



## **The Discovery, Use and Impact of Platinum Salts as Chemotherapy Agents for Cancer**

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# THE DISCOVERY, USE AND IMPACT OF PLATINUM SALTS AS CHEMOTHERAPY AGENTS FOR CANCER

The transcript of a Witness Seminar held by the Wellcome Trust Centre  
for the History of Medicine at UCL, London, on 4 April 2006

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

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## Abbreviations

<b>AFP</b>	alpha fetoprotein
<b>AMD473</b>	picoplatin, [ <i>cis</i> -amminedichloro (2-methylpyridine) platinum]
<b>ASCO</b>	American Society of Clinical Oncology
<b>AUC</b>	area under the curve
<b>BRL 43694</b>	granisetron
<b>CHIP</b>	<i>see</i> JM9
<b>Cisplatin</b>	<i>cis</i> -dichlorodiammineplatinum II
<b>FDA</b>	Food and Drug Administration
<b>GFR</b>	glomerular filtration rate
<b>GR 38032F</b>	later ondansetron, or Zofran®
<b>HPLC</b>	high pressure liquid chromatography
<b>5HT</b>	5-hydroxytryptamine
<b>ICS 205-930</b>	tropisetron
<b>JM</b>	Johnson Matthey
<b>JM216</b>	[ <i>cis</i> -, <i>trans</i> - 5(O <sub>2</sub> CCH <sub>3</sub> ) <sub>2</sub> (NH <sub>3</sub> ) (cyclohexylamine)]
<b>JM8</b>	carboplatin, [ <i>cis</i> -diammine (1,1-cyclobutanedicarboxylato) platinum (II)], Paraplatin®
<b>JM9</b>	iproplatin, <i>cis</i> -dichlorobis (isopropylamine) <i>trans</i> -dihydroxyplatinum (IV)
<b>MRC</b>	Medical Research Council
<b>MSU</b>	Michigan State University
<b>6-MP</b>	6-mercaptopurine
<b>NCI</b>	National Cancer Institute
<b>NIH</b>	National Institutes of Health



<b>OPB</b>	Paediatric Oncology Group of Benelux
<b>PhRMA</b>	Pharmaceutical Research and Manufacturers of America Association
<b>SIOPEL</b>	International Childhood Liver Tumour Strategy Group
<b>STS</b>	sodium thiosulfate
<b>UEA</b>	University of East Anglia

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

In 1990 the Wellcome Trust created a History of Twentieth Century Medicine Group, associated with 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 benefits 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 UCL 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 nearly 50 such meetings, most of which have been published, as listed on pages xvi–xx.

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

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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 UCL.

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

As with all our meetings, we hope that even if the precise details of some of the technical sections are not clear to the non-specialist, the sense and significance of the events will be 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, 2006–07**

**Dr Tilli Tansey** – Reader in History of Modern Medical Sciences, Wellcome Trust Centre for the History of Medicine at UCL (WTCHM) and Chair

**Sir Christopher Booth** – WTCHM, former Director, Clinical Research Centre, Northwick Park Hospital, London

**Dr Robert Bud** – Principal Curator of Medicine and Manager of Electronic Content, Science Museum, London

**Dr Daphne Christie** – Senior Research Assistant, WTCHM, and Organizing Secretary

**Dr John Ford** – Retired General Practitioner, Tonbridge

**Professor Mark Jackson** – Centre for Medical History, Exeter

**Professor Ian McDonald**<sup>†</sup> – WTCHM, former Professor of Neurology, Institute of Neurology, London

**Dr Helga Satzinger** – Reader in History of Twentieth Century Biomedicine, WTCHM

**Professor Lawrence Weaver** – Professor of Child Health, University of Glasgow, and Consultant Paediatrician in the Royal Hospital for Sick Children, Glasgow

<sup>†</sup>Died 13 December 2006

## ACKNOWLEDGEMENTS

The discovery, use and impact of platinum salts as chemotherapy agents for cancer was suggested as a suitable topic for a Witness Seminar by Mark Walport, Director of the Wellcome Trust. We are very grateful to Professor Sir Kenneth Calman for his excellent chairing of the occasion. We thank Professor Matti Aapro for writing the Introduction to these published proceedings, and Dr Tony Woods, who read through an earlier draft of the transcript. Our additional thanks go to Professor Paul Andrews who assisted us in planning the meeting. We thank the contributors for their help with the Glossary and Professor Andrew Thomson who provided the figures.

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 and the Medical Photographic Library; Mr Akio Morishima, who has supervised the design and production of this volume; our indexer, Ms Liza Furnival; and our readers, Ms Fiona Plowman, Mrs Sarah Beanland 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*



# HISTORY OF TWENTIETH CENTURY MEDICINE WITNESS SEMINARS, 1993–2007

- 1993    **Monoclonal antibodies**
- 1994    **The early history of renal transplantation**  
**Pneumoconiosis of coal workers**
- 1995    **Self and non-self: A history of autoimmunity**  
**Ashes to ashes: The history of smoking and health**  
**Oral contraceptives**  
**Endogenous opiates**
- 1996    **Committee on Safety of Drugs**  
**Making the body more transparent: The impact of nuclear  
magnetic resonance and magnetic resonance imaging**
- 1997    **Research in general practice**  
**Drugs in psychiatric practice**  
**The MRC Common Cold Unit**  
**The first heart transplant in the UK**
- 1998    **Haemophilia: Recent history of clinical management**  
**Obstetric ultrasound: Historical perspectives**  
**Post penicillin antibiotics**  
**Clinical research in Britain, 1950–1980**

- 1999**    **Intestinal absorption**
- The MRC Epidemiology Unit (South Wales)**
- Neonatal intensive care**
- British contributions to medicine in Africa after  
the Second World War**
- 2000**    **Childhood asthma, and beyond**
- Peptic ulcer: Rise and fall**
- Maternal care**
- 2001**    **Leukaemia**
- The MRC Applied Psychology Unit**
- Genetic testing**
- Foot and mouth disease: The 1967 outbreak and its aftermath**
- 2002**    **Environmental toxicology: The legacy of *Silent Spring***
- Cystic fibrosis**
- Innovation in pain management**
- 2003**    **Thrombolysis**
- Beyond the asylum: Anti-psychiatry and care in the community**
- The Rhesus factor and disease prevention**
- Platelets in thrombosis and other disorders**

- 2004    **Short-course chemotherapy for tuberculosis**
- Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
- Public health in the 1980s and 1990s: Decline and rise?**
- 2005    **The history of cholesterol, atherosclerosis and coronary disease, 1950–2000**
- Development of physics applied to medicine in the UK, 1945–90**
- 2006    **Early development of total hip replacement**
- The discovery, use and impact of platinum salts as chemotherapy agents for cancer**
- Medical ethics education in Britain, 1963–93**
- Superbugs and superdrugs: The history of MRSA**
- 2007    **Clinical pharmacology in the UK, c. 1950–2000**
- The resurgence of breast-feeding, 1975–2000**
- DNA fingerprinting: From discovery to database**
- The development of sports medicine in twentieth-century Britain**
- Clinical pharmacology in the UK, c. 1950–2000: Industrial and regulatory aspects**



## PUBLISHED MEETINGS

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

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

### **Technology transfer in Britain: The case of monoclonal antibodies Self and non-self: A history of autoimmunity**

#### **Endogenous opiates**

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

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

### **Making the human body transparent: The impact of NMR and MRI Research in general practice**

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

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

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

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

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

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

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

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

### **Peptic ulcer: Rise and fall**

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### **Leukaemia**

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### **Early development of total hip replacement**

Reynolds L A, Tansey E M. (eds) (2007) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 29. London: The Wellcome Trust Centre for the History of Medicine at UCL, 198pp. ISBN 978 085484 111 0

**The discovery, use and impact of platinum salts as chemotherapy agents for cancer**

Christie D A, Tansey E M. (eds) (2007) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 30. London: The Wellcome Trust Centre for the History of Medicine at UCL. This volume. ISBN 978 085484 112 7

**Medical ethics education in Britain, 1963–93**

Reynolds L A, Tansey E M. (eds) (2007) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 31. London: The Wellcome Trust Centre for the History of Medicine at UCL. In press. ISBN 978 085484 113 4

**Superbugs and superdrugs: The history of MRSA**

Reynolds L A, Tansey E M. (eds) (2008) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 32. London: The Wellcome Trust Centre for the History of Medicine at UCL. In press. ISBN 978 085484 114 1

**Clinical pharmacology in the UK, c. 1950–2000**

Christie D A, Tansey E M. (eds) (2008) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 33. London: The Wellcome Trust Centre for the History of Medicine at UCL. In press.

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Other publications

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

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

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

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

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

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

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

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

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

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

**Witnessing the witnesses: Pitfalls and potentials of the Witness Seminar in twentieth century medicine**

E M Tansey. In: Doel R, Søderqvist T. (eds) (2006) *Writing Recent Science: The historiography of contemporary science, technology and medicine*. London: Routledge, 260–78.



## INTRODUCTION

Platinum is one of many medically useful metals, possibly the key example. Upon the invitation of the Chairman, Kenneth Calman, Andrew Thomson described the fascinating story of the laboratory where Barney Rosenberg, with his technician Loretta Van Camp, made the discovery that led ultimately to the development of platinum salts as anticancer agents. The development of this class of agents, as Robert Williams rightly points out, was not immediately perceived as useful, rather the opposite. He suggests that the Americans were scared stiff of platinum drugs and would not let them be tested in any hospital under NIH control (page 19). The development of anticancer drugs is full of such stories. For example, overcoming the allergic reactions that initially led to paclitaxel being shelved took some persistence,<sup>1</sup> and prior to that, the understanding that etoposide had to be given on repeated days to be active was a similar example.<sup>2</sup>

The development of cisplatin was slowed by two issues: nephrotoxicity and emesis. Eve Wiltshaw and others describe how the early observations of remarkable antitumour activity encouraged some clinicians to continue the development of the drug, which others discarded (pages 24–26). Almost in parallel, carboplatin was developed, and became one of the rare drugs that an oncologist can use in an ‘intelligent’ way, where the dose is adapted to renal function, nicely described by Hilary Calvert, whose formula is well known (page 28, note 68). Richard Gralla pays appropriate tribute to Esteban (Steve) Cvitkovic, whose intelligent persistence was key in the development of the hydration schemes that allow the use of medium- and high-dose cisplatin safely (pages 31–32).

Cisplatin was the key drug prompting the need to develop effective antiemetic agents, another fascinating story related by Paul Andrews and others (pages 44–45). Today’s nursing and medical staff cannot imagine what an oncology outpatient service, let alone the inpatient ward, was like in the late 1970s and early 1980s (page 42). The contributions in this volume correctly highlight the incredible debate about the cost of new effective antiemetics: ‘comfort drugs’ that were ‘ruining the NHS’ (page 61). Cured patients can still feel, years later, that the drug that saved their life has left its own mark in their body, mainly in terms of ototoxicity and

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<sup>1</sup> Adams *et al.* (1993).

<sup>2</sup> Cavalli (1982).



neurotoxicity. But while one needs to take these difficulties into account, they are not sufficient reason to cease using cisplatin, to which so many patients owe their life.<sup>3</sup>

But while it can be argued today that cisplatin and other platinum, like carboplatin and oxaliplatin, play a major role in oncology, will they disappear the way other ‘medical metals’ have done, or are they just as ‘essential’ as potassium? Thinking of the most precious metals, after platinum, one has immediately to cite silver and gold (the ‘noble’ metals). Until recently Silver has played a major role in medicine, as part of the coating of films used to capture X-ray images, and more modern radiographs. The electronic age has meant its almost complete disappearance, as digitalized image processing is becoming standard. Gold was used in medicine for rheumatoid arthritis, inflammatory bowel disease, psoriatic arthritis, and several other diseases, but nowadays is rarely used, except in some cases which are unresponsive to non-steroidal anti-inflammatory drugs, or methotrexate (see Kenneth Calman’s ‘praise poem’ in this volume, pages 78–81).<sup>4</sup> Arsenic has a long history of medical use, and came to prominence in the early twentieth century as a component of Salvarsan and Neosalvarsan as treatments for syphilis. Discovered in the laboratory of Paul Ehrlich in Frankfurt, Germany, these treatments were the result of the first organized team effort to optimize the biological activity of compounds through systematic chemical modifications. This is considered by many to be the basis of modern pharmaceutical research. More recently, another arsenic-based agent has entered the oncohaematological field: arsenic trioxide (was it actually Madame Bovary’s poison?) is used to treat acute promyelocytic leukaemia resistant to all-trans retinoic acid.<sup>5</sup> Boron still has some place in the treatment of glioblastoma multiforme,<sup>6</sup> but mercury, once the mainstay of antisyphilis treatment, is basically banned nowadays, after having caused disasters like the one in Minamata Bay.<sup>7</sup> However, mercury is still used in some vaccine preparations as a conservative agent (thiomersal) and in dental amalgams.<sup>8</sup>

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<sup>3</sup> For example, the use of neomycin instead of streptomycin in which the patient was cured of his infection but was stone deaf after his treatment, see Tansey and Reynolds (eds) (2000): 23.

<sup>4</sup> See also Eisler (2003).

<sup>5</sup> See, for example, Flaubert (1998); Zhu *et al.* (2002). See also Christie and Tansey (eds) (2003): 10, 13, 20.

<sup>6</sup> Barth and Joensuu (2007).

<sup>7</sup> See Harada (1995); Christie and Tansey (eds) (2004): 36–7.

<sup>8</sup> Marks and Beatty (1975).

Bringing together many of those involved in the development of the platinum compounds in oncology, this Witness Seminar is a remarkable resource for the study of modern medical history. Let us hope many more such seminars will enlighten us.

