair in 1971. See Scott R B. (1982) Gordon Hamilton-Fairley. *Munk's Roll* 6: 215–216. See also Klipstein F A. (1976) In memoriam: Gordon Hamilton-Fairley 1930–1975. *Blood* 47: 523–524.

#### **Professor Frank Hayhoe**

FRCP FRCPath (b. 1920) qualified in 1944 from Cambridge and St Thomas's Hospital, London. He was appointed University Lecturer and Honorary Consultant Physician at Addenbrooke's Hospital, Cambridge, in 1951, and was Leukaemia Research Fund Professor of Haematological Medicine from 1968 to 1988.

#### **Dr George Hitchings**

FRS HonFRSC (1905–98) began his work on nucleic acid precursors during the 1930s in the Harvard Laboratory of C H Fiske. In 1942 he established a research programme on pyrimidine and purine analogues at the Laboratories of Burroughs Wellcome Co. in New York. Gertrude Elion (see earlier) became his major associate in 1988 and shared the Nobel Prize for Medicine with him and Sir James Black. Drugs resulting from his purine work included the anti-cancer agents 6-mercaptopurine (1952) and in the 1960s, azathioprine. Fox D M, Meldrum M, Rezak I. (eds) (1990) Nobel Laureates in Medicine or Physiology. New York, London: Garland Publishing, Inc, 252–254. op. cit. notes 20 and 143.

#### **Professor Victor Hoffbrand**

DM FRCP FRCPath DSc (b. 1935) qualified from the London Hospital and Oxford University in 1959. He worked at the Royal Postgraduate Medical School, London, from 1962 until 1974, when he was appointed Professor of Haematology at the Royal Free Hospital School of Medicine. His research was initially in megaloblastic anaemia and

subsequently in biochemical and molecular aspects of leukaemia. He has also helped to develop an orally active iron-chelating drug. He is, with Dr J E Pettit, the author of *Essential Haematology* and *Clinical Atlas of Haematology* and co-edits *Postgraduate Haematology*.

#### **Dr Peter Hunter**

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

#### **Professor Humphrey Kay**

FRCP FRCPath (b. 1923) graduated from St Thomas's Hospital in 1945 and was in charge of Haematology at the Royal Marsden Hospital, London, from 1956 to 1984. From 1967 to 1984 he was Secretary to the MRC Committee on Clinical Trials in Leukaemia and Co-ordinator of the trials in childhood leukaemias.

#### **Sir Ernest Kennaway**

Kt FRS FRCP (1881–1958) qualified from the Middlesex Hospital in 1907, was Demonstrator in Physiology at Guy's Hospital, London, from 1909 to 1914, and later chemical pathologist at the Bland-Sutton Institute, Middlesex Hospital, from 1914 to 1921. In 1921 he joined the Research Institute, Cancer Hospital, and was Director and Professor of Experimental Pathology, from 1931 to 1946. He was Honorary Fellow of New College, Oxford. See Cook J W. (1958) Ernest Laurence Kennaway. *Biographical Memoirs of Fellows of the Royal Society* 4: 139–154. See also Waller R E. (1994) 60 years of chemical carcinogens: Sir Ernest Kennaway in retirement. *Journal of the Royal Society of Medicine* 87: 96–97.

**Professor Sir John Lilleyman**

FRCP FRCPATH FRCPCH (b. 1945) has been Mark Ridgwell Professor of Paediatric Oncology at St Bartholomew's Hospital and The London School of Medicine, Queen Mary, University of London, since 1995. From 1975 to 1995 he was Consultant Haematologist to the Children's Hospital, Sheffield, and from 1999 to 2002 was President of the Royal College of Pathologists.

**Professor Ian MacLennan**

FRCP FRCPATH FMedSci (b. 1939) has been Professor of Immunology, since 1979, and Director of the MRC Centre for Immune Regulation, at the University of Birmingham since 1999. He was co-ordinator of the MRC trials in multiple myeloma from 1980 to 1998 and was on the Working Party on Leukaemia in Adults from 1982 to 1992.

**Dr Gordon Piller**

OBE FRCP(Ed) HonDVMS(Glas) HonFRCPCH (b. 1925) was at Great Ormond Street Hospital for Children, London, from 1952 and its House Governor for ten years from 1960. He was a Founder of the Leukaemia Research Fund in 1960 and was Director from 1970 to 1990. He has an honorary fellowship at the Institute of Child Health (University of London) and an Honorary Visiting Research Fellowship at the University of Leeds.

**Professor Raymond (Ray) Powles**

CBE FRCP FRCPATH (b. 1938) has been Physician-in-Charge, since 1974, and Group Head, Haemato-Oncology, since 1993, of the Leukaemia and Myeloma Units at the Royal Marsden Hospital. He has been Professor of Haemato-Oncology at the University of London, Institute of Cancer Research, since 1977, and member of the MRC Working Party on Leukaemia since 1974.

**Professor Cornelius Rhoads**

(1898–1959) was Chief, Medical Division of the Chemical Warfare Service, from 1943 to 1945, Director of the Sloan-Kettering Institute for Cancer Research (1945), Scientific Director, Memorial Center for Cancer and Allied Diseases (1953), and Professor of Pathology, Department of Biology and Growth, Sloan-Kettering Division of Cornell University Medical College (1952). See Rhoads C P. (1946) The sword and the ploughshare. *Journal of the Mount Sinai Hospital* 13: 299–309. Anonymous. (1978) Cornelius Packard Rhoads 1898–1959. *CA: Cancer Journal for Clinicians* 28: 304–312.

**Dr Rosemary Shannon**

FRCP FRCPCH (b. 1943) was appointed in 1980 to Leicester Royal Infirmary as a Consultant Paediatric Oncologist after training in Glasgow and Birmingham. She is a member of the United Kingdom Children's Cancer Study Group.