**Matti Aapro,**  
Genolier, Switzerland



# THE DISCOVERY, USE AND IMPACT OF PLATINUM SALTS AS CHEMOTHERAPY AGENTS FOR CANCER

The transcript of a Witness Seminar held by the Wellcome Trust Centre  
for the History of Medicine at UCL, London, on 4 April 2006

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

# THE DISCOVERY, USE AND IMPACT OF PLATINUM SALTS AS CHEMOTHERAPY AGENTS FOR CANCER

## Participants

Professor Paul Andrews	Mr Wesley Miner
Professor Kenneth Bagshawe	Professor Robert Naylor
Dr Penelope Brock	Mrs Brenda Reynolds
Professor Sir Kenneth Calman	Dr John Rudd
Professor Hilary Calvert	Dr Gareth Sanger
Professor David Grahame-Smith	Dr Tilli Tansey
Professor Richard Gralla	Dr David Tattersall
Professor Kenneth Harrap	Professor Andrew Thomson
Dr James Hoeschele	Professor Robert Williams
Professor Ian Judson	Dr Eve Wiltshaw

**Among those attending the meeting:** Dr Jeffrey Aronson, Dr Chris Barnard, Dr Barry Murrer, Dr Mark Walport, Mrs Julie Wenn, Dr Lise Wilkinson, Dr Tony Woods

**Apologies include:** Professor Matti Aapro, Professor Richard Begent, Professor Peter Blower, Professor Sir Christopher Booth, Dr Michael Cleare, Professor Derek Crowther, Professor David Cunningham, Dr Mike Davies, Professor Adrian Harris, Dr Trevor Hince, Dr Duncan Jodrell, Professor Lloyd Kelland, Professor David Kerr, Professor Gordon McVie, Professor Pat Price, Dr Jon Pritchard<sup>†</sup>, Dr John Reynolds, Professor Michael Richards, Dr Vicky Robinson, Dr Tim Root, Professor Barnett Rosenberg, Professor Peter Sadler, Professor John Smyth, Professor Mike Stratton

<sup>†</sup>Died 20 January 2007

**Dr Tilli Tansey:** Good afternoon, ladies and gentlemen. May I welcome you to this Witness Seminar on platinum compounds? I am the Convenor of the History of Twentieth Century Medicine Group. This was established by the Wellcome Trust in 1990 to bring together clinicians, scientists, historians of medicine and others interested in what we call the recent history of medicine; that is, post-Second World War. We devised a number of strategies to reach this objective, including this format of Witness Seminars, where we gather together a group of people who have been involved in a particular discovery, or a development, and get them to talk, candidly we hope, in a chairman-led discussion. The proceedings of this are recorded, and the transcripts are edited and published.<sup>1</sup>

This meeting came about because of a suggestion made to me by Mark Walport, Director of the Wellcome Trust, and it tied in with a suggestion that I had been discussing with Paul Andrews from St George's Hospital Medical School, University of London, and Tony Woods, also of the Wellcome Trust.<sup>2</sup> I had been talking with Paul and Tony about having a meeting on antiemetics, and it seemed to be a very good idea to combine both ideas in this one meeting. Of course, metals in medicine have a very long history; you need only think of things like arsenic and mercury.<sup>3</sup> But it wasn't until 1965 that Barnett Rosenberg, in a study looking at the effect of electrical currents on cultured bacteria, noticed that he could get growth inhibition around his platinum electrodes.<sup>4</sup> He said rather laconically in reminiscence, that he made the intuitive step of testing the platinum compounds as an anticancer agent on cell tissue cultures.<sup>5</sup> This led to the rapid development of more than 2000 compounds which were tested by Bristol-Myers [NY, USA] for example, and in 1971 some platinum compounds first went into clinical trials in the US. Barnett Rosenberg worked on platinum analogues at Michigan State University (MSU) in East Lansing

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<sup>1</sup> All volumes of Wellcome Witnesses to Twentieth Century Medicine are freely available to download at [www.ucl.ac.uk/histmed](http://www.ucl.ac.uk/histmed), following the links to Publications/Wellcome Witnesses. For a list see pages xvi–xx.

<sup>2</sup> Dr Mark Walport was appointed Director of the Wellcome Trust in June 2003. Dr Tony Woods is Head of Medicine, Society and History Grants, Wellcome Trust. Professor Paul Andrews is Professor of Comparative Physiology at St George's Hospital Medical School, London (see page 98).

<sup>3</sup> See, for example, Graeme and Pollack (1998). See also Introduction, page xxiv.

<sup>4</sup> Professor Andrew Thomson wrote: 'Cis-platin [cis-diamminedichloroplatinum (II)] was identified in the laboratory of Barnett Rosenberg as one of the agents responsible for the filamentous forms of bacteria observed after applying an electric current between platinum electrodes. See Rosenberg *et al.* (1965, 1967a).' Letter to Dr Daphne Christie, 18 February 2007.

<sup>5</sup> See Rosenberg (1978).

with commercial partners and research corporations, and in this country with the cancer institution, the Royal Marsden, at Sutton, and Johnson Matthey (JM),<sup>6</sup> all looked at platinum analogues. Of these, cisplatin<sup>7</sup> was a very active chemotherapeutic, but it had problems, nephrotoxicity and neurotoxicity problems, and there was also the problem of platinum resistance.<sup>8</sup> Another major problem was that of emesis – severe nausea and vomiting in response to platinum compounds – which led, particularly in the 1980s, to an upsurge of interest in the physiology and pharmacology of nausea and vomiting, and in the mid-1980s to the identification of the 5HT<sub>3</sub> receptor antagonists.<sup>9</sup>

I believe this is the first time that we have had representatives from all stages of that history together in one room, so we are looking forward to hearing the debate and discussion that will emerge this afternoon. In addition to identifying and locating participants to take part in this meeting, we spent a long time thinking about who could chair the meeting, and we are delighted that Sir Kenneth Calman has been able to accept our invitation. Sir Kenneth was Chief Medical Officer for Scotland and for England, and is now the Vice-Chancellor of the University of Durham, but he started his career as a lecturer in oncology at the University of Glasgow, as a research fellow at the Chester Beatty Research Institute, later becoming Professor of Oncology and Postgraduate Dean at the University of Glasgow. Among his unpublished works is a poem in praise of methotrexate. If I can just quote from it:<sup>10</sup>

Get big cell kill from fluorouracil,  
be a medicine man with melphalan,  
keep things pristine with vincristine,  
shout with glee with 6MP...  
but, and this is important for today,  
you can flatten 'em, with platinum.

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<sup>6</sup> Johnson Matthey is a specialist chemicals company and a world leader in advanced materials technology. It was founded as a precious metals assayer in 1817 and is now the world's largest fabricator and distributor of platinum group metals; it developed the platinum-based anticancer drugs, cisplatin and carboplatin. For a history, see [www.matthey.com/about/history.htm](http://www.matthey.com/about/history.htm) (visited 29 November 2006). See also [www.chemcases.com/cisplat/index.htm](http://www.chemcases.com/cisplat/index.htm) (visited 15 March 2007).

<sup>7</sup> Cisplatin, *cis*-dichlorodiammineplatinum (II) is also referred to as cisplatin or cis-platin in the transcript.

<sup>8</sup> See, for example, Cleare and Hoeschele (1973b); Judson (1993): 45–58; Kelland *et al.* (1999).

<sup>9</sup> For example, ondansetron, granisetron and tropisetron (see Appendix 2). This is discussed later on pages 44–5, 46 and 49–69. See, for example, Hesketh *et al.* (1989); van Wijngaarden *et al.* (1993).

<sup>10</sup> Professor Sir Kenneth Calman's complete poem is given in Appendix 1.

I think that's a very suitable sentiment to introduce our Chairman, Sir Kenneth Calman.

**Professor Sir Kenneth Calman:** Thank you very much. The poem was written in praise of methotrexate, and the verse, I think, is, 'You can fix it with methotrexate'.

I am delighted to be here and, as Tilli has said, I had an MRC fellowship at the Chester Beatty with one or two distinguished people around this room in 1972 and went back to be Professor of Oncology in Glasgow in 1974, at a ridiculously early age, which would never happen now, and, as Professor Bagshawe has already reminded me, as a surgeon at the time doing vascular and transplant surgery, and to become a Professor of Medical Oncology wasn't all that difficult at the time.

Things that you can't do now are interesting: I suspect that one of the themes that has repeatedly arisen in a number of these Witness Seminars in the past has been that 'you couldn't quite do it now'.<sup>11</sup> One of the issues I think, for the Wellcome Trust and other funders, is how do you fund a Barnett Rosenberg? To think he should just try platinum on cancer cells; it just doesn't happen that way any more, we have to be so prescriptive, sometimes, in terms of research funding. But that's just a small personal observation, which no doubt some of you will want to pick up on.

When I began in 1974, very few patients, if any, were referred for anything like testicular or ovarian disease of a teratomatous nature. When I left in 1984, we had a significant series of patients, and cisplatin was a remarkable, and effective drug. In the audience today, we have a patient who was treated in the early 1980s.<sup>12</sup> Suddenly things changed. You could do things with patients, which would make a huge difference to their long-term survival, although in the short-term it was quite difficult in terms of the side-effects, particularly vomiting.

But the other thing that was very important for me – and we'll perhaps pick this up at the end of this meeting – is what I have called the 'wider implications'. Not only was this an effective treatment for a disease that was difficult to treat, but we were dealing with young people, particularly young men in Glasgow, as it happened, who needed to know what was going on. When I arrived in

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<sup>11</sup> A list of Witness Seminars is given on pages xiii–xv.

<sup>12</sup> See contribution (page 71) by Mrs Brenda Reynolds, mother of Julie [Wenn], a survivor of cisplatin treatment for ovarian and lung tumours.



Glasgow, most people didn't know what their diagnosis was, or why they had been referred to an oncology unit. That's only 30 years ago. That changed over that period, because you had young men who asked – 'Tell me about the AFP (alpha fetoprotein) results? What's my scan like?' – all of this, was important for me. It allowed the doors to be opened to a much wider range of patient questions. I will perhaps say a little bit more about that later.

Sperm storage, which might not have been thought about but for that group of patients, suddenly became relevant, because they were young people, going to have quite serious treatment and quality-of-life issues around vomiting – and, in case I forget, people used to vomit when they saw me; some of you will have noticed this, as they went past a hospital they would just vomit. That's something that Pavlov said some time ago.<sup>13</sup> So it is really interesting to reflect.

Today, we want your recollections. Most of them will be scientific, but some of them, I hope, will be quite personal, about what it was like to be there and how things changed; cisplatin's development, which we will begin with, its use in clinical practice, side-effects and other consequences. As I said before, when you read that little phrase from Rosenberg's paper, 'I just thought, by intuition, I might try it', is a really interesting comment on how we fund and develop clinical research work. There are four broad areas today; there are one or two people who may start the discussion, but I hope it's up to you to take it further. The four sections are: chemistry and microbiology; oncology, including preclinical aspects, right through to treatment; the antiemetic side of things; and there's a catchall at the end which is called 'broader aspects', which is partly about some of the issues that I mentioned – the change in the communication with individual patients, how that made a much bigger difference to a wider group of patients. I am going to ask Andrew Thomson to say a little bit about the beginning.

**Professor Andrew Thomson:** I am an inorganic chemist by background. I am currently at the University of East Anglia (UEA) in the School of Chemical Sciences and Pharmacy, and I am told that the origin of this meeting was a consequence of the visit by Dr Mark Walport to the University of East Anglia a couple of years ago. It was my pleasure and duty to show him some of the science going on, and he had done quite a lot of his homework, because he said to me, 'I understand you were involved in the early chemistry of cisplatin', and so we fell to talking about this topic. When he came back to the Wellcome Trust

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<sup>13</sup> On the conditioned reflex, see Pavlov (1927).

he then suggested that this might form a suitable topic for the Witness Seminar series.<sup>14</sup> So it is a great pleasure for me to be here today and to see some old faces that I haven't seen for over 30 years.

I have not worked in this field myself for the last 20 or so years, but I was in the laboratory of Barney Rosenberg between September 1965 and August 1967 as a postdoctoral fellow, at the time when it was necessary to unravel some chemistry of platinum. I happened to know some platinum chemistry, and the reason for that is due to the man sitting over there, Professor R J P (Bob) Williams, from the University of Oxford, who is celebrating his eightieth birthday this year, I am delighted to tell you. Studying for my DPhil with him at Oxford, I was looking at some square planar platinum compounds, studying their colours.<sup>15</sup> In the course of that doctorate, as it came to the end, I began to think about postdoctoral work. Bob Williams alerted me to the fact that Barney Rosenberg had made an interesting discovery. By putting a couple of platinum electrodes into a growth medium of *E. coli* and passing an AC current he observed after a while that they grew in filaments.<sup>16</sup> Rosenberg, with his technician Loretta Van Camp, was conducting these experiments, to see if they could interfere with cell division processes by applying electric fields. Rosenberg was a physicist by background, and he was intrigued by the pictures of mitotic spindles when cells divide. The fact that *E. coli* had no mitotic spindles did not inhibit him from trying this experiment. They quickly discovered that the alternating electric current caused some platinum to dissolve from the electrodes. A series of remarkable observations made by his technician, Loretta Van Camp, who unfortunately is not here, followed, and she soon showed that it was nothing to do with the electric field *per se*. She tested a number of platinum salts. There are two things you need to know about platinum chemistry: that it has two common oxidation states, II and IV, and each oxidation state dictates a different stereochemistry on a surrounding group of ligands. In the platinum (IV) state it forms a six-coordinate octahedral complex [Figure 1].

On your chairs, you will find a handout, which is in fact the handout I give to third-year undergraduates at UEA when I give these lectures.<sup>17</sup> I am not

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<sup>14</sup> See pages xiii–xv.

<sup>15</sup> Day *et al.* (1965a and b).

<sup>16</sup> Rosenberg *et al.* (1965).

<sup>17</sup> The handout will be deposited with the tapes, correspondence and records of this meeting in Archives and Manuscripts, Wellcome Library, London.

going to go through it all, of course, but there are some pictures there that you might find of interest. In Figure 2 you will see a picture of a platinum (IV) complex, which is an octahedral complex; it binds to six groups. It dictates that stereochemistry on the surrounding ligands. But the lower oxidation state, platinum (II), superimposes a square planar geometry on four ligands.<sup>18</sup> The salt used was  $[\text{PtCl}_6]^{2-}$ , a platinum (IV) complex. This compound loses its ligands in response to light, the process of photo-ejection.

When Rosenberg and Van Camp first tested  $[\text{PtCl}_6]^{2-}$ , the only platinum compound available on the laboratory shelf, it seemed to kill all the *E. coli* cells. But if you leave the culture in the light, then slowly the platinum is transformed into a form that then forces filamentous growth of *E. coli* cells.

What was that photochemical process? What was the active ingredient that was giving rise to filamentous growth? That was the chemistry that I studied in Rosenberg's lab with a graduate student called Eugene Grimley. We did curtain electrophoresis<sup>19</sup> to separate by charge, and it became clear to us that the chemical species that was causing filamentous growth of *E. coli* was a neutral species of platinum (IV).<sup>20</sup> Figure 2 shows the best answer we could come to, namely, that the active product was platinum (IV) with four chloride ions around it and two ammonias. Rosenberg was a physicist and I said to him, 'Well, of course that species has two stereoisomers, *cis* and *trans*'. 'What are stereoisomers?', was Barney's reply.<sup>21</sup> I remember standing at his blackboard and giving him a tutorial on the chemistry of platinum. So it was clear that I had to synthesize both the *cis* and *trans* isomers and test them to see whether the two stereoisomers had different biological effects.

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<sup>18</sup> Note that cisplatin consists of a central platinum atom surrounded by four ligands: two ammonias and two chlorides. A high antitumour activity results when the two chloride ligands are bi-aquated in aqueous physiological environments; cisplatin can then react directly with DNA and display cytotoxic activity.

<sup>19</sup> Professor Andrew Thomson wrote: 'Curtain electrophoresis is the process where a mixture of analytes is flowed under gravity, in a suitable solvent, down a vertical sheet of absorbent chromatography paper, while a high DC electric field is applied across the sheet horizontally so that oppositely charged species are deflected to the right and left, whereas a neutral analyte flows vertically down the sheet. The analytes are thus fractionated according to charge across the width of the paper and each can be collected in tubes held below the paper.' Letter to Dr Daphne Christie, 18 February 2007.

<sup>20</sup> Rosenberg *et al.* (1967a).

<sup>21</sup> Professor Andrew Thomson wrote: 'Rosenberg is known as "Barney".' Note on draft transcript, 18 February 2007.

The synthesis was first done in 1844 by Peyrone.<sup>22</sup> The synthesis of the platinum (IV) *cis* and *trans* goes via the platinum (II) oxidation state [Figure 3].

Platinum (II) is very remarkable. It dictates a square planar stereochemistry and the ligands do not exchange very fast. I will come back to this point. So the synthetic route enables one to make both the *cis* and *trans* platinum (II) isomers, which you can oxidize to the platinum (IV) state.