**Dr John Stock**

CCChem FRSC (b. 1919) began his career as a laboratory technician with British Cellophane Ltd, in Bridgewater, Somerset, from 1938 to 1940. After service in the Royal Air Force (1940–45), he became a full-time London external degree student at Portsmouth Technical College (now University of Portsmouth) (1946–49). He held the 1949/50 Neil Arnott Postgraduate Studentship in Chemistry, which he took up at the National Institute for Medical Research in London, where he worked on potential antitubercular compounds, and for two further (MRC-financed) Studentship years on the same topic. In 1952, he joined the staff of the Institute of Cancer Research in London (the Chester Beatty Laboratories), where he synthesized potential tumour-inhibitory derivatives of mainly amino acids, peptides and nucleosides. He was Deputy Dean from 1983 to 1985 and retired in 1986.

**Dr Tilli Tansey**

HonMRCP (b. 1953) is Convenor of the History of Twentieth Century Medicine Group and Reader in the History of Modern Medical Sciences at the Wellcome Trust Centre for the History of Medicine, University College London.

**Professor John Walker-Smith**

FRCP FRACP FRCPCH (b. 1936) was appointed Consultant/Senior Lecturer in Child Health at Bart's and Queen Elizabeth Hospital for children in 1973, and became Professor of Paediatric Gastroenterology in 1985. He transferred to the Royal Free Hospital, London, in 1995 and spent a sabbatical in History of Medicine with Dr Tilli Tansey in 1993. He retired in October 2000, and has been Emeritus Professor of Paediatric Gastroenterology and Research Associate in the History of Medicine since October 2000, and a member of the History of Twentieth Century Medicine Group since 1993.

**Dr John Wilkinson**

FRCP CChem FRSC (1897–1998) was Consulting Haematologist at the United Manchester Hospitals and Director of the Department of Haematology, University and Royal Infirmary of Manchester, from 1947 to 1962. Together with Leslie Witts he founded the British Society for Haematology, was President of the European Society in 1959 and 'life councillor and founder' of the International Society of Haematology. See Black D. John Frederick Wilkinson. *Munk's Roll* 11. [www.rcplondon.ac.uk/scripts/](http://www.rcplondon.ac.uk/scripts/) (site accessed 3 April 2003)

**Dr Eve Wiltshaw**

OBE MD FRCP FRCOG (b. 1927) qualified in 1952 from the University of Wales and researched clinical haematology in Boston, USA, from 1953 to 1955. She joined the Institute of Cancer Research and Royal Marsden Hospital in 1955 to

work on drug treatment of cancer patients and was Medical Director, from 1986 to 1994. She is best known for the introduction of cisplatin and carboplatin into clinical practice in the UK. See Wiltshaw E. (1998) *A History of the Royal Marsden Hospital*. London: Altman Publishing.

**Professor Maxwell Wintrobe**

FACP (1901–1986) was appointed Professor of Internal Medicine and Chairman of the Department of Medicine at the University of Utah College of Medicine in 1943. He directed the Laboratory for the Study of Hereditary and Metabolic Disorders from 1945 to 1973, and served as Director of the Cardiovascular Research and Training Institute from 1969 to 1973. He was one of the pioneers of treatments for cancer through chemotherapy. His many publications include Wintrobe M M. (1980) *Blood, Pure and Eloquent. A Story of Discovery, of People, and of Ideas*. New York: McGraw-Hill. See Valentine W N. (1990) Maxwell Myer Wintrobe: October 27, 1901–December 9, 1996. *Biographical Memoirs of the National Academy of Sciences* 59: 447–472.

**Professor Leslie Witts**

CBE FRCP (1898–1982) was Nuffield Professor of Clinical Medicine at Oxford from 1938 to 1965 and Fellow of Magdalen College. From 1963 to 1968 he was a member of the Committee on Safety of Drugs and Chairman of the Subcommittee on Adverse Reactions. See Black D. (1984) Leslie John Witts. *Munk's Roll* 7: 618–620.



## Glossary

### Aciclovir (Zovirax)

An antiviral used to treat shingles as well as the herpes simplex virus and other types of herpesvirus infections.

### Acute lymphoblastic leukaemia (ALL)

(see **lymphoblast**) Acute leukaemia in which the abnormal cells are almost totally blast forms of the lymphocytic series.

### Acute myeloid (myeloblastic) leukaemia (AML)

(see **myeloblast**) A form of acute leukaemia in which there are large numbers of **myeloblasts** in the bone marrow.

### Acute promyelocytic leukaemia (APML)

Acute leukaemia presenting as a severe bleeding disorder with infiltration of the bone marrow by abnormal promyelocytes and myelocytes, a low plasma fibrinogen, and defective coagulation (also known as AML-FAB-M3).

### ALL

See **acute lymphoblastic leukaemia**.

### Aminopterin

A **folic acid** antagonist resulting in remission in **ALL** of children. *op. cit.* note 11.

### AML

See **acute myeloid leukaemia**.

### APML

See **acute promyelocytic leukaemia**.

### Azaserine

An antibiotic inhibitor of purine synthesis, mutagenic and antitumorogenic. See notes 20 and 143.

### Azathioprine (Imuran)

A derivative of **6-mercaptopurine** used as an immunosuppressive drug and in the treatment of **leukaemia**.

### Breakpoint cluster region (BCR)

The location within the BCR gene where DNA is transected in **chronic myeloid leukaemia**.

### Busulphan (Myleran)

An alkylating agent introduced for the treatment of **chronic myeloid leukaemia**. Side effects include bone marrow suppression and increased pigmentation of the skin.

### CGL

See **chronic granulocytic leukaemia**.

### Chemotherapy

The use of chemicals, especially drugs, in the treatment of cancer.

### Chronic granulocytic leukaemia (CGL)

A form of **leukaemia** characterized by an uncontrolled proliferation of myeloid cells in the bone marrow and in extramedullary sites, and the presence of large numbers of immature and mature granulocytic forms in various tissues and organs, and in the circulating blood. Now more commonly referred to as **CML**.