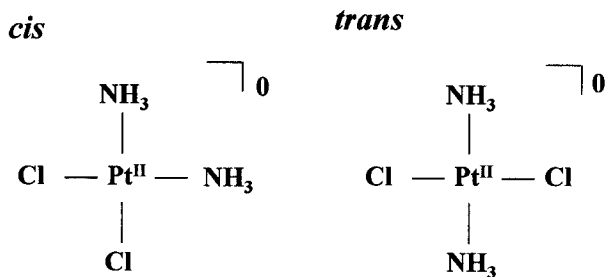
So that was the chemistry I carried out in the Rosenberg laboratory. It was nineteenth-century chemistry, it wasn't new, but I happened to know where to find it, being an inorganic chemist. If you have a compound, then you can test it. And so we tested the platinum (II) isomers for filamentous growth, as well as the platinum (IV) isomers. It was clear that the *cis* platinum (II) was much more effective at forcing filamentous growth than anything else. The *cis* platinum (IV) isomer was also effective.<sup>23</sup> That work was reported in the *Journal of Biological Chemistry* in 1967, by myself and Rosenberg and Grimley.<sup>24</sup>

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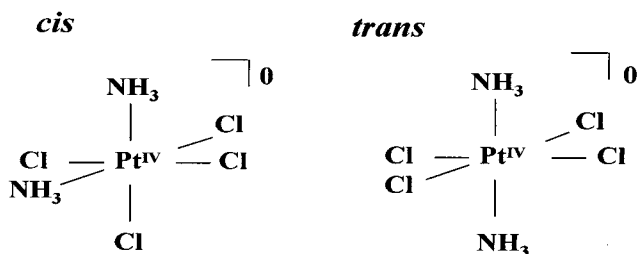
<sup>22</sup> Professor Andrew Thomson wrote: 'Cis-Pt(II)(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, cis-platin, was first synthesized by M Peyrone in 1844 [Peyrone (1844)] and has been called Peyrone's chloride [cis-dichlorodiammineplatinum (II)], or its higher oxidation state equivalent, cis-tetrachloro-diammineplatinum (IV)]. Its structure was first elucidated by Alfred Werner in 1893.' Letter to Dr Daphne Christie, 20 August 2006. See Figure 3. Professor Alfred Werner (1866–1919) won the Nobel Prize in Chemistry in 1913 for proposing the octahedral configuration of transition metal complexes. See [http://nobelprize.org/nobel\\_prizes/chemistry/laureates/1913/werner-bio.html](http://nobelprize.org/nobel_prizes/chemistry/laureates/1913/werner-bio.html) (visited 28 March 2007).

<sup>23</sup> Professor Andrew Thomson wrote: 'In the Rosenberg laboratory in October 1966, as recorded in his lab notebook, A J Thomson synthesized, by standard methods, the four compounds, *cis*- and *trans*- Pt(II) (NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and *cis*- and *trans*- Pt(IV)(NH<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub>. On 2 November 1966, these samples were used by L Van Camp to test which of them was capable of forcing filamentous growth of *E. coli*. The *cis*-, not the *trans*-, isomer of Pt(IV)(NH<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub> was effective in causing filamentous growth. However, the *cis*-, but not the *trans*-, isomer of Pt(II)(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> was even more effective at inducing filaments in *E. coli*. For this reason further testing of biological efficacy focused almost exclusively on *cis*-Pt(II)(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> rather than the *cis*-Pt(IV) complex. The initial testing of antitumour activity against sarcoma 180 in mice and on L1210 leukaemia cells in tissue culture by the National Cancer Institute (NCI), Washington, was carried out on the sample of *cis*-Pt(II)(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> synthesized by A J Thomson. Hence, it was the need to synthesize *cis*-Pt(II)(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> as an intermediate in the synthesis of *cis*-Pt(II)(NH<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub> that gave rise to the idea by A J Thomson to test *cis*-Pt(II)(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (*cis*-platin). See *Cancer Under Siege* [Goodfield (1975): 139–66]. June Goodfield attended the Second International Symposium on Platinum Coordination Complexes in Cancer Chemotherapy, in Oxford in April 1973. She quoted Barnett Rosenberg as follows: "Andy (Thomson) was the first to synthesize the drug (*cis*-platin) and confirm its structure in relation to its antitumour activity. He is the true discoverer and is entitled to establish the name for the whole field".' Excerpt from a letter to Dr Daphne Christie, 20 August 2006. See also Connors (1973); Connors and Roberts (1974).

<sup>24</sup> Rosenberg *et al.* (1967a).



Planar four-coordinate platinum (II) complexes.



Octahedral six-coordinate platinum (IV) complexes.

Figure 1: Platinum (II) (top) and platinum (IV) ions (bottom) dictate different coordination numbers and geometries on a set of surrounding ligands.

Legend provided by Professor Andrew Thomson.

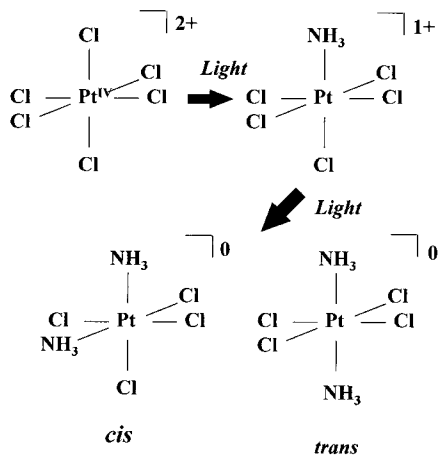


Figure 2: Metal dissolves from the platinum electrodes under the influence of an AC electric field in a buffer medium of  $\text{Cl}^-$  and  $\text{NH}_4^+$  to yield  $[\text{Pt}(\text{IV})\text{Cl}_6]^{2-}$ . Under the influence of light, ligand exchange occurs to yield a mixture of *cis* and *trans* isomers. The *cis* isomer causes filamentous growth in *E. coli* whereas the *trans* isomer does not.  $[\text{Pt}(\text{IV})\text{Cl}_6]^{2-}$  is inhibitory to cell growth.

Legend provided by Professor Andrew Thomson.

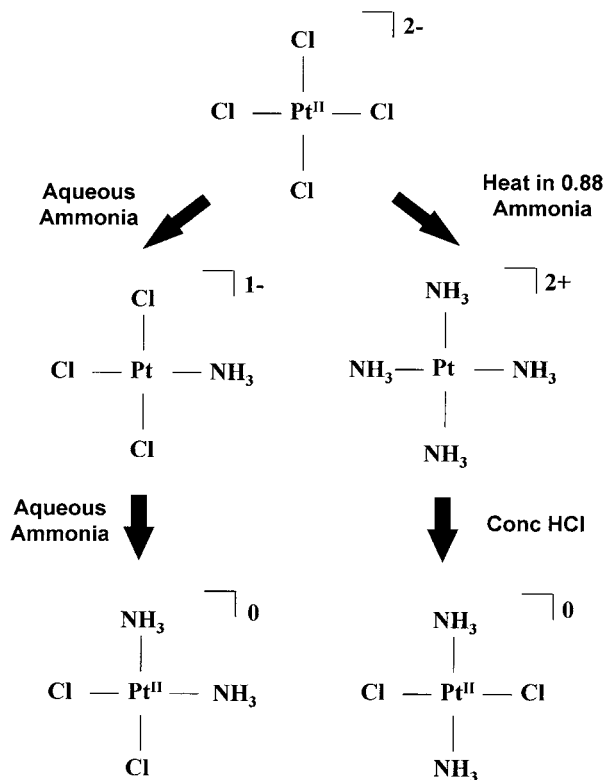


Figure 3: Synthesis of *cis* and *trans* isomers of diamminodichloro Pt (II).

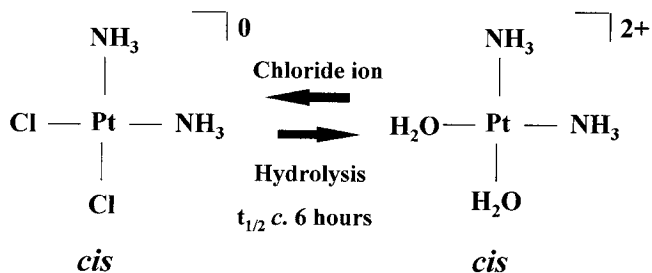


Figure 4: Chemical properties of *cis*-platin relevant to drug action. It is a bifunctional reagent since the pair of *cis* chloride ions are labile to nucleophilic substitution whereas the pair of *cis* ammine groups remain inert to substitution. The di-chloro form is maintained by a high  $\text{Cl}^-$  concentration as a neutral complex that will cross cell membranes but inside the cell, in a lower chloride medium, will become labile undergoing hydrolysis.

Legend provided by Professor Andrew Thomson.

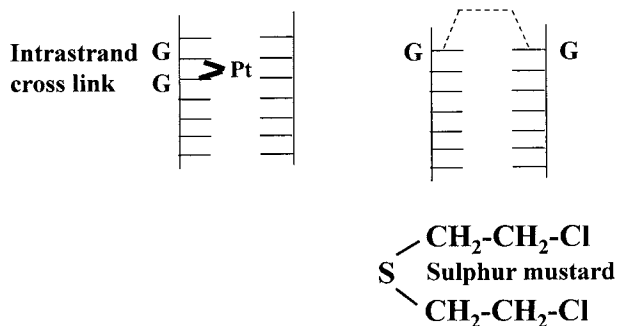


Figure 5: Binding modes to DNA of platinumating and alkylating agents. Cis-platin cross links via N7 of guanine bases on the *same* strand of DNA. Sulphur mustard cross links DNA strands by reaction with the N7 of guanine bases on *opposite* strands.

Legend provided by Professor Andrew Thomson.

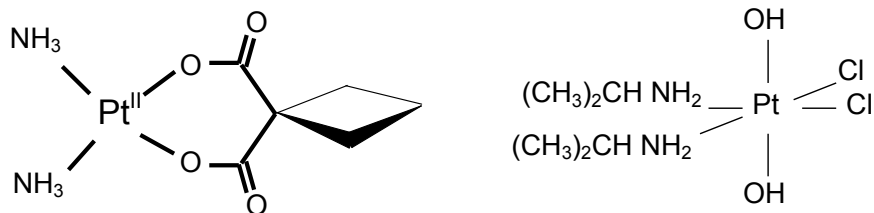


Figure 6: Structures of some second generation platinum drugs.

Left. Carboplatin (JM8) cis-diammine (1,1-cyclobutane-dicarboxylato) platinum (II). Right. Iproplatin (JM9) cis-dichlorobis (isopropylamine) trans-dihydroxyplatinum (IV).

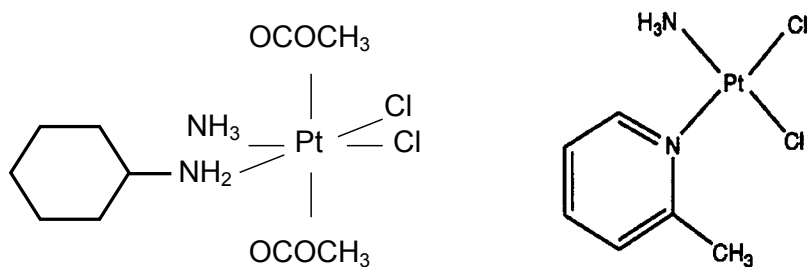


Figure 7: Chemical structures of JM216 (left) and AMD473 (right).

So we knew that there was this very interesting stereochemical difference, with quite different biological properties of the *cis* and the *trans* forms.<sup>25</sup> So what is the significant chemistry of the *cis* isomer? Bob Williams was much involved in these discussions, of course, at that time.<sup>26</sup> The cisplatinum (II) isomer will exchange two of its ligands; the two chloride ions will exchange rather rapidly [Figure 4]. If you put it into water with no chloride, the water will displace the chloride ions. If you raise the chloride ion concentration again, then the chloride ions will be taken up and will reform the *cis* complex. Hydrolysis occurs with a half-life of about six hours. But the amines do not exchange for many, many weeks.

This remarkable chemistry of platinum ensures that some of the ligands will exchange within a matter of hours, and some are so kinetically inert that they cannot be exchanged over months. In that sense platinum (II) chemistry has some analogies with carbon chemistry. So this was really a bifunctional reagent that we had discovered, with two leaving groups on the *cis* side, on the same side, of the molecule. The amines were kinetically inert. It was also a neutral complex, so we guessed that it could pass across membranes and into cells.

At that time, one area of interest was in classical alkylating agents, and the differences between the so-called 'bifunctional' and 'monofunctional' alkylating agents, and if you look at a picture of a famous sulphur mustard [Figure 5], which, of course, is the classical bifunctional alkylating agent. We had a bifunctional agent. But the question was, 'What was its target?' I will come back to that point in a moment.

While we were looking at targets, Rosenberg had the notion that if we had an agent which inhibited cell division in *E. coli* and could cause filamentation, perhaps it would kill higher cells. I am not sure whether Barney knew this or not – Bob Williams may speak to this point – but certainly it was known by microbiologists that there was a correlation between those agents that cause filamentation and can induce lysis in lysogenic bacteria, and some of the functionality of classical alkylating agents.<sup>27</sup> But I am not sure that Barney knew that. Nevertheless, he brought in half a dozen mice carrying sarcoma 180, I made the compounds, and Loretta Van Camp injected them into the mice. You can imagine the jokes in the lab. Only in the USA would you inject platinum

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<sup>25</sup> See Connors *et al.* (1972); Cleare and Hoeschele (1973a).

<sup>26</sup> Thomson *et al.* (1972).

<sup>27</sup> Loveless (1966).



into an animal.<sup>28</sup> Within eight days there was regression from the *cis* but not the *trans* isomers. That work was published in *Nature* in 1969.<sup>29</sup> Once that paper had appeared in *Nature*, then the UK scene became very active. The reason for that – and I shall stand corrected, perhaps, by Eve Wiltshaw – was that Alexander Haddow, who was Director of the Chester Beatty at the time, picked up that paper. The reason he said that he picked it up was because Haddow had consulted on nickel carcinogenesis in the South Wales metallurgical industry and he knew enough inorganic chemistry to know that platinum and nickel were in the same group in the periodic table. There was a paradox called ‘Haddow’s paradox’, which said that all things that cause cancer will also cure cancer,<sup>30</sup> which presumably was a statement about attacking DNA, whether you mutate it, or whether you kill it. So Haddow thought maybe the fact that platinum would appear to cure cancer, and nickel would cause it, was another example of ‘Haddow’s paradox’. Once Haddow had picked this up it, of course, meant that the whole power of the Chester Beatty Research Institute then became very interested in this problem.<sup>31</sup> It led to the setting up of a group of people in the early 1970s in the UK, which was funded by a man called Ken Maxwell, from Rustenburg Platinum Mines, and also by Johnson Matthey.<sup>32</sup> It was a very interesting group. It consisted of clinicians: Eve Wiltshaw was part of that in the early 1970s, Tom Connors was the pharmacologist; he is no longer with us.<sup>33</sup> There was an inorganic chemist from UCL called Martin Tobe making new platinum compounds, and Mike Cleare from Johnson Matthey.<sup>34</sup> I was studying molecular mechanisms, and John Roberts started to look at DNA repair mechanisms.<sup>35</sup> That group worked together in the UK for a number of years with funding from Rustenburg Platinum Mines. The work of that group meant that the clinical work, I think, went much more rapidly. In the USA it

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<sup>28</sup> Professor Andrew Thomson wrote: ‘This was in reference to the extravagance (by the then UK standards) of research budgets at that time in the USA.’ Note on draft transcript, 1 April 2007.