### Chronic lymphocytic leukaemia (CLL)

A variety of **leukaemia** characterized by lymphocytosis and an uncontrolled proliferation and conspicuous enlargement of lymphoid tissue at various sites such as lymph nodes, spleen and bone marrow.

### Chronic myeloid leukaemia (CML)

See **CGL** above.

### Chlorambucil

An alkylating drug that was introduced for the treatment of chronic lymphocytic leukaemia.

### CML progenitor cells

Immature cells present in the blood and bone marrow in CML.

### Cyclosporin A

An immunosuppressive agent commonly used in organ transplantation. It inhibits T-cell formation and interleukin-2 production.

### Daunorubicin

An antibiotic that interferes with DNA synthesis and is used in the treatment of acute leukaemia.

### Folic acid

A B vitamin necessary for DNA and RNA synthesis that allows the growth and reproduction of cells. It helps in the formation of red blood cells.

### Giemsa stain

A mixture of methylene blue and eosin, used for distinguishing different types of white blood cell and for detecting parasitic microorganisms in blood smears. It is one of the **Romanowsky stains**.

### Gleevec or Glivec

Also known as **imatinib** or **STI571**. A new drug for CML. See page 42.

### Granulocyte

A white blood cell that, when stained with **Romanowsky stains**, are seen to contain granules in their cytoplasm.

### Granulocyte colony-stimulating factor (GCSF)

A cytokine that stimulates proliferation of myeloid cells.

### Haemopoietic stem cells

The most primitive blood-forming cell in the bone marrow.

### Haemopoiesis

The process of formation and development of the various types of blood cells.

### Imatinib

See **Gleevec**, **Glivec**.

### Leishmann stain

A neutral stain for blood smears devised by the British surgeon Sir William Leishmann (1865–1926). It consists of a mixture of eosin (an acidic stain), and methylene blue (a basic stain) in alcohol and is usually diluted and buffered before use. It stains the different components of blood in a range of shades between red and blue.

### Leucapheresis

A procedure in which **leucocytes** are removed from blood outside the body and the remaining blood is retransfused into the donor.

### Leucocyte

A white blood cell. Leucocytes are nucleated and lack haemoglobin. They form part of the immune system. See **lymphocyte**.

### Leukaemia

Any of a group of malignant diseases in which the bone marrow and other blood-forming organs produce increased numbers of certain types of white blood cells (**leucocytes**). It is classified by the dominant cell type (for example **ALL**, **AML**, etc.) and by duration from onset to death (acute or chronic) if untreated. In 'acute' leukaemia, death often ensued within a few months. It is associated with acute symptoms such as severe anaemia, haemorrhage and fever. The duration of 'chronic' leukaemia is measured in years, with graded onset of anemia or enlargement of spleen, liver or lymph nodes.

### Lymphoblast

An early lymphocyte precursor present in the bone marrow and blood in **lymphoblastic leukaemia**.

**Lymphocyte**

A type of white blood cell (**leucocyte**). They are formed in the lymph nodes, bone marrow, spleen, and provide about one-quarter of all circulating **leucocytes**. They are important in the body's defence and are responsible for immune reactions. There are two populations of lymphocytes: B lymphocytes, which produce circulating antibodies and are responsible for humoral immunity; and T lymphocytes, which are responsible for cell-mediated immunity.

**May–Grünwald–Giemsa**

A Romanowsky stain used for blood and bone marrow films.

**Megaloblastic anaemia**

A form of anaemia caused by shortage of vitamin B12 or **folic acid**.

**Melphalan**

An alkylating drug used for the treatment of **myeloma**.

**6-mercaptopurine (6-MP)**

An antineoplastic agent developed by **Gertrude Elion** and **George Hitchings**. See pages 65 and 67 and note 143.

**Methotrexate**

A variant of **folic acid** that interferes with cell growth and is used to treat **leukaemia**.

**Myeloblast**

The earliest identifiable cell that gives rise to a **granulocyte**, having a large nucleus and scanty cytoplasm. It is normally found in the blood-forming tissue of the bone marrow, but may appear in the blood in a variety of diseases, most notably in **acute myeloblastic leukaemia (AML)**.

**Myeloma**

Cancer of the plasma cells of the bone marrow.

**Myelopoiesis**

Formation of **leucocytes** usually in the bone marrow.

**Nitrogen mustard**

Compounds of the general formula  $R-N(CH_2CH_2Cl)_2$ , used for their destructive action upon lymphoid tissue in **leukaemia**, Hodgkin's disease and other cancers.

**Pancytopenia**

Reduction in the number of erythrocytes, white blood cells and platelets in circulating blood.

**Platelet**

Platelets are cells present in large numbers in blood and play an important role in blood clotting.

**Promyelocytic leukaemia**

A form of **AML** characterized by propensity to bleed excessively (also known as **AML-FAB-M3**).

**Protooncogene**

A gene involved in the regulation of normal cell growth or proliferation and which when mutated may induce malignancy.

**Romanowsky stains**

A group of stains used for microscopic examination of blood cells. Romanowsky stains give characteristic staining patterns, on the basis of which blood cells are classified, for example, into neutrophils, eosinophils and basophils. The group includes the stains of **Leishmann**, **Wright** and **May–Grünwald–Giemsa**.

**Sternberg lymphoma**

A form of lymphoma present in the mediastinum and involving cells of T lineage.

**STI571 (Imatinib)**

See **Gleevec**.

### Terminal deoxynucleotidyl transferase

Terminal deoxynucleotidyl transferase (TdT) is an enzyme that catalyses the random addition of mononucleotides from dNTPs to the terminal 3'-OH of a DNA initiator, accompanied by the release of inorganic phosphate. The enzyme thus provides a unique method for the labelling of the 3' termini of DNA.

### Vinblastine (Velbe)

A cytotoxic drug that is given by intravascular injection mainly in the treatment of cancers of the immune system, such as Hodgkin's disease. It is highly toxic, since it also acts on normal tissues; common side effects include nausea, vomiting, diarrhoea, and depression of bone marrow function.

### Vinca alkaloids

A group of antimitotic drugs derived from the Madagascar periwinkle (*Vinca rosea* – also called *Catharanthus roseus*) that are used especially to treat leukaemias and lymphomas. The group includes **vinblastine** and **vincristine**.

### Vincristine (Oncovin)

A cytotoxic drug with uses and side effects similar to those of **vinblastine**.

### Wright's stain

Wright's stain is one of the **Romanowsky** stains.



## Index: Subject

- ABL protooncogene, 40–41  
 aciclovir, 61, 71  
 ACTH, 29, 44  
 acute leukaemias  
   chromosome abnormalities, 32  
   classification, 16, 31, 34, 36–37, 38, 72  
   diagnostic markers, 37–38  
   MRC trials, 53–54  
   *see also* acute lymphoblastic leukaemia; acute myeloid leukaemia  
 acute lymphoblastic leukaemia (ALL), 16, 71  
   adult, 15  
   childhood *see* childhood acute lymphoblastic leukaemia (ALL)  
   haematopoietic stem cell rescue, 19  
   T-cell (T-ALL), 35, 38, 39  
 acute myeloid leukaemia (AML), 16, 71  
   bone marrow transplantation, 58, 60  
   chemotherapy, 9, 15–16, 17, 53–54, 56–57, 71  
   childhood, 48  
   haematopoietic stem cell rescue, 19  
   immunotherapy, 17, 53, 58–59  
   M3 *see* acute promyelocytic leukaemia  
   M5 (acute monocytic leukaemia), 22  
   MRC trials, 53–54, 56–57  
 acute promyelocytic leukaemia (APML) (M3 AML), 16, 19, 37, 42, 71, 73  
 adrenocorticotrophic hormone (ACTH), 29, 44  
 agar, sloppy, 4  
 alkaline phosphatase anti-alkaline phosphatase (APAAP) technique, 33  
 alkylating agents, 4–6, 7, 47  
   *see also* busulphan; chlorambucil; melphalan  
 ALL *see* acute lymphoblastic leukaemia  
 All-India Institute of Medical Sciences, New Delhi, India, 20  
 all-*trans*-retinoic acid, 19, 42  
 alpha-interferon, 18, 41  
 American Society of Clinical Oncology (ASCO), 15, 42  
 amethopterin *see* methotrexate  
 AMGEN, 18  
 aminopterin, 7–8, 22, 43–44, 71  
   *see also* folic acid antagonists  
 AML *see* acute myeloid leukaemia  
 animal blood, transfusions using, 28, 29  
 Ann Arbor, Michigan, USA, 10  
 anthracycline, 15  
   *see also* daunorubicin  
 antibiotics, 28, 43, 51  
 antigens, cell surface, 33  
 antimetabolites, 7–9, 8–9  
 APML *see* acute promyelocytic leukaemia  
 arabinosyl cytosine *see* cytosine arabinoside  
 Argentina, 25, 34  
 arsenic, 10, 13, 20  
 ASCO (American Society of Clinical Oncology), 15, 42  
 Association of Clinical Pathologists, 10–11  
 Australia, 18, 19, 35  
 avidin–biotin peroxidase methods, 33  
 ayurvedic medicine, 20  
 azaserine, 9, 71  
 azathioprine, 9, 65, 67, 71  
 azure B, 30  
  
 Bart's *see* St Bartholomew's Hospital, London  
 B-cells, malignant, 35  
 BCG vaccine, 16–17, 26, 49, 58–59  
 BCR gene, 40, 71  
 BCR–ABL fusion gene, 41  
 blast cells, 35, 39, 45–46  
 bleeding, 27  
 blood cell separators, 60

- blood transfusions, 27–29, 43, 50–51
- BMT *see* bone marrow transplantation
- bone marrow
  - aspiration biopsy, 52
  - failure (pancytopenia), 16, 21, 22–23, 73
  - toxicity (myelotoxicity), 57
- bone marrow transplantation (BMT), 17–18, 19, 58
  - allogeneic, 18, 58, 59, 60
  - early, 22–23
  - HLA-matched, 18
  - mismatched, 18, 60
- Bordetella pertussis*, 16–17
- Boston, Massachusetts, USA, 11, 23–24
- breakpoint cluster region (BCR), 40, 71
- British Journal of Haematology*, 29
- British Medical Journal*, 35
- Burroughs Wellcome, Tuckahoe, NY, USA, 48
- busulphan, 5, 13–14, 20, 22–23, 71
- butterfly cannulas, 27
  
- Calman reforms, 62
- Cambridge, UK, 10, 29, 30–31, 32
- cancer research, 61, 62
- cardiotoxicity, daunorubicin-induced, 15, 26
- career structure, clinical scientists, 61–62
- Catharanthus roseus*, 14, 74
- CB1348 *see* chlorambucil
- CBRI *see* Chester Beatty Research Institute
- CD3, 38
- central nervous system (CNS), radiotherapy
  - (prophylaxis), 15, 26, 49, 58
- central venous lines, 51
- CGL, *see* chronic granulocytic leukaemia
- charity commissioners, 64
- Chemical Warfare Service, US, 11
- Chemotherapy, 71
  - combination, 15–16, 45, 49, 56–57
  - early development, 4–6, 7–16, 44–48
  - intensification, 17, 49, 54
  - maintenance, 15, 45–46, 47, 52
  - myeloablative, 17, 18, 19
  - single agent, 14, 56
  - toxic effects, 15, 25–26, 45, 47, 50, 54–55, 57
  - vs* radiotherapy, 21, 23
- Chester Beatty Research Institute (CBRI),
  - London, 4–7, 10, 12, 14
  - see also* Institute of Cancer Research
- childhood acute lymphoblastic leukaemia (ALL),
  - 42–48, 49–51, 52, 71
  - blood transfusions, 29, 43
  - boys *vs* girls, 47, 52
  - immunotherapy, 16–17, 46, 49
  - MRC (UKALL) trials, 46–48, 49, 51
  - pre-1948 treatment, 43
  - ‘Total Therapy,’ 14–15, 45–46
- childhood leukaemia, 42–43, 61
  - AML, 48
  - cure, 26–27
  - research needs, 62
  - T lymphoblastic (T-ALL), 35, 38, 39
  - Treatment-associated toxicity, 54
- Children’s Cancer Group (CCG), USA, 47
- China, 19
- chlorambucil, 5, 10, 14, 72
- chloramphenicol, 28
- Christie Hospital, Manchester, 13, 20
- chromosomes
  - abnormalities, 32–33, 37, 39–41, 50
  - number of human, 31
  - Philadelphia (Ph), 32, 39–41
  - translocations, 19, 32, 37
- chronic granulocytic leukaemia (CGL), 23, 32, 39, 40, 71
  - see also* chronic myeloid leukaemia
- chronic leukaemias
  - classification, 31, 37, 71, 72
  - diagnostic tests, 38
  - see also* chronic lymphocytic leukaemia; chronic myeloid leukaemia
- chronic lymphocytic leukaemia (CLL), 14, 34, 71