<sup>29</sup> Rosenberg *et al.* (1969).

<sup>30</sup> According to Haddow’s paradox, anticancer agents may also be carcinogenic. See Haddow *et al.* (1948); Reslová-Vasilukova and Williams (1979): 28.

<sup>31</sup> Haddow (1961); Jeney and Lapis (1985).

<sup>32</sup> Mr Ken Maxwell was Managing Director of Rustenburg Platinum Mines Limited, South Africa.

<sup>33</sup> Professor Thomas A Connors died on 4 February 2002. See Double (2002).

<sup>34</sup> For biographical note see page 99.

<sup>35</sup> Roberts and Thomson (1979); Roberts (1980); Brookes and Venitt (1991).

didn't go quite as fast. There progress was dependent on the NCI (National Cancer Institute), but the influence of the Chester Beatty here, working in that group, pushed the clinical work forward extremely rapidly. Perhaps I should stop there. That is my recollection of how it all got going.

**Calman:** What a wonderful tutorial on chemistry and the beginnings of this debate, and I hope that others will have their personal recollections of that time. But maybe I should ask whether you, Professor Williams, would like to say something at this stage in terms of your own background, since you have been referred to so often in this?

**Professor Robert [Bob] Williams:** I started research as a young man in 1948 with a deep interest, gathered at school, in the way metal ions may interact with any living system, and I have worked on that for the whole of my life. My last book is published now – it is the last piece of work I will do – called *The Chemistry of Evolution*.<sup>36</sup> The chemistry of evolution, according to me, is totally dependent on metal ions. You may not want to believe that, you may think it is totally dependent on DNA, but I believe that's a thundering mistake. Let me start then with my own career, which was biased by school education towards physics, chemistry and mathematics. You have to remember that in those days in education, if you went to the kind of school I did, a boys' grammar school,<sup>37</sup> you were not allowed to touch biology, because biology was for girls, just like that, and if you said you wanted to do biology, they would say to you that you must be stupid because all doctors are stupid and so are all vets, and so it's only stupid people who do medicine – there is no system whatsoever in biological sciences. So we were drilled and when I went to the University of Oxford, it was exactly the same. I said to the first tutor I met there that I wanted to study biology at the same time that I studied chemistry, and he replied, 'Oh, don't bother to do that, you can learn all of biology later'. That was the total attitude to education in biological sciences. Despite these attitudes, my mind was made up – I wished to study metal ions in biological systems. Now this is all relevant – since I was well-trained in physical sciences by 1950 but had read a good deal on biological sciences for myself. What happened next in this story? Andy has introduced some parts of it very nicely but didn't explain how I met Barney Rosenberg.

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<sup>36</sup> Williams and Fraústo da Silva (2006).

<sup>37</sup> Wallasey Grammar School, Wallasey.

Because of my interest in metal ions in biology, I thought that there must be a way electrons passed through biological materials using these ions. If you read the literature between 1950 and 1970, there's intense general interest by biophysicists in the way in which electrons pass through biomaterials. There were people, including famous names like Szent-Györgyi, who always thought that cancer was somehow related to this problem. In fact, there was a Ciba Foundation Symposium on this subject, where I was the Chairman, which is dedicated to Szent-Györgyi.<sup>38</sup> I remember that I got up and said that I thought what Szent-Györgyi was saying and thinking was nonsense. Well, that didn't go down very well, as I was supposed to be the Chairman of the whole meeting and I said that at the very beginning. So, having cleared the air, we started to fight, and it was very interesting and good fun, from which I learnt a great deal.

Going back to my meeting with Barney Rosenberg, I had developed these interests in electron transfer properties before 1960, and so had Barney. My work by 1961 led to the proposal of how bioenergetics work through electron and proton transfer.<sup>39</sup> I didn't invent chemiosmosis, I won't claim that, that's due later to Peter Mitchell,<sup>40</sup> but I proposed that bioenergization goes through electron and proton gradients. So when there were meetings in the USA on the bio-electrochemistry of protons and electrons to which I was invited, and so was Barney, who had similar interests, I went to one of those meetings in California, where Barney Rosenberg was present.<sup>41</sup> Barney was a biophysicist and you could call me by then, a biochemist. When we met we obviously had a common interest in electron conduction in proteins, and the results of his attitudes were, I think, that platinum is the only drug that will ever be discovered by a biophysicist. The way he came to it is very strange.<sup>42</sup> Because he believed that electrons or electricity affected bacterial growth – Andrew has described the way he looked at this probability<sup>43</sup> – he designed his experiments of passing current through a bacterial cell suspension using platinum electrodes. He didn't think the consequences had anything to do with chemistry, because he knew very little chemistry. He was a physicist. And that's why he called on me. He found

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<sup>38</sup> Wolstenholme *et al.* (eds) (1979).

<sup>39</sup> Williams (1961, 1974, 1989).

<sup>40</sup> See Mitchell (1970, 1977).

<sup>41</sup> Williams (1964).

<sup>42</sup> See page 3, notes 4 and 5.

<sup>43</sup> See pages 6–15.

out from somebody, and I didn't know who it was, that it was the platinum that dissolved in the water from the electrodes that was causing the observed changes in the bacterial cells: it was not the electrode fields. Barney phoned me up and said that he had seen that I had done something on platinum chemistry.<sup>44</sup> This work was published with Andrew earlier and was pure physical chemistry.

By the way, I should say I did experiments all the time in chemistry – to try to model what was happening in biology – but I did not necessarily tell my pupils the reason why they were doing the experiments, simply because I thought they would have been totally lost. They were so trained in chemistry that they wouldn't have seen how I could move over from their subject into the biological sciences.

To continue: Barney rang me up and said, 'Bob, I am in difficulty, I don't understand much about platinum chemistry. Will you be my consultant?' I said, 'No, I can't work as a consultant with somebody 5000 miles away, we will just get into a terrible jumble, but what I will do is find a pupil of mine, who is well versed in chemistry, who can come to work with you'. I knew he had to be an adaptable and a very good scientist. I told Barney that he will come one bright day and help you. I didn't have a man in mind at that time, until Andy came to work with me and had worked on platinum chemistry. The reason we worked on platinum I needn't go into, it's all to do purely with how to do a certain form of spectroscopy.<sup>45</sup> At the same time my group also looked at certain electron transfer systems so that Andrew became knowledgeable in this topic too.

Now, you know that careers are funny things. I was then tutoring chemistry mainly. In the middle of 1966 though, which was just a little later than this, I went across to Harvard University for a year, determined to get out of chemistry and to find a university which would allow me to do biology. So I worked in the Peter Bent Brigham Hospital [Boston, MA] at Harvard with Professor Bert Vallee<sup>46</sup> and learnt some chemistry, biology and metal chemistry in proteins. This helped me a very great deal I have to say, learning biology there. I came back to Oxford in 1967 and said to my colleagues: I am not going to teach any of this chemistry stuff any more, I am teaching biochemistry or nothing. So I

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<sup>44</sup> Day *et al.* (1965a).

<sup>45</sup> Professor Robert Williams wrote: 'We wished to understand polarized transitions using new equipment.' Letter to Dr Daphne Christie, 27 January 2007.

<sup>46</sup> Professor Bert Vallee, Professor of Biochemical and Biophysical Sciences and Medicine, Harvard University, Boston, MA, USA.

asked, 'Can I come back on those terms?' They said, 'OK, you can come back but your salary is reduced'.

This period in Harvard helped us in thinking about platinum. Later on, because interest in metal ions began to grow, and partly perhaps because of these platinum drugs, I was made a Napier Royal Society Research Professor in 1974, and the strange thing is that the fund money was left by Napier, who had died of cancer.<sup>47</sup> Napier had left money to the Royal Society and initially it had been given to cancer research. They were very disappointed with the results of that, because, of course, one man on his own, doing cancer research, was clearly a complete waste of effort; you had to have a big organization or team. What happened then was, very simply, that they got hold of me and said, 'Look, there are loads of diseases we don't understand. Will you investigate them, that is investigate in a general sort of way, the causes of diseases of an unknown cause?' So that was my brief from the Royal Society, and I loved that brief. I have worked on it for 20 years, often on different types of drugs, but platinum has been but one of great interest.

I would like to say one or two other things about Rosenberg, and a couple of other people who have been involved, who have not necessarily been mentioned sufficiently by Andy, but it is obvious that you can't include everyone. Rosenberg did learn some biology, but basically he was often, shall we say, wild in his thinking, perhaps very imaginative is a better way to put it. I think all who knew Barney then will agree with that. Much of what he proposed you did not believe and you had to go away and ask, 'Was it possible?' For example, he believed, somehow or other, that platinum was affecting the immune system. He didn't think it was anything necessarily to do with DNA at first, and we used to argue about this. Here he had a piece of luck, he employed various Czech scientists, and it's a pity one of them couldn't be here to represent their work: Gerry Droknic and a young woman called Scarlett Reslová, his pupil. She was called Scarlett after the well-known Scarlett in *Gone with the Wind* by her father, who had, I believe, been an airforce pilot in the war and seen the film.<sup>48</sup> She discovered a very interesting possibility concerning the action of cisplatin. She had done microbiology, and this is where, as so often, microbiology comes

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<sup>47</sup> The Napier Research Professorship is for research with the object of ascertaining the cause of cancer, including any corresponding allied disease and the means of prevention, cure and alleviation. See [www.admin.cam.ac.uk/reporter/1999-2000/weekly/5819/58.html](http://www.admin.cam.ac.uk/reporter/1999-2000/weekly/5819/58.html) (visited 26 April 2007).

<sup>48</sup> *Gone with the Wind* by Margaret Mitchell, published in 1936, won the Pulitzer Prize in 1937 and was filmed in 1939 with Vivien Leigh as Scarlett O'Hara.

into cell studies. She had seen that if she treated with platinum, *E. coli* cells that had inserted phage, then the phage was liberated. She immediately concluded that platinum acted by an attack on DNA. That led to a big argument between her and Rosenberg, and in the end she published her work on her own, possibly because he didn't think she was right. It's a very short paper, and it was actually a very fine paper.<sup>49</sup> The result of that was twofold – I am sorry to go on a little bit, but there are some very amusing aspects of all this. Several Czechs went back to Czechoslovakia – she was one of them – just at the time when the Dubcek era collapsed.<sup>50</sup> I had been very, very foolish; I had told her from the USA to go back. I said, 'You have to go back to your own country, somebody has to look after the place', but I had never been in an occupied country. So I went there repeatedly, about four times, between 1968–75, carrying platinum compounds that were to be tested in Czechoslovakia, mostly in microbiological assays. I won't go on about that, but as a consequence, Reslová, myself and Andy wrote a long review in 1972,<sup>51</sup> and in that review we suggested quite a number of the possible platinum-complex variants which you could work with, including the oxalate, I think that is right. I did very few additional experiments, but I do want to say one thing about the Americans.

The Americans were scared stiff of this drug; they would not let it be tested in any hospital under NIH control. The result was that Barney could not even run an open meeting in the USA on the drug, so he appealed to me to run one in Oxford. The first open [international] platinum meeting was run in Oxford in 1973, and basically I organized it at Wadham College and in the inorganic chemistry laboratory, which is totally appropriate, as cisplatin is inorganic.<sup>52</sup> Almost all previous drugs were to do with organic chemistry. One outcome was that NIH were furious and sent a man across to lecture us on why this drug was completely unsuitable and would be poisonous and therefore would not be effective in any circumstances. Of course there was a big risk, there's no doubt about that, and I later investigated a little bit about platinum protein chemistry

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<sup>49</sup> Reslová (1971/2); Thomson *et al.* (1972).

<sup>50</sup> See, for example, Golan (1973).

<sup>51</sup> Thomson *et al.* (1972). Professor Robert Williams wrote: 'Dr Scarlett Reslová on return to Prague worked mainly in microbiology. She was very resistant to the authorities until Havel came to power. For a short while she was a high-up adviser to his government and wrote a brief note in *Nature* concerning the future of science in Czechoslovakia. She became unwell and is now semi-retired.' Note on draft transcript 4 April 2007.

<sup>52</sup> See note 23.

with the biophysicists and other people in Oxford. Platinum does attack a great variety of biological polymers. There are small things I can add, but I want to get across that this was a very strange and fortuitous development. There could not be anything more like a series of steps, which one could only call good luck, plus Barney's determination and belief. Everything could have gone wrong at almost every step, when the work could have been stopped entirely. One item, I think, that Andy didn't remember is the name of L Woff. He was a microbiologist, a French Nobel Prize winner, who in fact knew about filamentous growth and phage release from bacteria.<sup>53</sup> He did not say anything specifically, but just that sometimes there's a correlation between cancers and filamentous growth. He rather pushed that on one side. Remember, this assumption was central to Barney's thinking. He [Woff] did say that anything that releases phage from bacteria is much more likely to be an anticancer agent, and that's where Reslová, who was a microbiologist, got her lead.<sup>54</sup> But the start of platinum drugs is really a biophysics study, which is a very strange starting place. That is my view of the history, but I may interrupt later, with various bits and pieces I know about.

**Calman:** It really is fascinating. Just in the first two comments from Andrew Thomson and Professor Williams, you can begin to see how this started.

**Dr James Hoeschele:** I want to add a few facts. I overlapped with Andrew at MSU – actually I preceded him. I was a graduate student at MSU from 1959 to 1965. I knew of Dr Rosenberg, but wasn't working for him at that time. I was working as a graduate student in the chemistry department doing electron transfer reaction studies. But Dr Tom (Thomas) Krigas, whose name has not been mentioned so far, and who had a role in the platinum project, was hired by Dr Rosenberg while a chemistry graduate student to do some synthetic work making some platinum chloroam(m)ine compounds. He was earning his keep, basically, doing this. And so he would come to my laboratory off and on, and we talked about the whole process (the potential role of platinum in the filamentation of bacteria), back in 1963 and/or 1964. We talked specifically about what might be causing this effect, and it was mentioned during our discussion that it was possibly the electrolysis. Now that seemed a little far-fetched at the time, because my understanding of electrolysis was in the context of DC electrolysis and not AC electrolysis. But it was only under AC electrolysis

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<sup>53</sup> Professor Robert Williams wrote: 'L Woff worked in the period before and after the Second World War.' Note on draft transcript 4 April 2007.

<sup>54</sup> See, for example, Reslová (1971/2); Harder (1974): 98–112.

that the filamentation occurred. It happens only when the frequency ranges between something like 5000–10 000 cycles per second.

So then I joined the Rosenberg group as his first postdoc student in February of 1970, having left and then returned to Michigan State University. Barney [Rosenberg] was interested in me because I had radiochemical experience: radiochemical experience to radiolabel *cis*- and *trans*- platinum and other compounds that we did, in studying the uptake, distribution, and retention of platinum in mice. And along with the distribution studies, Mike Cleare joined the group in mid-1970, and he and I laid out a programme of synthesis of cisplatin analogues. Mike had much more prior experience in coordination chemistry than I did, but together we designed (based on earlier work) a whole programme of synthesis in which you could vary the metal, and both neutral and anionic ligands. And we divided up this work and set about to find out what the structure–activity relationships were. Mike was fresh out of graduate school in England, and working with Johnson Matthey, but on loan to Barney Rosenberg. So that was my involvement. While I was there, the very first platinum meeting was held not in Oxford but at Michigan State. It was in 1971. I think you were there, Bob [Williams]. Were you, Andy [Thomson], there as well?<sup>55</sup> It was a small group. It included John Venditti from the NCI, Sir Alexander Haddow and Peter Brookes from the Chester Beatty Research Institute in England, and others. John Roberts was also there, I believe. And that was the start of the collaboration with Europe, at least as I knew it, at that point.

One very personal incident that I had, and want to share with you, is that Mike Cleare and I took Sir Alexander Haddow (and his wife) to an American football game. Now he was blind, as most of you probably know, but we took him to a MSU football game. He sat right in the very front row of the upper deck and I never saw anyone enjoy a football game as much as he did. It was a really rare experience – he was a wonderful man.

**Calman:** Thanks very much. Before we move on to Ken Harrap, are there any other contributions on that very early period, defining the first meeting on cisplatin; it is now 1971. Any other comments on the early chemistry?

**Williams:** I wonder if Tom Connors' name ought to be mentioned again, because he was very forward in helping in the involvement of the MRC, I think.

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<sup>55</sup> Professor Andrew Thomson wrote: 'Andy Thomson attended, Bob Williams did not.' Note on draft transcript, 18 February 2007.



I think he was from the Chester Beatty and was the one who often remembered Haddow's work.<sup>56</sup>

**Calman:** I am sure Ken Harrap will pick that up. It brings back enormously happy memories for me at the Chester Beatty with Tom [Connors] and Ken [Harrap] and others at the time.

**Professor Kenneth Harrap:** It's very difficult to distinguish them, everyone at the Chester Beatty was mad; you didn't get a job there unless you were mad. But it was from the early work [**From the floor:** Would it be Tony Loveless?] Thank you, that's his name.<sup>57</sup>

**Calman:** Any other comments from that early period of inorganic chemistry of platinum, early meetings, reflections of Rosenberg *et al.*?

**Williams:** On the bacterial filamentous growth, if you read the literature you will find that if you treat *Escherichia coli* with excess magnesium in the water, you will get filamentous growth of *E. coli*. You don't [only] need platinum.<sup>58</sup>

**Calman:** Perhaps I could ask Ken Harrap, who was at the Chester Beatty, to speak. He and I met in 1972; it seems like a long time ago, but he looks just the same.

**Harrap:** At the time that we are talking of, or just before, Tom Connors and I did our PhDs at the Chester Beatty Research Institute, as it was called then, in the Fulham Road, London, and we were both in the chemistry department.<sup>59</sup> My supervisor was Professor Franz Bergel, and I was doing biochemical-type things with enzymes and Tom Connors was doing pharmacological-type things with alkylating agents, which was the major interest of the Chester Beatty Institute. There was a huge investment in alkylating drugs and, in fact, you are probably aware that many of the compounds that were first produced in the chemistry department there are still available for regular use: myeleran, melphalan, chlorambucil. Eve Wiltshaw – who is fortunately here – was involved in the clinical evaluation of these early alkylating drugs. I remember the time that you mentioned, when Alex Haddow came back from this particular meeting

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<sup>56</sup> Professor Tom Connors is mentioned earlier, see page 14, note 33. See also pages 99–100.

<sup>57</sup> See page 13, note 27.

<sup>58</sup> Rosenberg *et al.* (1967a and b); Lusk *et al.* (1967).

<sup>59</sup> The Chester Beatty Research Institute – Institute of Cancer Research, Royal Cancer Hospital. See Royal Cancer Hospital, London (1951). See also Haddow (1961); Brunning and Dukes (1965).

in Barney Rosenberg's lab and summoned Tom and, I think, he summoned you as well, Eve, didn't he at one stage? And he said, 'Look, there is all this platinum stuff going on in the USA, it is really very exciting, they are showing activity in animals, but this drug is so terribly toxic that the US FDA (Food and Drug Administration) won't allow them to run a clinical study. Well, that's nonsense, we can do this here'. So Tom Connors started a collaboration with JM, that's already been mentioned, particularly with Mike Cleare, and he and Mike Cleare and other chemists at JM started looking at analogues, looking for a drug which might perhaps be more potent than cisplatin, so that you could use less of it, and perhaps get less toxicity. On the other hand, Eve Wiltshaw and her group pursued the first Phase 1 study of cisplatin and I do hope we are going to hear something about the clinical work fairly soon, because this is what has driven everything that has happened since, it really is. It is the toxicity of cisplatin, allied to its extremely potent antitumour activity in the clinic, that has driven everything that has happened subsequently.<sup>60</sup> So where I came into the picture was after Tom had left to become Director at the MRC Toxicology Unit at Carshalton, Tom's people were allocated to me and I became much more interested in pharmacology than biochemistry, and ergo, there was an interest in platinum with that, and we started trying to look for a less toxic analogue, but equiactive cisplatin. On the way we came across carboplatin, JM8 [cis-diammine (1,1-cyclobutanedicarboxylato) platinum (II)], Paraplatin® [Figure 6], which proved to be a good candidate.

Hilary Calvert was responsible for the clinical study in the Marsden of carboplatin, and made some extremely forward-looking observations on the clinical pharmacology of that compound; I will leave him to tell you about that.<sup>61</sup> Subsequently, we discovered other analogues, and I should emphasize that the JM connection was paramount here; it was paramount in all of Tom's work, and in my work, because we had no platinum chemistry in the Institute.<sup>62</sup> All the chemistry was done at JM, and this had always been a chemistry-driven programme. It's been a delight to work with JM. As we learnt a little more about platinum, it became clear that there were limitations in carboplatin. Incidentally, I notice Andy Thomson's handout says that carboplatin is active in resistant tumours but, in fact, there is extremely slender evidence for that. So what we

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<sup>60</sup> Wiltshaw and Carr (1974).

<sup>61</sup> See page 27 and Calvert *et al.* (1989); van Warmerdam *et al.* (1995); for a review see Kelland (1993).

<sup>62</sup> Professor Andrew Thomson wrote: 'Many analogues were also synthesized in the laboratory of the late Professor Martin Tobe, in Chemistry at University College, London.' Note on proofs, 7 August 2007.

started to do was to look for compounds that might be active in platinum-resistant tumours, and we came up with one which is still in clinical development; it is now called picoplatin, AMD473 [*cis*-amminedichloro (2-methylpyridine) platinum]. Our second compound, JM216, *cis*-, *trans*-[PtCl<sub>2</sub>(O<sub>2</sub>CCH<sub>3</sub>)<sub>2</sub>(NH<sub>3</sub>) (cyclohexylamine), Figure 7], was developed predominantly to produce an oral formulation. And JM216 is one such, and is pursuing clinical development, it is known as satraplatin. So there is a lot of subsequent development after cisplatin. I think we ought to hear a bit about the clinical utility of cisplatin and maybe have some comments from the audience on that.

**Calman:** Thanks, Ken, you bring back huge memories for me, because it was meeting Tom, you, Hilary and others, on an annual basis – we had a meeting at Burnham Beeches, which was good fun – and had us playing rugby in the middle of the bar for large periods of the evening. Clearly there was also some exchange of clinical and scientific information. And that for me, and I will perhaps say a little bit about this in winding up, many of these things seemed to be about people and groups, we knew each other, we already identified that quite clearly, and groups keep together and share that kind of information in a way that is just astonishing. But you are going to reply?

**Harrap:** Just to say that it was Tom Connors who was responsible for this strange athletic phenomenon which always happened after a scientific meeting and it was always in the bar when people were very drunk. Hilary has also been involved in these tournaments. It is called ‘Jumbo’, rugby football played on your hands and knees with a match box as a ball; one team defends one wall and the other team defends the opposite wall. It gets very bloody and expensive.

**Calman:** I am not sure whether Wellcome would allow us to demonstrate this evening.

**Dr Eve Wiltshaw:** We have talked about Barney Rosenberg – and I don’t want to go into that anymore because I think we have his life history more or less – and Alex Haddow. I have learnt quite a lot this afternoon about Alex Haddow’s interests in platinum compounds. Because when he came to see us, that is David Galton and myself, about testing cisplatin on patients, he didn’t say much, except ‘this is another alkylating agent’. We had been testing alkylating agents for 20 years, and we were not impressed by another one. He didn’t say anything about the special things that he apparently knew about the platinum compounds, but he did say this was a new series of drugs and that, because there was a metal involved in the chemistry, one might have quite unexpected

results, both in terms of toxicity and in terms of efficacy. So, although we were not keen, we did start a study in 1971.

Let me just say what it was like then to do medical oncology. Haddow had started with a clinical medical oncology unit in the 1950s. There was no other unit in the country, and almost no other unit in the world that was doing clinical studies in drugs, and as you can imagine, we were not favoured doctors at the time. And, in fact, we were called the ‘death-watch beetles’, because we had to go to see people who were dying, and try to treat them with totally ineffective drugs. Nitrogen mustard was about the only drug that resulted in any kind of improvement. The situation in the 1970s was that we had this tiny medical unit that had no staff; there were two doctors, David Galton and myself, or David Galton and somebody else.<sup>63</sup> There were no junior staff and we relied on David Galton’s international reputation to attract fellows from abroad to help us with the work, and these people were funded by themselves or by their countries; there was no such thing as funding for a clinical fellow for medical oncology. Nevertheless, they did come and that was a great help to us. There was no senior house officer, there was no registrar, and there was certainly no nurse to help you. So we did all our IV therapy and work, blood products and so on ourselves. It was impossible to do things in a big way at that time. To consider a collaborative trial was impossible. There was no unit to which you could hand out helpful hints and ask them to collaborate with us. Again, remember, there were no nurse data managers, so it was a slow business.

The other side of the coin at the time was that there were few restrictions on trials: virtually no ethical permission was needed, and the hospital relied on the doctors not to do anything that might be considered detrimental to cancer patients. Again, all our patients knew the diagnosis in the 1970s. They might not have known it when they came to the hospital, but they were told when they arrived. We found that when they were asked if they would enter a study, often comparing drug A with drug B, very few refused. However, that kind of permission given by patients was well below what you would have to do now. Patients were not told about all the hazards that might occur.

I don’t want to go back on what has already been said. We are talking about ‘luck’ in terms of platinum compounds, and one of the things that we decided was to treat patients with ovarian cancer, not because we thought that this was the drug for ovarian cancer, but for another reason. One was that I had a small practice

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<sup>63</sup> See Christie and Tansey (eds) (2003).

in ovarian cancer patients. The second was that we knew that this was about the only adenocarcinoma that responded, however badly, to alkylating agents: chlorambucil, cyclophosphamide and so on. They did have a small response rate, and therefore we thought that this might be amenable to the new drug. That turned out to be a very appropriate way to go, since I already had experience of the natural history of ovarian cancer and the rather pathetic response sometimes seen using chlorambucil. The first use of cisplatin was impressive to me, and I reported this to the cisplatin group at the Oxford conference in 1972/3.<sup>64</sup> Twenty patients were treated and several showed dramatic regression of tumour masses and the disappearance of ascites – this was despite the fact that most were seriously ill before having this drug. Indeed, all had had previous treatment – and remember that ovarian cancer was at that time treated by pelvic radiotherapy or pelvic plus whole abdominal radiotherapy. So the effects on the blood counts were more extreme than you would expect with previously untreated patients.

When we spoke at this meeting in Oxford, there were about six US groups also speaking on clinical trials. The only person who also had a positive outlook about cisplatin was Higby and his colleagues who had treated testicular cancer and had found that it was very responsive to cisplatin, and so it was; although it turned out that you had to have a combination of drugs to get real cures.<sup>65</sup> As far as ovarian cancer was concerned, they were not interested in the USA; they thought that cisplatin was far too toxic to be used on a large scale. They had used it in head and neck tumours in particular, and among the things that they had done with other alkylating agents was to escalate the dose, and they produced dreadful renal damage and neurological damage. We were lucky; because people vomited so much with cisplatin, we gave them post-cisplatin IV fluids, for the vomiting, not for the renal function, and it worked; we hardly ever saw renal damage. And so, we were able to continue where others weren't.

**Calman:** What a remarkable testimony that was, and it shows, I think, two things: one, the courage of the oncologists but, just as importantly, the courage of the patients to be part of that process. You also mentioned the death-watch beetle bit. Sixty per cent of the patients referred to me in Glasgow in the first

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<sup>64</sup> Dr Eve Wiltshaw wrote: 'There was one previous conference on the subject of platinum complexes I think in Dallas, Texas but a book was published after Oxford to the participants.' Letter to Dr Daphne Christie, 31 January 2007. See Connors and Roberts (1974): 178–182. See also note 23.

<sup>65</sup> Higby *et al.* (1974).

six months of my appointment there died within the month without treatment. That was the referral practice, which many of us saw in the early 1970s, and things changed at just about that time.

**Professor Hilary Calvert:** It is nicer to be one of the younger members of the audience for a change; it doesn't happen very often any more.

When Bob Williams started working on metals in biology, I had just been born, but only just. I am really going to talk about carboplatin, but my first acquaintance was with cisplatin, and that was in 1974 when I got a job at the Marsden, because the interviews were the day before those at the National Heart Hospital. I was assigned to be Eve Wiltshaw's houseman, so she did have a houseman by 1974. One of the things that I had to do was to give this platinum stuff to a patient with ovarian cancer. I, of course, had been taught that you couldn't treat people with advanced cancer and that the drugs didn't work and that they always died. The patient got very sick and looked a bit peaky, but came back about two weeks later without any cancer. That was what converted me to spending the rest of my career as a medical oncologist.

I got a research post with Ken Harrap and worked on the famous methotrexate for quite a few years, and eventually became a consultant at the Marsden, with the specific job of doing new drug trials, which was the first time they had appointed anybody to specialize in new drug trials. And Ken said, 'Well, we have this carboplatin stuff, you had better do that'. And so that was my first drug to do a Phase 1 trial with. I had made pretty much no contribution to the development up to that point, I think, except for one thing where Ken may be able to contradict me, but Ken had done a series of very detailed toxicological studies in rats, with about eight different platinum compounds, and two of them came up clearly ahead for having reduced toxicity: one was carboplatin and one was CHIP or JM9 [iproplatin, *cis*-dichlorobis(isopropylamine)-*trans*-dihydroxyplatinum IV), Figure 6]. There wasn't much to pick and choose between the two. We had one meeting and there was one xenograft that worked, so I said, 'Why don't we try it on that?' And we did, and the carboplatin worked better. I think that's what finally tipped us into doing the study with carboplatin.<sup>66</sup>

I think there were two things that really stand out now on the clinical development of carboplatin: one was technical, getting the stuff to work; and the second was political, because a lot of people didn't want us to do it. So, I will start with the

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<sup>66</sup> Calvert *et al.* (1982).

first. We did the Phase 1 study of carboplatin with what is now, of course, a fairly conventional methodology of increasing doses and looking at the toxicity, and the chief toxicity was myelosuppression with thrombocytopenia coming out as the major feature. And the other toxicities associated with cisplatin, like the renal toxicity, were much less, and the vomiting was less severe. But one thing that was quite curious and hard to understand was that there was a great deal of difference in the different patients, in the way they tolerated it. So you'd get some patients that I could give 500 or 600 mg/m<sup>2</sup> to, and they wouldn't have much in the way of toxicity, and others on about 200 mg/m<sup>2</sup> would get really crashing thrombocytopenia that would last for a long time and be dangerous. And we were thinking about this, and there was at that time a growing interest in pharmacokinetics in correlation with the toxicity of anticancer drugs, and in particular the idea of 'systemic exposure' or the 'area under the curve' (AUC) was coming in.<sup>67</sup> For the chemists it is a pretty easy concept, because it's just the law of mass action, so that the idea is that the effect of a drug – the toxic or the therapeutic effect – is proportional to the area under the concentration curve or the concentration time. And, of course, for a platinum analogue that made sense, because we knew it was reacting with DNA, and presumably the bigger the area under the curve, the more DNA adducts you form. It turned out that carboplatin had very predictable pharmacokinetics, but was very strongly affected by renal function, because it is almost all excreted by the kidneys, and it is almost all excreted by glomerular filtration, and glomerular filtration was something that we could measure. So we were able to put together a little model, and work out in advance what dose of carboplatin we would need to give to a patient to get a particular 'area under the curve'. And with my colleagues, including Steve Harland and Herbie Newell, who aren't here, and Ian Judson who is, we treated a bunch of patients with variable renal function and worked out a formula that was published, which has subsequently – and nothing to do with me – become known as the 'Calvert formula'.<sup>68</sup> It has an unbelievably large number of citations, because there are an unbelievably large number of people who use carboplatin out there.<sup>69</sup> And if I am in Japan at a medical meeting, I am

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<sup>67</sup> The total area under the concentration/time curve (AUC). See Seymour (1993): 9–39.