- classification, 31, 37, 72
- haematopoietic stem cell rescue, 19
- chronic myeloid leukaemia (CML), 71
  - alpha-interferon therapy, 18, 41
  - bone marrow transplantation, 18, 22–23, 60
  - classification, 31, 37, 71, 72
  - early chemotherapy, 10, 13–14
  - haematopoietic stem cell rescue, 19
  - patient treated in India, 19–20
  - Philadelphia (Ph) chromosome, 32, 39–41
  - progenitor cells, 41, 72
  - STI571 (imatinib) therapy, 42
- Ciba Geigy, 41
- classification of leukaemia, 16, 30–31, 34, 72
  - diagnostic markers, 35–36, 37–38
  - FAB group, 36–37, 38–39
- clinical scientists, career structure, 61–62
- clinical trials
  - future needs, 62, 63–64
  - MRC *see* Medical Research Council
  - randomized, 47–48, 57, 58
- CLL *see* chronic lymphocytic leukaemia
- CML *see* chronic myeloid leukaemia
- CNS *see* central nervous system
- colitis, paralytic, 25–26
- combinatorial chemistry, 6
- common ALL antigen, 33, 36
- compliance, physicians with chemotherapy
  - protocols, 47, 51
- Concord trial, 26, 46, 58–59
- cortisone, 29, 44
- co-trimoxazole (Septrin), 51
- CRC Centre for Cancer Therapeutics, 6
- cure, 26–27
- cyclophosphamide, 57
- cyclosporin A, 60, 72
  - see also* nephrotoxicity
- cytarabine *see* cytosine arabinoside
- cytochemistry, 31, 34, 36
- cytogenetics, 31–33, 37, 39–41, 50, 62
- cytosine arabinoside (cytarabine), 15, 16, 53, 54
- DAT chemotherapy regimens, 53–54
- daunorubicin (daunomycin), 15, 16, 26, 72
  - in DAT regimens, 53, 54
- Delhi, India, 19–20
- deoxynucleotide triphosphates, 37
- Department of Health and Social Security (DHSS), 53
- Detroit, Michigan, USA, 8–9
- Duke University, Durham, North Carolina, USA, 21
- Edinburgh, 12, 39–40, 50
- electron microscopy, 34
- encephalitis, 54
- eosin Y, 30
- erythrocyte rosettes, sheep, 35, 36
- erythromycin, 28
- ethyl carbamate (urethane), 13, 20–21
- FAB (French–American–British) group, 36–37, 38–39
- FDA (Food and Drug Administration), 42, 61
- fluorescence *in situ* hybridization (FISH), 32–33
- folic acid, 8, 72
  - antagonists, 7–8, 22, 29, 44
  - see also* aminopterin
- Food and Drug Administration (FDA), 42, 61
- France, 15, 26, 33, 36, 40, 46, 59
- French–American–British (FAB) group, 36–37, 38–39
- funding
  - leukaemia research and therapy, 48–49, 53, 61–64
  - National Health Service, 50–51, 53
- G-CSF, *see* granulocyte colony-stimulating factor
- gender differences, response to therapy, 47, 52
- Germany (including West Germany), 46, 47, 49, 59

- Giemsa banding (stain), 32, 72  
 Glasgow, 50  
 Gleevec, Glivec (STI571, imatinib), 40, 41–42, 44, 72  
 GM-CSF, *see* granulocyte-macrophage colony-stimulating factor  
 graft-versus-host disease (GVHD), 17–18, 60  
 graft-versus-leukaemia reaction, 18  
 granulocyte, 19, 72  
 granulocyte colony-stimulating factor (G-CSF), 18, 19, 72  
 granulocyte-macrophage colony-stimulating factor (GM-CSF), 18  
 Great Ormond Street Hospital for Sick Children, London, 29, 31, 52  
 growth factors, haemopoietic, 18, 19  
 GVHD *see* graft-versus-host disease  
  
 ‘Haddow’ phenomenon, 5  
 haematology, laboratory *vs* clinical, 24–25  
 haemopoiesis, 72  
 haemopoietic growth factors, 18, 19  
 haemopoietic stem cells, 19, 72  
 haemorrhage, 27  
 Hammersmith Hospital, London, 3, 21, 22, 23, 24–25, 34–35, 37, 39  
 Henry Ford Hospital, Detroit, Michigan, 8–9  
 herpes viruses, 61  
 Heyl stain, 30  
 HN2 (nitrogen mustard), 6, 10, 11, 12, 73  
 Hodgkin’s disease, 10, 15–16  
 Houston, Texas, USA, 16  
  
 imatinib (STI571), 40, 41–42, 44, 72  
 immunological techniques, 33, 34, 35, 36  
 immunotherapy, 26, 58–60  
     in AML, 17, 53, 58–59  
     in childhood ALL, 16–17, 46, 49  
     post-transplant, 59, 60  
 Imperial College School of Medicine, Hammersmith Hospital, London, 3  
 Imuran (azathioprine), 9, 65, 67, 71  
 India, 19–20  
 infections, 28  
 Institute of Cancer Research, Royal Cancer Hospital, London, 4, 6, 23–24  
     *see also* Chester Beatty Research Institute; Royal Cancer Hospital  
 alpha-interferon, 18, 41  
 intravenous drips, 25, 27  
  
 kidney transplantation, 60  
 King’s College Hospital, London, 31  
  
 Lady Tata Memorial Hospital, Mumbai, India, 20  
*Lancet*, 9, 35, 43  
 Leishmann stain, 30, 72  
 leucapheresis, 60, 72  
 leucocyte, 72  
 leukaemia, definition, 72  
*Leukaemia: Research and Clinical Practice* (Hayhoe 1960), 34  
 leukaemia cells, 50  
     detection of residual, 38  
     irradiated, 16–17, 49  
     morphology, 30–41  
     origin and nature, 38  
 Leukaemia Research Fund (LRF), 18, 19–20, 61–64  
     Centre for Adult Leukaemia, 3  
 Leukaemia Unit, MRC, 3–4, 25  
*Leukemia and Allied Disorders* (Forkner 1938), 30  
 LRF *see* Leukaemia Research Fund  
 lymphoblast, 72  
     *see also* ALL, blast cells  
 lymphocyte, 35, 38, 73  
 lymphoid leukaemias, 35–36  
     *see also* acute lymphoblastic leukaemia; chronic lymphocytic leukaemia  
 lymphoma, 23  
     Sternberg (T lymphoblastic

- leukaemia/lymphoma), 35, 39, 73  
*see also* Hodgkin's disease
- maintenance treatment, 14, 45–46, 47, 52
- Manchester, 12, 13, 18, 20, 52
- 'Manchester drug,' 21
- Manchester Royal Infirmary, Manchester, 13
- Massachusetts Institute of Technology, Cambridge, Massachusetts, USA, 41
- May–Grünwald–Giemsa stain, 30, 73
- measles (and measles vaccine), 52, 54
- Medical Research Council (MRC)  
 Cancer Committee, 55  
 clinical trials, 16, 23, 51, 53–59  
   annual review, 58  
   childhood ALL (UKALL), 46–48, 49, 51  
   Concord trial, 26, 46, 58–59  
   myeloma, 35, 54–55, 56, 57  
 Cytogenetics Group, 39–40  
 financial support, 53  
 Leukaemia Unit, 3–4, 25  
 Leukaemia Working Parties, 23, 30–31, 46, 48, 53, 55
- megaloblastic anaemia, 37, 73
- Melbourne, Australia, 18, 19
- melfhalan, 5, 6, 14, 57, 73
- Memorial Hospital, New York, 16
- 6-mercaptopurine (6-MP), 9, 14, 44, 49, 56, 73  
 discovery, 48  
 maintenance therapy, 15, 52
- methotrexate, 8, 49, 73  
 bone marrow transplantation and, 60  
 maintenance therapy, 15, 45, 52  
 toxicity, 45, 50
- Middlesex Hospital, London, 28
- minimal residual disease (MRD), 38, 62
- molecular biology, 18, 32–33, 42
- monoclonal antibodies, 33, 34
- morphology, leukaemia cells, 30–41
- 6-MP *see* 6-mercaptopurine
- MRC *see* Medical Research Council
- mustard gas, 11
- myeloablative chemotherapy, 17, 18, 19
- myeloblast, 73
- myelodysplasia, 37
- myeloid leukaemias, 36  
*see also* acute myeloid (myelogenous) leukaemia;  
 chronic myeloid leukaemia
- myeloma (myelogenous), multiple (myelomatosis), 14, 21, 34–35, 73  
 MRC trials, 35, 54–55, 56, 57
- myelopoiesis, 73
- myeloproliferative diseases, 38
- myelotoxicity, 57
- Myleran *see* busulphan
- National Cancer Institute, 44–45
- National Cancer Research Institute, 55
- National Cancer Research Network, 63
- National Health Service (NHS)  
 clinical scientists and, 62  
 establishment, 43  
 funding, 50–51, 53
- nausea and vomiting, 21
- nephrotoxicity, cyclosporin, 60
- neurotoxicity, methotrexate, 50
- New York, 8–9, 11, 16  
*New York Times*, 9
- NHS *see* National Health Service
- nitrogen mustard (HN2), 6, 10, 11, 12, 73
- Nobel Prize winners, 44, 59, 61, 65, 67
- Novartis, 41–42
- nursing staff, 25, 51
- oncology, medical, 17, 24
- pancytopenia (bone marrow failure), 16, 21, 22–23, 73
- panoptic staining, 30–31
- para-amino benzoic acid (PABA), 48