<sup>68</sup> The Calvert formula can be used to calculate the carboplatin dose accurately in order to obtain a target AUC (area under curve) by using only the GFR (glomerular filtration rate). The formula is: dose (mg) = AUC (mg ml<sup>-1</sup> min) x [GFR (ml/min) + 25 (ml/min)]. See Calvert *et al.* (1989); van Warmerdam *et al.* (1995).

<sup>69</sup> Professor Hilary Calvert wrote: '1038 citations reported by the Web of Knowledge'. Note on draft transcript, 30 March 2007.

quite likely to hear among a lot of stuff that I don't understand at all, the words 'Calvert formula' appearing from time to time, which is always quite interesting and gratifying. When we published the Calvert formula, I felt, 'Well, this is very neat pharmacology, it will get me a paper in the *Journal of Clinical Oncology*; that was about the highest impact I could have hoped for in this field, and then probably nobody will take any notice of it, because doctors aren't interested in that sort of thing'. And that's pretty much exactly what happened for about two years. But then the marketing manager for carboplatin in the USA working for Bristol-Myers picked up on my paper and gave me a phone call and said, 'Look, we are having real problems with this drug, because the oncologists think it is an erratic drug that is hard to use, and occasionally their patients fall apart, and they really don't want to use it and they are sticking with cisplatin and would your formula help?' And I said, 'Well, it might, but nobody really uses it'. So he said, 'Well, we need some marketing'. So he took me on a course and trained me in presentation and everything, and I did tours of various medical centres in many parts of the world, hundreds of air miles, and over a period of two or three years they converted about 20 per cent of people using carboplatin, where a platinum drug was indicated, to about 80 per cent, and I think they put their sales up in a similar proportion, and from that time carboplatin has been the most commonly prescribed platinum analogue, although cisplatin is still used. So, without a bit of pharmacokinetics, but also a bit of marketing of science if you like, I don't think the drug would ever have taken off and become the big drug it is.<sup>70</sup>

The other curious thing was that from the medical side there was quite a lot of opposition to the introduction of carboplatin. People had finally found out how to give cisplatin without causing too many dreadful effects: by giving the right regimen, hydration, diuresis and the right antiemetic regimes and so on, so that you could actually give cisplatin to patients. I think many people felt this was a big achievement of medical oncologists, and it was also something the surgeons didn't know how to do, so it made the oncologists feel better than the surgeons. And so when somebody [Hilary Calvert] came along and said, 'Well, if you use carboplatin you don't have to bother with all that stuff', the oncologists weren't particularly pleased.

I think another feature was that the commercial partner, Bristol-Myers, also was looking for a second-generation platinum analogue although by this time

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<sup>70</sup> Professor Hilary Calvert wrote: 'It is the standard treatment for ovarian cancer and, combined with paclitaxel, it is the most popular treatment for non-small cell lung cancer. It is generic, but Bristol-Myers Squibb report sales of \$246 million in 2003.' Note on draft transcript, 30 March 2007.



cisplatin was doing very well. Their favoured second-generation analogue was one that had been developed in Holland, called TNO-6 [1,1-diaminomethyl cyclohexane sulphato platinum II].<sup>71</sup> I think the Dutch had got ahead of the English in setting up well-recognized, internationally-recognized, Phase 1 drug evaluation centres, and I was pretty much unknown and there weren't really any other people doing it in the UK. So there tended to be more plausibility towards the Dutch data. And early on the drug material was provided by JM. We formulated some of it ourselves. I was, frankly, rather discouraged from continuing with the trials. There were also quite serious supply problems, because although JM had made enough, Bristol-Myers after a while, volunteered to formulate it, but then it had some problem with its formulation plant and we didn't have the raw material, and we didn't have the formulated product back, and we were only able to continue by two routes: one was by acquiring some more material and formulating it in the Marsden itself, and the second was because the NCI, who by that time had decided to do trials with it, generously gave us quite a large chunk of their own stock that they had set up for their own trials, which allowed us to go forward. And then, of course, Eve [Wiltshaw] set up the first randomized trial of carboplatin versus cisplatin in ovarian cancer, which she did on the back of what she calls her very tiny ovarian cancer practice, which I think was probably the biggest in the country, and we were able to do the trial, and show that carboplatin was just as good as cisplatin, but a lot less toxic. And to this day, carboplatin remains the most important single drug, and the preferred platinum analogue, for treating ovarian cancer. There have been countless other trials making the same comparison, and they all give the same answer virtually, except for one US trial that suggests that carboplatin may be a little bit better.<sup>72</sup>

**Calman:** Thanks, Hilary. Any further comments?

**Professor Richard Gralla:** I'm from New York. Maybe I should take up the story from the 1973 Oxford meeting and what happened in the USA, unless Dr Harrap wants to go ahead. I was asked here mainly to talk about antiemetics, but I am going to reserve that for a little bit later. I was a witness to the early clinical studies after the Oxford meeting, and I started my medical oncology career at the same time as Hilary, in 1974, at the Memorial Sloan-Kettering Cancer Center. I read this nice blue book that the Proceedings of the Oxford

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<sup>71</sup> See Sørensen *et al.* (1985).

<sup>72</sup> Bookman *et al.* (2003).

Conference were in, which was most fascinating in the first half of the book, because it talked about the chemistry, and most discouraging in the second half – a very fine, excellent anticancer drug, unfortunately too toxic to give to people. Certainly the NCI had that view. Steve Carter<sup>73</sup> was one of the leaders of the meeting, and the real change, in my view, was the fact that there was another generation of physicians who were not invited to that meeting, who looked at it in another way. Now, as fortuitous as the use of cisplatin was in ovarian cancer – and again this is going back to the comment that was made earlier, that at any point this could have gone awry, and it was so wonderful that Don Higby had the testicular observations, Dr Harrap had the testicular observations, and that Dr Wiltshaw had the ovarian observations – but head and neck cancer was the exact opposite of this, there couldn't have been a worse choice. Even though the drug is active there, because of the nature of head and neck cancer, the patients were all dehydrated before they got the cisplatin. So even at relatively lower doses, the drug was terrifically toxic, and excellent oncologists such as Alan Yagoda and Bob Wittes at that time said they didn't want to touch it.<sup>74</sup>

We have now reached 1974. I had the advantage of having so little knowledge, which had always been a plus in my career, that it was very helpful. And at that point a major figure in the development of these drugs, Steve [Esteban] Cvitkovic, who is now in Paris, came along, and Steve is a most irreverent individual; for those who know Steve, irreverent would be a soft word.<sup>75</sup> Steve [Cvitkovic] was also interested in testicular cancer, and had as a research fellow done the first bleomycin infusions and could see that bleomycin was a drug of usefulness in this disease [testicular, head and neck cancer], but certainly with the older agents was of only very limited value.<sup>76</sup> And that's why Steve became particularly interested in cisplatin. Steve then asked, 'How would you handle this kind of renal toxicity?', which was the number one limiting factor in this area. He thought, 'Well, when you read the literature you would either give a

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<sup>73</sup> Dr Stephen (Steve) K Carter was Associate Director of Cancer Therapy Evaluation, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland.

<sup>74</sup> Professor Richard Gralla wrote: 'Alan Yagoda and Bob Wittes were at Memorial Sloan-Kettering Cancer Center in New York at that time'. E-mail to Dr Daphne Christie, 5 June 2007.

<sup>75</sup> Dr Esteban [Steve] Cvitkovic has held appointments at Memorial Sloan-Kettering Cancer Center (New York), Columbia Presbyterian (New York), Instituto Mario Negri (Milan), Institut Gustave Roussy (Villejuif), Hôpital Paul Brousse (Villejuif, France) and Hôpital St Louis (Paris) and was Senior Medical Consultant to AAI Oncology.

<sup>76</sup> See Carter and Blum (1974).

chelating agent,’ – which made no sense medically as far as he was concerned – ‘Or you would, as with mercury poisoning, give an osmotic diuresis’. So Steve then followed with hyperhydration and with an osmotic diuresis caused by simply giving mannitol. But Steve, being an extremely ethical physician, did not start with patients, he started with dogs. And, to do this, was exactly the observation that Sir Kenneth made, which was how you were able to just do that then. You could never do this today, and Steve always wanted answers quickly. So he went to the laboratory of Willet Whitmore, the famous urologist,<sup>77</sup> and asked, ‘Can I borrow a dog or two?’ I think Dr Whitmore thought that he meant to walk it or something like that. Steve then went with the hyperhydration and the mannitol, which worked extremely well, and also tested some dogs with exactly the same dose of *cis* [*cis*-platinum] without the hydration mannitol, and it didn’t go well. This was published in 1977 in a series of three papers with both the histological deficits that were caused in the kidney by cisplatin with the preclinical safety and with the clinical effects in cancer.<sup>78</sup>

I remember one of the very first patients to receive high-dose cisplatin, which was then given with a very fancy hydrational aspect and later with mannitol, and it was to a young woman with a germ cell malignancy, with choriocarcinoma who had had everything, methotrexate, and 10 or 15 other drugs for brain metastases. I looked at my colleagues and asked, ‘Are you really going to treat her?’ Remarkably, she did very well, and at that point we knew that something special was going on.

You have to look at the Memorial Sloan-Kettering at that time, a 600-bed hospital, all cancer patients. They had provided two closets for the administration of chemotherapy. It was an afterthought when they redesigned the building in the early 1970s, and there were no research nurses, etc., etc. Everything had to be done on its own. Cisplatin was treated as yet another Phase 1 drug, but one with a bad history, and another alkylating agent. Then these special things started to happen. Even Dr Robert Good, who was in charge of Memorial Sloan-Kettering at that time, felt that cancer would be cured by the immunologists, very quickly, and that Memorial Sloane-Kettering would be an immunobiology institution.<sup>79</sup> Therefore, as Steve and others were showing repeated cures in testicular cancer with Bob Golbey, they had to keep quiet about it, because this was as politically

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<sup>77</sup> See Anon (1997).

<sup>78</sup> See Hayes *et al.* (1977); Cvitkovic *et al.* (1977).

<sup>79</sup> Dr Robert A Good (1922–2003) was Director of Sloan-Kettering Institute in 1973. See Hanson (2003).

incorrect a development as one could have. So it was a remarkable occurrence at the time, but fortunately this improvement continued.

I must mention another oncologist, Dr Lawrence (Larry) Einhorn, on the US side, who did wonderful work to complement the work that Drs Harrap and Wiltshaw were doing, which we knew very well.<sup>80</sup> Larry took a different view: 'Let's just divide the dose, give a small dose daily for five days and won't this be safe?' And by 1976, Larry Einhorn and Steve's method of VAB-3 was presented at the American Society of Clinical Oncology (ASCO) in Toronto, Canada, which worked in all regimes for testicular cancer, complementing much of the work that was done here in the UK.<sup>81</sup>

The last comment I will make on this is that the other contribution that Dr Rosenberg made over all this time was shepherding this drug, and he continued to have an extremely great interest in how the research was going from the preclinical to the clinical. He was at the meetings, he asked all the good questions, and he met everyone and was very interested in everyone's research, and made sure that everybody stayed connected. This, I think, was a dramatic contribution to back up his initial remarkable observations.

**Calman:** Thank you very much. I feel my past coming before me as I listen to all this because, like many people, I used to visit the Memorial Sloan-Kettering on a regular basis. I have two memories: one is I bought a set of cufflinks, and its logo is SKCC,<sup>82</sup> which is also Sir Kenneth Charles Calman, and they are really nice to have. The second is that its full name, if you remember, is the Memorial Hospital for Cancer and Allied Diseases, and I remember seeing a patient there. I said, 'Tell me what's wrong with you', and he said, 'I've got an allied disease'. These are issues of communication which are pan-national.

**Harrap:** I just wanted to link the chemistry to the clinical activity of cisplatin on the basis of a couple of remarks that Hilary [Calvert] made. He mentioned TNO-6,<sup>83</sup> which is such a reactive compound; its solid-state structure just doesn't exist in an aqueous solution. So reactivity is very important. One of the

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<sup>80</sup> See Einhorn (2001).

<sup>81</sup> VAB-3 protocol including vinblastine, actinomycin D and bleomycin. See, for example, Reynolds *et al.* (1981).

<sup>82</sup> For a history and overview of the Memorial Sloan-Kettering Cancer Center (MSKCC) see [www.mskcc.org/mskcc/html/511.cfm](http://www.mskcc.org/mskcc/html/511.cfm) (visited 2 May 2007).

<sup>83</sup> See page 30.

driving forces that led us towards carboplatin was the notion that in various structure–activity studies we had been doing, it was quite clear that kidney toxicity, which is the dose-limiting toxicity of cisplatin, appeared to relate to the chemical reactivity of the molecule. Now, of course, if you are trying to displace the nephrotoxicity of cisplatin in an analogue, you can monitor blood urea nitrogen in the structure–toxicity studies quite happily in rats and mice. But for the other toxicities, for example emesis, rodents don't vomit, although rats do get stomach bloat. So we could look at stomach bloat and we could look at renal function in the rat. The other thing you can do, ultimately, if you are prepared to spend the money, is a ferret emesis test – and that's a glorious opportunity for someone who wants to sit up all hours of the day and night, watching ferrets vomit.<sup>84</sup> It's very unpleasant, more so for the ferrets, I imagine. But anyway, we could do those three things, and that led us, as Hilary mentioned, to two compounds, carboplatin and JM-9, and again luck comes through and we went with carboplatin. But I didn't want to give the impression that carboplatin just appeared, without there being any logic: there was a chemistry-linked logic, through to the pharmacology that led us to carboplatin, and then onwards to those platinum drugs which could be given orally and other platinum species that evaded the resistance mechanisms attributable to cisplatin resistance.<sup>85</sup>

**Calman:** I think you are making a very good story out of it.

**Professor David Grahame-Smith:** I am a retired clinical pharmacologist and I want to ask Richard Gralla a question. The pharmacokinetics and pharmacodynamics of anticancer drugs have always been a great puzzle to me. Some years ago Adrian Harris and I investigated the pharmacokinetics, pharmacodynamics and therapeutic effects of cytosine arabinoside. That taught me how complicated these processes were. But you said you did a forced diuresis with mannitol and with lots of fluid to decrease the platinum-induced renal toxicity. What does that do to the half-life of the cisplatin, because you are presumably getting rid of it and diluting it? So what is all this doing to the plasma and intracellular concentrations of cisplatin and its anticancer action? I didn't quite understand this, because it flashed by me. One says, 'Oh my goodness that's great, the patients aren't getting nephrotoxicity, and they are still

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<sup>84</sup> Ferrets are the animal model of choice for evaluating a compound's antiemetic properties, because of the similarity to humans in neuroanatomy of the brain stem and stomach, and sensitivity to emesis-inducing agents. See Florczyk *et al.* (1981, 1982); Costall *et al.* (1987); Rudd *et al.* (1994). See also Wesley Miner's contribution on pages 54–6 and Paul Andrew's contribution on pages 44–6.