- Paris, France, 15, 26, 29, 36, 59
- Paterson Institute, Manchester, 18
- periodic acid–Schiff (PAS), 31
- phase-contrast microscopy, 33–34
- Philadelphia, Pennsylvania, USA, 26, 39–40
- Philadelphia (Ph) chromosome, 32, 39–41
- platelet, 19, 20, 35, 45, 49, 73
- platelet transfusions, 26, 27, 28, 45
- pneumonia, interstitial, 54
- polycythaemia, 57
- prednisolone, 29, 49, 57
- prednisone, 15
- progenitor cell, 41, 72
- promyelocytic leukaemia (M3) *see acute promyelocytic leukaemia*
- protooncogene, 40, 41, 73
- Public Health Laboratory Service, Colindale, 49
- purine analogues, 44, 48
- Q banding, 32
- quality of life, 57–58
- Queen Elizabeth (liner), 7, 8
- quinacrine banding, 32
- radiotherapists, 21, 23
- radiotherapy (X-ray therapy), 10
  - central nervous system (CNS) (prophylaxis), 15, 26, 49, 58
  - in T lymphoblastic disease, 39
  - testicular, 47, 57
  - vs* chemotherapy, 21, 23
- Ramayana* (Sanskrit poem), 13
- randomization, total *vs* partial, 57
- randomized clinical trials, 47–48, 57, 58
- recombinant DNA technology, 18
- remission
  - complete, 16
  - detection of minimal residual disease, 38
  - induction, 57
- renal failure, in myeloma, 21, 54–55
- research
  - funding, 48–49, 53, 61–64
  - translational, 61–62
- response rates, early chemotherapeutic agents, 16
- all-*trans*-retinoic acid, 19, 42
- Romanowsky stains, 30, 73
  - see also* Leishmann, Wright and May–Grünwald–Giemsa
- rosettes, sheep erythrocyte, 35, 36
- Royal Cancer Hospital, London, 4, 13, 20–21
  - see also* Chester Beatty Research Institute; Institute of Cancer Research
- Royal Free Hospital, London, 37
- Royal Marsden Hospital, 21, 23, 30
  - Fulham Road, London, 7
  - Sutton, Surrey, 26, 49, 60
- Science*, 39–40, 41
- Scottish Health Service, funding, 50–51
- screening, in drug discovery, 6
- Second World War, 11, 12
- Seattle, Washington, USA, 17–18, 59
- Septtrin (co-trimoxazole), 51
- sheep erythrocyte rosettes, 35, 36
- Sloan Kettering Institute, New York, 9, 11, 48
- St Bartholomew’s Hospital, London (Bart’s)
  - in 1960s, 14–16, 25
  - blood transfusion, 28, 29
  - bone marrow aspiration, 52
  - chemotherapy regimens (Bart’s 3, Bart’s 4 etc.), 53–54, 56–57
  - immunotherapy studies, 58, 59
- St George’s Hospital, London, 32
- St Jude Children’s Research Hospital, Memphis, Tennessee, USA, 14–15, 26, 45–46, 49
- St Thomas’ Hospital, London, 27–28
- staining techniques, 30–31
- statisticians, 50, 55–56, 57–58
- stem cell factor, 18

- stem cells,  
  haemopoietic, 19, 72
- Sternberg (T lymphoblastic) lymphoma, 35, 39, 73
- steroids, 44  
  *see also* cortisone; prednisolone; prednisone
- STI571 (imatinib), 40, 41–42, 44, 73
- Sudan black, 31
- sulphanilamide, 48
- supportive care, 51, 54
- survival, 8, 25, 26–27  
  long-term, 16, 17, 45, 56–57  
  rates, 17, 43, 47, 48, 53, 62
- Switzerland, 20, 22, 33
- T-cells, malignant, 35
- T lymphoblastic leukaemia/lymphoma (Sternberg lymphoma), 35, 39, 73
- terminal deoxynucleotidyl transferase (TdT),  
  35–36, 37–38, 74
- testicular irradiation, 47, 57
- thioguanine, 16, 53, 54
- thymus gland, 35, 39
- ‘Total Therapy,’ 14–15, 45–46
- toxicity, chemotherapeutic drugs, 15, 25–26, 45,  
  47, 50, 54–55, 57
- translational research, 61–62
- translocations, chromosome, 19, 32, 37
- UKALL trials, 46–48, 49, 51
- United States (USA), 52  
  chemotherapy protocols, 47  
  childhood ALL therapy, 14–15  
  classification of leukaemia, 30, 39  
  early development of chemotherapy, 8–11, 12,  
  16, 45–46, 48  
  haematology, 24  
  travel to, 7, 8
- University College Hospital (UCH), London, 21
- urethane (ethyl carbamate), 13, 20–21
- VAMP chemotherapy regimen, 49
- Velbe *see* vinblastine
- vinblastine, 25–26, 74
- vinca alkaloids, 14, 44–45, 74
- vincristine, 15, 45, 49, 74
- vomiting, 21
- wards, Nightingale, 25
- Wellcome Clinical Research Fellow, 14
- Wellcome Trust, 3, 64
- Westminster Hospital, London, 33–34
- Whitehead Institute for Biomedical Research,  
  Cambridge, Massachusetts, USA, 41
- Woods and Fildes’s hypothesis, 48
- Wright’s stain, 30, 74
- X-ray therapy *see* radiotherapy
- Zovirax (aciclovir), 61, 71





## Index: Names

Biographical notes appear in bold

- Alexander, Peter, 17, 26
- Baltimore, David, 41
- Beatty, Chester, 7
- Bennett, John, 36
- Bergel, Franz, 5–6, 12
- Bernard, Jean, 15, 16, 29
- Bessis, Marcel, 29, 34
- Bethell, Frank, 8
- Bichel, Jorgen, 8
- Blackburn, Eddie, 31
- Booth, Sir Christopher, 3, 25, 52, 64, **65**
- Borella, L, 35
- Boyland, Eric (Dick), 12, 22, **65**
- Bradstock, Ken, 38
- Brain, Michael, 24, 25
- Bronchud, Miguel, 18
- Brown, Bill Court, 39
- Burchenal, Joseph (Joe), 8–9, 11, 26, 44
- Callender, George, 28
- Callender, Sheila, 30
- Calne, Sir Roy, 60
- Caspersson, T, 32
- Catovsky, Daniel, 3, 24–25, 34–36, 37, 38, 58, **65**
- Cawley, John, 34
- Clarkson, Barney, 16
- Cohen, Lord, 55
- Crowther, Derek, 12–19, 25, 26, 27, 28, 52, 53, 56–57, 58, **65**
- Dacie, Sir John, 3, 22, 24, 25, 29, 30, 34–35, 52, 63, **65**
- Daley, George, 41
- Dameshek, William, 23–24
- Daniel, Marie-Thérèse, 36
- Dausset, Jean, 33–34
- Davidson, Bill, 31
- Djerassi, Isaac, 26
- Dock, George, 10
- Doll, Sir Richard, 55–56
- Druker, Brian, 41
- Easson, Eric, 31
- Ehrlich, Paul, 30
- Elion, Gertrude (Trudy), 44, 48, 61, **65**
- Farber, Sidney, 7–8, 11, 14, 22, 24, 43–44, **65–66**
- Fildes, Paul, 48
- Flandrin, George, 36
- Fletcher, Frank, 12
- Ford, C E, 32
- Ford, John, 41
- Forkner, C E, 30
- Fountain, James, 31
- Fraser, Russell, 21
- Freireich, Emil J, 16, 56, 57, **66**
- Galton, David, 3, 4–5, 7, 8, 12, 13–14, 20–23, 24, 25, 27–28, 29, 30, 34, 35, 36, 38–40, 44, 52, 53, 55–56, **66**
- Ganeshaguru, K, 37
- Gee, Tim, 16
- Gilman, Alfred, 12
- Goldman, John, 3–4, 5, 7, 8, 10, 12, 18, 19–20, 23, 24, 25, 26, 27, 28, 29, 30, 34, 37, 40–42, 42, 48, 49, 51, 52, 53, 56, 57, 58, 59, 60, 61, 62, 63, 64, **66**
- Goodman, J R, 34
- Gralnick, Harvey, 36
- Grant, David, 61–62, 63–64, **66**
- Greaves, Mel, 33, 35, 38, 50, **66**