<sup>85</sup> Leyland-Jones *et al.* (1999); see also Ohmichi *et al.* (2005).

getting better'. But can you explain the process to me, because it doesn't make much sense?

**Gralla:** I think the important fact is that I was truly a witness to this, and not the person who came up with what I think is a very good idea, so I don't want to take credit for it. My understanding is that again you are driving a certain percentage of the cisplatin across the cells. You are basically giving it in excess. You need to be sure that you still have the chloride present, and once you get this across the cells, only a very small percentage of the cisplatin that you give is actually getting to where you need for it to become intracellular. So you need to get rid of the other 99 per cent, or 99+ per cent. However, this would be better answered by my clinical pharmacology colleagues.

**Calvert:** I can give a slightly more technical answer. Cisplatin is fairly chemically reactive, and when you give a dose to somebody, you only ever get about 30 per cent of it back by urinary excretion, because the rest remains covalently bound to tissues. I think you can work out that someone, say, who has been treated for testicular cancer, and dies of something else 30 years later, will probably have more platinum in him, than the stuff they dig up in South Africa. So to a large part the excretion of cisplatin isn't an issue because it doesn't happen, it's just partitioned out of the blood by covalent binding. But the 30 per cent or so that is excreted in the kidneys is excreted partly by glomerular filtration and partly by tubular secretion, because the clearance of platinum is 2.6 times higher than the glomerular filtration rate. I think the role of the hydration is that it increases the chloride content in the tubules and reduces the amount of reactive platinum there.<sup>86</sup>

**Professor Paul Andrews:** I wanted to pick up on something that Ken Harrap said about screening for the toxicity. You mentioned the gastric stasis model in the rodent. Can I check who came across that phenomenon as a potential as an index for emesis in non-vomiting species? Because the first paper I know is one – I think it is 1980 – with Bradner and Schurig, and they made an interesting comment in the paper that that observation was an accidental discovery by one of the technicians who was doing post mortems on mice.<sup>87</sup> That was the Bristol-Myers group in the USA, but I just wondered what your recollection is, because people are still publishing on that model today, including ourselves. Can you tell us about the origin of it?

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<sup>86</sup> See, for example, Walker and Gale (1981).

<sup>87</sup> See Bradner and Schurig (1981), in particular page 99: 'A second new test which is the result of a fortuitous observation by alert technicians is the so-called GI stasis model'. See also Florczyk *et al.* (1980).

**Harrap:** I think it was you [Paul Andrews] who suggested stomach bloat to us when we talked about it, so we are grateful to you for that. And yes, you are right; it is the Bristol-Myers group, John Schurig and colleagues, who suggested we think about the ferret emesis model.<sup>88</sup> That's quite right.

**Andrews:** So, it is somewhere pre-1980 that people recognized the gastric bloat.

**Calman:** We are going to talk quite a bit about the emesis area after tea, so we can perhaps pick up some of the areas around the early clinical development.

**Thomson:** I would like to make a couple of comments from the point of view of the chemistry. Cisplatin, as I explained, will lose its chloride ions rather readily, either in the absence of chloride or if it encounters another group that is a very effective nucleophile. Thiol is such a group. And, of course, the kidney damage presumably results from the platinum sticking to the thiol residues in the kidneys. I suppose we would call carboplatin a pro-drug today. So, replacing the chloride ions with a chelating group, which will bind much more strongly to the platinum, yields something that is no longer a drug since it is quite unreactive to nucleophilic substitution. But, presumably, there's a metabolic activation of the *cis* side of the molecule.

I just want to pick up on one other point that has been aired, and that is the question of the comparison that was made early on between cisplatin and the classical alkylating agents. Although at first sight – and I drew the analogy myself – that seemed to be so, there were a lot of mechanistic studies in tissue culture, particularly by John Roberts at the Chester Beatty, to look at mechanism of action and ability of cells to repair DNA damage by cisplatin.<sup>89</sup> It became clear that it was not a classical alkylating agent, and in fact we now understand some of the mechanism of action from the work of Steven Lippard and others, exactly how it binds to DNA and causes the DNA to kink [Figure 5].<sup>90</sup> I remember in the early days, in the 1970s, there was a lot of discussion about the use of combination therapy. The notion being that if you had two drugs that had different mechanisms of action, then you would indeed have the effect of combination therapy. So I remember that being talked about as a driver for pushing platinum, because the mechanism of action was unlikely to be the same as a classical alkylating agent.

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<sup>88</sup> See Florczyk *et al.* (1982).

<sup>89</sup> Thomson (1977); Roberts and Thomson (1979).

<sup>90</sup> Steven Lippard from the Massachusetts Institute of Technology. See Cohen *et al.* (1979).

Perhaps I may make quite a different point, while I have the microphone. Rosenberg was very interested in the commercialization of everything he did. As a solid-state physicist before he came into this area, he discovered a phenomenon called persistent internal polarization in solid state physics, which was a process that underpinned the Xerox process; he just missed out being a multimillionaire by not holding a patent on the Xerox process. So patents for cisplatin were granted in 1979 and 1982.<sup>91</sup> Barney always insisted that if such discoveries were not patented, then they would go no further, since the commercialization would not take place. There are some very interesting issues around that point, but not of consequence to this meeting.<sup>92</sup>

**Williams:** A very interesting feature for me, as a chemist, listening to the more clinical people here, is that I don't know whether it has ever struck them, but cisplatin is a very strange drug. In fact it doesn't seem to have chemistry which is at all specific. There's no built-in optical activity, there's no built-in stereospecificity. So it will attack all proteins and nucleotides basically. And in fact crystallographers use platinum chemicals regularly for X-ray crystallography, because it's a heavy atom which will bind to almost anything. I investigated

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<sup>91</sup> Dr James Hoeschele wrote: 'The anticancer activity of cisplatin and carboplatin were both discovered by Dr Barnett Rosenberg and his group at MSU. MSU held patents on both of these compounds. The inventions were exclusively licensed to Bristol-Myers, USA.' E-mail to Dr Daphne Christie, 22 February 2007. US Patent 4,177,263 December 4, 1979. Anti-animal tumour method. Rosenberg B, Van Camp L, Krigas T. US Patent 4,339,437 July 13, 1982. Antitumour method. Rosenberg B, Van Camp L, Krigas T.

<sup>92</sup> Professor Andrew Thomson wrote: 'The original US patent, no. 4,177,263 on the use of cis-platin as an antitumour agent, was awarded in the names of Rosenberg, Van Camp and Krigas and assigned to the Research Corporation (RC). [The RC, a US charitable foundation established in 1912 to promote "the advancement and extension of technical and scientific investigation, research, experimentation and education" by making grants, known today as Research Corporation Technology (RCT), 405 Lexington Avenue, New York.] In 1981 A J Thomson asked B Rosenberg to explain the reasons for his exclusion from the patent given the published statement by Rosenberg that he, A J T, was the "the true discoverer" of cisplatin (see note 23). Legal advice concluded that the inventorship "is correctly stated" in patent 4,177,263 and that the exclusion of A J Thomson from the patent was a "technical matter of US Patent Law" not further specified [letter from Robert J Saunders, Jr, counsel for the RC dated 8 January 1982]. In 2000 four generic drug companies found themselves defending a charge of infringing a cis-platin patent (no. 5,562,925) against the RC and Bristol-Myers (exclusive licensee of cis-platin). This latter patent, issued in 1996, was identical to the original patent, 4,177,263, other than "protect from light" had been added. This patent was declared invalid in a judgment in July 2000 by the US District Court of New Jersey on several grounds, but notably that the necessity to protect cis-platin from light was already published in 1967 in the *Journal of Biological Chemistry* **242**: 1347, by Rosenberg, Grimley, Van Camp and Thomson. Hence, four generic companies began the formulation of cis-platin, substantially lowering the cost of a course of treatment.' Note to Dr Daphne Christie, 18 February 2007.



that a little with Sir David Phillips' group and it just binds to most proteins.<sup>93</sup> So when you think about the toxicity, I think cisplatinum toxicity is to some degree everywhere, and it happens to be lucky that in some way it gets through a little bit better to the cancer cell than to other cells. Exactly how that happens would be very interesting to know, because if we knew that, we might learn a great deal about how drugs can actually work, which is nothing to do with old-fashioned ideas of specificity.

**Professor Kenneth Bagshawe:** There has been a certain amount of reminiscing about the early days of clinical oncology, and I would like to add to that. Fifty years ago I was a senior registrar at St Mary's Hospital, London, along by Paddington Railway station. I was a senior registrar in medicine, with a vague idea about becoming a cardiologist. One day there was a patient who came in; she was 17 years of age, and she was the most breathless person I have ever seen in my life. She had crawled into the hospital. The casualty admission card read, 'hysterical hyperventilation, good teaching case'. I looked at her and, as a budding cardiologist, I found she had a biggish right heart and the chest X-ray was clear. She denied having been pregnant, but she had pulmonary hypertension, hypertension in the pulmonary circuit. She died three days later, and the autopsy was done on a Saturday morning by the Professor of Pathology, M Price, and he said, 'Oh, look, she's been a naughty girl, she's had pelvic sepsis and it's spread to her lungs'. But my predecessor was at the autopsy, a senior registrar, Dr Adrian Joekes, who had been a senior registrar for about 20 years, and he said, 'That's not pelvic sepsis, that's choriocarcinoma. There was a case like this at the Hammersmith ten years ago'. And it proved to be choriocarcinoma, occluding her pulmonary blood vessels.

Six months later, I was called to the gynaecology ward to see a woman who had had a hysterectomy for bleeding, but the uterus didn't contain any tumour and she went home on anticoagulants and a diagnosis of pulmonary embolism – a very common event after hysterectomy. She came back to the hospital a few weeks later, short of breath, and by chance it was our admission day, and we put her back on anticoagulants, but she continued to deteriorate. I thought it couldn't be another case of choriocarcinoma, but still went to see the pathologists, and they said, 'Ken, you have got it on your brain, you're crazy, it couldn't be another case of choriocarcinoma, they are very rare anyway, and that Hammersmith case is unique, it is the only one in the literature'. So she continued to deteriorate and after about four or five weeks she was in an oxygen tent, because you weren't allowed to die in the 1950s without being put in an oxygen tent, it hastened

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<sup>93</sup> Petsko *et al.* (1978).

one's departure, but that wasn't known until a few years later.<sup>94</sup> There was one other way of making sure it could be a choriocarcinoma, and that was to have a pregnancy test, but there were no pregnancy tests available at that time, other than very crude biological tests, one called the Friedman test.<sup>95</sup> So I took her urine to the lab. The man who ran the lab had lost an eye, and when he was confronted by a junior doctor asking for something that he thought was stupid, he removed his glass eye, polished it on a red and white spotted handkerchief that he kept in his top pocket. If you were still there when he put his eye back in its socket, which wasn't usual, because you usually disappeared on these occasions, anticipating his conclusion, he said he wasn't going to sacrifice a rabbit for a woman who couldn't be pregnant and the pathologists said there was no tumour in the uterus. Anyway she was obviously dying, and that was on a Wednesday. As I came back from the lab I met the medical superintendent and he said, 'Well, old so and so is always very interested in hospital scandal, so why didn't I send the urine under a pseudonym?' So we went through all the bits of hospital scandal we knew at the time, and one of the chief surgeons was alleged to be having an affair with one of the nurses.

So I found this lass, and asked if she would mind sending in this urine under her name. She thought that was a great joke. So off it went on the Wednesday. On the Friday afternoon the consultant came round and said, 'You had better phone the husband, she is not going to last the weekend'. That evening after the ward round, the nurse appeared with this form saying, 'I must be very pregnant, it says Friedman test strongly positive'. So this *was* another choriocarcinoma. The pharmacy was closed. I got 6-mercaptopurine from the pharmacy, and we gave her big doses of 6-MP over the weekend, and on the Monday morning when I went in she was out of the oxygen tent, sitting up eating breakfast. She is still alive 49 years later.<sup>96</sup> And then we had another case of a girl presenting with a retinal metastasis from choriocarcinoma, and she is also still alive 48 years later. So this led me to look at gestational choriocarcinoma.

And then, of course, because there are testicular tumours that also have choriocarcinoma-like elements, I began to get these referred. And jumping ahead a few years, we were getting about 65–70 per cent of the gestational

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<sup>94</sup> See, for example, Davis (1952).

<sup>95</sup> A pregnancy test in which a female rabbit is given an intravenous injection of urine from the patient; formation of corpora lutea in the ovaries indicates a positive test. See McNeile and Reynolds (1933).

<sup>96</sup> Bagshawe and Brooks (1959).

tumours through into remission.<sup>97</sup> We were getting nowhere with the germ cell tumours. Between 1962 and 1968 I treated 28 patients, who presented with massive disease, and they responded to methotrexate, they also responded to other drugs that we threw at them, but none of them went into remission. And then in 1968 we got two patients through sustained remission and from then on the remission rate started to improve. We were juggling with quite a number of drugs at the time. I was involved in the early discussions around cisplatin and when it became available we got some. It was very disappointing in the gestational tumours, it didn't really add very much, and that was a big disappointment, but we did use it in the germ cell tumours, the testicular cancers, teratomas and ovarian germ cell cancers, and we began to get much improved results. But, of course, it was overtaken as a drug, both in gestational trophoblastic tumours and in the germ cell tumours, by etoposide, which came along. I think we were the first to use etoposide in those tumours, in 1977.<sup>98</sup>

**Calman:** These stories, and some of you will know I have a particular interest in storytelling, become very real, and again those of us who were around at that time remember that background very vividly. Any other comments about clinical things?

**Calvert:** Just going back to stories. In the early 1980s when we were doing the Phase 1 of carboplatin, there was a patient who came from overseas, where they didn't have a good health care system, but who couldn't afford to pay any more for the private treatment he had been receiving, and so he volunteered to go on to the Phase 1. He had a seminoma, very advanced seminoma, with metastases all over the place, which shrivelled up and disappeared promptly after his first dose of carboplatin. And that was the first indication that a single dose of carboplatin might be adequate treatment for seminoma. Subsequently, after I moved to Newcastle, people were normally getting four doses, because nobody dared to give them less really, nobody was clear whether you actually needed to give four. And we had a patient from Franklyn Jail, who had done something particularly nasty in the past, so he used to come along chained to warders to get his chemotherapy. And he got his first dose and when he came back for his second dose, I was a bit annoyed that morning, because I hadn't been able to get into my parking space, because there was a white van in it, and as he arrived at the hospital, a load of chaps jumped out of the white van and fired guns in

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<sup>97</sup> See Bagshawe (1969).

<sup>98</sup> Newlands and Bagshawe (1977).

the air, and extracted him, and took him away, so that in fact he never received his second dose of chemotherapy. So we were very interested in this, because we thought they would find him eventually, and we could follow him up to see whether he actually needed a second dose or not. [**From the floor:** This is not randomized.] But in fact that experiment didn't work because the people who sprang him didn't have a charitable intention and he's buried under a motorway somewhere now, I think. But the end of the story is that there have been formal studies done now, and although I don't treat them myself, I think it's fairly common practice to give just the single dose.