- Groffen, J, 40  
Grosveld, G, 40
- Haddow, Sir Alexander, 4–5, 6, 7, 12, 13, 20–21, 22, 24, **66**
- Hamilton-Fairley, Gordon, 14, 15–16, 17, 26, 51, 60, **66–67**
- Hancock, Percy Thompson, 21
- Hardisty, Roger, 30–31, 46
- Harman, John, 21
- Hay, John, 3
- Hayhoe, Frank, 8–10, 28, 29, 30–34, 34, 37, 39, 54, 63, **67**
- Heisterkamp, N, 40
- Hill, Sir Austin Bradford, 55
- Himsworth, Sir Harold, 21
- Hitchings, George, 44, 48, **67**
- Hoffbrand, Victor, 7–8, 35–36, 37–38, **67**
- Holman, C A, 31
- Huang, M E, 19
- Hungerford, D A, 39–40
- Hunter, Peter, 28, 42, 48, **67**
- Illingworth, Ronald, 45
- Jacobs, Patricia, 32, 39–40
- Janossy, George, 35, 37, 38
- Jarman, Michael, 6
- Karnofsky, David, 11
- Kay, Humphrey, 22–23, 26, 27, 46, 48, 49–51, 55, 57–58, **67**
- Kemp, N H, 32
- Kennaway, Sir Ernest, 4, **67**
- Kilmann, Sven-Åge, 40
- Köhler, Georges, 33
- Koller, Peo, 12
- Kon, S K, 12
- Lajtha, Lazlo G, 32
- Ledlie, Elspeth, 23
- Levan, Albert, 31
- Lilleyman, Sir John, 26, 42–48, 52, **68**
- Lissauer, H, 13
- MacLennan, Ian, 53–55, **68**
- Malpas, Jim, 15, 26, 51
- Mathé, Georges, 16, 17–18, 26, 49, 58–59
- Matthias, John, 26
- McCaffrey, R P, 35–36
- McElwain, Tim, 46
- McMichael, Sir John, 21, 22, 25
- Metcalf, Don, 18
- Milstein, César, 33
- Moeschlin, Sven, 33–34
- Nossal, G J, 35
- Nowell, Peter C, 39–40
- Osler, Sir William, 10, 61
- Paterson, Edith, 13, 20
- Paterson, James Ralston, 13, 20
- Pearce, Mila, 52
- Peto, Sir Richard, 55–56, 57, 58
- Philips, Fred, 11, 12
- Pike, Malcolm, 58
- Piller, Gordon, 4, 8, 10–12, 19, 29, 61, 63, 64, **68**
- Pinkel, Donald, 14, 45, 49
- Powles, Raymond (Ray), 7, 17, 25–26, 27, 28, 41, 58, 59–61, **68**
- Prakash, Vadya, 19–20
- Pulvertaft, R J V, 33–34
- Quaglino, Dennis, 32
- Rees, John, 54
- Rhoads, Cornelius, 11, 12, 48, **68**

- Rohr, Karl, 20  
Ross, Walter, 6, 12  
Rowley, Janet, 32, 40  
Rundles, Wayne, 21
- Scott, Sir Ronald Bodley, 14, 15–16, 21, 25,  
30–31, 51–52  
Secker-Walker, Lorna, 50  
Sen, L, 35  
Sexton, W A, 20  
Shannon, Rosemary, 51, 52, **68**  
Sheridan, W P, 19  
Smith, Ted Gordon, 24  
Smithers, David, 23  
Spiers, Alexander, 3, 25  
Stafford, J L, 32  
Stock, Chester C, 11  
Stock, John, 5–6, 7, 12, **68**  
Storb, Rainer, 59  
Subba Row, Yella, 8, 11  
Sultan, Claude, 36, 38–39  
Szur, Leon, 23
- Tanaka, Y, 34  
Tansey, E M (Tilli), 3, 64, **69**  
Tanzer, Joseph, 40  
Thomas, Donnall, 17, 59  
Thompson, R B, 31  
Timmis, Geoffrey, 12  
Tjio, Joe Hin, 31
- Virchow, Rudolf, 63
- Walker-Smith, John, 51, **69**  
Weatherall, Sir David, 3, 18, 24  
Wetherley-Mein, Gordon, 27, 30  
Whitby, Sir Lionel, 10–11, 28, 29, 63  
Wilkinson, John, 10, 12, 13, 52, **69**  
Wiltshaw, Eve, 23–24, 27, **69**
- Wintrobe, Maxwell, 10, 24, **69**  
Witts, Leslie, 26, 30, 49, **69**  
Wood, Constance, 23