**Calman:** Franklyn Jail, for those of you who don't know, is in my home town of Durham. So that is of interest to me, too. Now other comments, we have got about 10 minutes before we break for tea.

**Hoeschele:** This comment dips back in time. It's an historical comment. Even as cisplatin was showing good antitumour results *in vitro* and in clinical trials, there was still feeling on the part of Dr Rosenberg, primarily in the earlier phase of the preclinical studies, that there might still be a 'magical ingredient' in the prepared solutions (of cisplatin but not related to cisplatin) that could account for the activity being observed. Perhaps this was related to the feeling, as a result of the disappointing response and toxic response of arsenic and mercury compounds, that the idea of a metal compound being a useful entity still occupied a little bit of a question mark in his mind: not a strong feeling, but he mentioned it several times in the course of working with him.

**Dr Penelope Brock:** I have been asked to come here by Dr Jon Pritchard, who is my mentor and teacher.<sup>99</sup> I thought I would introduce, perhaps, the paediatric side, the clinical paediatric side. It was Eve Wiltshaw, I understand from Jon, who first mentioned cisplatin to him. He went to a meeting in Chicago, apparently at the end of the 1970s, and he heard [Larry] Einhorn speak and he came back very excited about using this new drug. But he had also read an abstract from a colleague from Turkey. We have quite a close-knit international paediatric oncology group, and he went over to Turkey and he looked at the notes – although he couldn't read the Turkish somebody helped him through the notes – to see that patients had been treated with cisplatin and were responding. So he came back to London – he was consultant oncologist and senior lecturer at Great Ormond Street [London] – and he decided to look

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<sup>99</sup> Dr Jon Pritchard (1942–2007) introduced cisplatin for the treatment of childhood liver tumours. He died shortly after this meeting, on 20 January 2007. See Brown (2007) and page 102.

into this drug. Julie here [Mrs Julie Wenn] is one of the first patients that Jon treated with cisplatin in 1981. I was able to find her notes [before this meeting] and she was treated in May 1981, I think. It was really very forward-looking of Jon Pritchard to start using cisplatin in children, because we were very, very nervous of this drug. I remember as a house officer being told about the drug and how dangerous it was and we were very nervous about giving it to children, particularly to infants, worried about whether their renal function would go on developing, because the glomerular filtration rate (GFR) in children only reaches a normal value at about the age of two years. Jon later on asked me to do my doctorate on cisplatin toxicity in infants and children. We were able to give it to a number of infants and then publish data on the toxicity of it.<sup>100</sup>

One other point that I would like to make which I haven't heard anything on yet, and I think this was very interesting, is that when I started looking at the toxicity, much of the early work was unable to tell us a lot of detail about the hearing loss, and when we started using it in children, what really struck us enormously was that their hearing went off.<sup>101</sup> When we started using it at high doses, at 200 mg/m<sup>2</sup>, per cycle,<sup>102</sup> the hearing would go off per cycle. It was Sue Bellman, who was the consultant audiologist at Great Ormond Street, who came up to me, a young enthusiastic registrar, and said, 'Penelope, we have got to look into this, these children are losing their hearing and they are losing it per cycle, what are you doing?' We had started using a higher dose of cisplatin, and it was then that I got interested in making a grading system which is now being used worldwide, known as Brock grading and used to grade toxicity in international clinical trials.<sup>103</sup> Because our tumours are so rare, we have to collaborate, and Jon Pritchard formed a liver tumour group using cisplatin and doxorubicin in a pilot study in the early 1980s. Liver tumours, particularly hepatoblastoma, which only occurs in children, is now studied in 36 different countries in a clinical trial group called the SIOPEL group.<sup>104</sup> We have been able to move on

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<sup>100</sup> Brock *et al.* (1992).

<sup>101</sup> Brock and Bellman (1991).

<sup>102</sup> Dr Penelope Brock wrote: 'Chemotherapy, as many other medications in children, is dosed in mg/m<sup>2</sup> or mg/kg body weight.' E-mail to Dr Daphne Christie, 6 June 2007.

<sup>103</sup> Brock *et al.* (1988, 1991).

<sup>104</sup> The International Childhood Liver Tumour Strategy Group (SIOPEL) is a group of medical specialists founded in 1988 under the umbrella of the International Society of Paediatric Oncology (SIOP), to promote basic and clinical research on childhood malignant neoplasm of the liver, mainly hepatoblastoma and hepatocellular carcinoma. See [www.siopep.org/](http://www.siopep.org/) (visited 12 February 2007).

to discover that cisplatin is the most active agent in hepatoblastoma and we now use cisplatin monotherapy in hepatoblastoma. I think it is an example where there are very few tumours where one drug is actually not only the best drug, but is adequate to cause more than an 80 per cent cure with surgery in standard risk malignant disease. So, that is part of the paediatric story.

**Gralla:** I would like to make a couple of comments on the ototoxicity which is indeed a neurotoxicity as well. And with the hydration and mannitol, again which was done in the early 1970s, no longer was nephrotoxicity the limiting toxicity, it was neurotoxicity, and the reason that we did not give 200 mg/m<sup>2</sup>, which, of course, was given for a while in ovarian cancer and some other cancers, was the neurotoxicity. The ototoxicity was well described in adults by the mid-1970s, and the summary paper by Dan Von Hoff, published in *Cancer Treatment Reports*, looks at that rather carefully as well.<sup>105</sup> But basically, it's not that one *could* not give more than 120 mg/m<sup>2</sup>, it's just one *should* not give more than 120 mg/m<sup>2</sup>, and unfortunately this was rediscovered in the 1980s.

I would like to make a comment also on another clinical aspect, how interesting carboplatin is and how interesting the research in ovarian cancer has been with carboplatin. As Hilary has mentioned, there are multiple studies that support the equality of the two platins in ovarian cancer. However, that does not occur in many other cancers, and cisplatin is the superior drug in testicular cancer as shown in randomized trials. This is not our topic for today exactly, but in testicular cancer it is most unusual for people to use carboplatin, and there will soon be published a third meta-analysis in lung cancer,<sup>106</sup> where platinum drugs are not very active, but they are a little active, and there is a modest improvement with cis over carbo. This is an area where Hilary and I have enjoyed arm wrestling for quite some time, but the interesting thing to me, relating to our seminar, is that going back to the late-1960s and early-1970s, cisplatin was identified as the important drug to carry forth in clinical trials, and it has been very difficult to replace this agent. Unfortunately, it's many, many years now. There is the addition of carboplatin and in appropriate patients oxaliplatin, which seems to expand the horizon of the platinum drugs, but it is interesting that it has been difficult to exceed cisplatin over this time. Getting back to Professor Williams's comments and the early observations, why in the world did this drug work, and

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<sup>105</sup> Von Hoff *et al.* (1979).

<sup>106</sup> Jiang *et al.* (2006).

how and why can we not identify its selectivity or the lack of selectivity, I think is very interesting. There is still a lot to learn.

**Calman:** I am going to call a break for tea now. We have had two eponyms this afternoon, with the Brock grading and the Calvert formula. Perhaps your task over tea is to see if there are any other eponyms that we could add.

We have covered chemistry and some of the early clinical work; now we have to move on to another big area that developed and that's related to the antiemetic area, and I want to ask Paul Andrews, perhaps, to say a few words at the beginning to stimulate discussion.

**Andrews:** I think this next section on antiemesis and some of the side-effects of chemotherapy is really an interesting story of, I suppose, two or three parts. One part is the development of the appropriate animal model to study emesis, and as we have heard, rodents – rats and mice – don't vomit, so clearly you can't study the emetic effects of cisplatin directly and thereby look at the antiemetic effects. So there is a key component here: the development of the animal model.

I was involved during my PhD thesis, fortuitously again, noticing that ferrets vomited very readily, even under anaesthesia. Then when I moved from Sheffield to Edinburgh and was looking for funding, I applied to the Smith Kline Foundation and received a £1200 grant to look at the role of the vagus in cisplatin-induced emesis and that was, I think, in 1981. So that was again looking at an appropriate model, and, of course, this has been taken on. Perhaps, we could talk to John Rudd later, who was one of the people who developed a model for delayed cisplatin emesis, and was one of the people who sat there for three days, looking at what happened to mimic the clinical situation; he might comment later.

So the model is critical, and this ferret model was very important, because it was used for the development of the 5HT<sub>3</sub> receptor antagonists, but also set the scene for the development of the NK<sub>1</sub> antagonists, which also are antiemetic, and which came into clinical use just a couple of years ago.<sup>107</sup> So the model clearly has two drug successes at predicting for antiemetic use in this area.

The second part of the story relates to the discovery of the 5HT<sub>3</sub> antagonists themselves, a whole new class of agent, which have very potent antiemetic effects.<sup>108</sup> It is a very interesting study of drug development which essentially,

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<sup>107</sup> Sanger (2004); Andrews and Rudd (2004): 359–440.

<sup>108</sup> See, for example, Oxford *et al.* (1992); Kilpatrick *et al.* (1990).



Figure 8: (left to right): Gareth Sanger, Wesley Miner, Robert Naylor, David Tattersall at the Witness Seminar, 4 April 2006. Photograph taken by Mrs Lois Reynolds, and provided by Dr Gareth Sanger.

at the time, involved on the emetic side, workers at Beecham in those days, and we will hear Gareth Sanger and Wes Miner, who were on one of the first two publications demonstrating the antiemetic effect of a 5HT<sub>3</sub> antagonist in the ferret.<sup>109</sup>

The other major group working at the time on emesis was at Glaxo, and representing them here today are Robert Naylor and David Tattersall, who were at Bradford University – Robert Naylor is still there – and involved very closely with the Glaxo programme, so they can comment on that aspect of development. It is a very interesting one, because I think, as they will both allude to the other component of this, which was a clinical observation. That clinical observation was made by Richard Gralla and used what we pharmacologists and physiologists would call ‘industrial’ doses of metoclopramide and found that it worked rather better than lower doses of metoclopramide as an antiemetic in chemotherapy patients.<sup>110</sup> And of course that, for anybody who was alert, that might set them wondering, ‘Well, can the pharmacology that we knew from metoclopramide explain this effect of a very, very high dose?’ And that

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<sup>109</sup> Miner and Sanger (1986).

<sup>110</sup> Gralla *et al.* (1981). See also Gralla (1983).



was one of the important clues in the discovery and development of the 5HT<sub>3</sub> antagonist. So there is quite a lot of serendipity again involved in even this part of the story. Perhaps I can hand back to the Chair. We have a number of the people here from the very first discoveries of the antiemetic effects.

**Gralla:** Cisplatin had an unintended but major contribution to make to medical oncology. The reason is that cisplatin led to great benefits because of this emesis and all the interest that there was in emesis and the study of the control of emesis now cuts across to almost every other anticancer drug where the control is as good or better. Cisplatin ultimately caused a revolution in cancer care, in that having the ability to control emesis meant that patients generally could be treated on an outpatient or ambulatory basis, rather than having to stay in the hospital because of the dehydration and electrolyte imbalance that often occurred. This benefit of looking at the emesis was definitely stirred by cisplatin.

My involvement with my first protocol with cisplatin was about 30 years ago – for a treatment-related protocol that is, not Phase 1 or 2 – and was with lung cancer. There we saw benefits against lung cancer with cisplatin.<sup>111</sup> Indeed the magnitude is nothing like that seen with ovarian or testicular cancer, but it was the first time that we had seen a duration of response that would imply the likelihood of survival benefit. This was something different, something that definitely bothered a lot of people for 10 or 15 years in lung cancer oncology; they didn't want to believe that you could actually improve survival in this disease. With the second protocol, we had an agent to marry with cisplatin, a vinca alkaloid at that point, and we started to see very excellent responses with this combination. The vinca alkaloids eventually led to vinblastine which is still one of the standard agents used with cisplatin, or carboplatin, in the treatment of lung cancer.<sup>112</sup> So when the problem of the renal toxicity had been answered, cisplatin's use became mandatory, but if we were going to continue to use cisplatin as a drug to produce modest benefits in survival and in palliation for other areas, we had to find a good antiemetic, and find a useful approach to dealing with emesis. It wasn't because there were editorials in journals at this point saying, 'Oh, we must find a good antiemetic'. It was because of people like my patients, a physician's patient, people like Julie who is with us here today, who were experiencing all this emesis at that time, while getting benefits from

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<sup>111</sup> Gralla *et al.* (1979).

<sup>112</sup> See, for example, Kris *et al.* (1985).

the cisplatin, but with these terribly discouraging, dispiriting and distressing side-effects of emesis.

Cisplatin was a perfect model and I have always held that the human predicts the animal fairly well. Sometimes the other way works too. But with the human, 100 per cent of patients getting cisplatin will have emesis. There is supposedly one report, and I would like to see the original case report, of somebody who just had horrible nausea and didn't vomit for about 24-and-a-half hours, but other than that, if you have a drug that prevents emesis with cisplatin, it's the drug that's doing it. So therefore you have a very good human model as far as emesis is concerned. Our approach in the late 1970s when we looked at the problem was to look first at the world literature of clinical trials with antiemetics. I did this, and because I am a slow reader it took me the entire Sunday afternoon to review the literature, and I was taking notes as I went along.

The other thing that we felt that we had to develop was a decent methodology. Our key to the methodology, for which we are given a fair amount of credit, was 'if you are going to measure an antiemetic, find out if it prevents emesis'. This seems like a very profound observation, but this was about it. What had happened before was that people measured things like satisfaction, psychological concepts, etc., and we said that an antiemetic should prevent nausea and vomiting; if it doesn't do that, what kind of antiemetic is it? It was that straightforward, maybe a little bit more. When we looked at the drugs that were available at the time, we knew that several of them were not good – phenothiazines, which block dopamine D<sub>2</sub> receptors, and the cannabinoids, which are widely publicized in the lay press.<sup>113</sup> These drugs do work, but not very well, which is unfortunate. And so we felt that we had to move on. Another advantage that we had in our group was a lack of experience with metoclopramide as an antiemetic. In the 1970s it was an investigational drug in the USA, even though it had been widely available in most countries in the world, and we felt that the dose was not well established for the indication of emesis. Clearly the pharmacodynamics of what happened in the gut were well known, but not the dose to prevent emesis. And so we thought about it from the viewpoint of Phase 1–2 doctors: 'Let's escalate the dose, let's see what happens. Is it safe?' I then looked at the world's suicide literature, and it looked as though it was impossible to kill yourself with the drug, so that sounded good. I called my colleagues in Europe and South

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<sup>113</sup> See, for example, Lucas (1983); Morris (1997); Voth and Schwartz (1997). See also Sanger (1993): 179–210.

America, who had a lot of experience with the drug, and they said, 'No, no, no, you cannot escalate the dose of this drug', and I said, 'Have you ever done it? Have you ever given more than 10 or 20 mg?' 'No', they said. So then I knew we were on to something. The lack of experience made me think that we could do this.

Sir Kenneth has talked about the way that protocols were written in those days. Our protocol looking at metoclopramide as an antiemetic was perhaps three pages long, the consent form was a good half page, and we only had three dose escalation steps in the protocol and then we had a fourth line which said further escalations may be done, but would not exceed 33 per cent. Once you get up to 1 mg/kg, 33 per cent is a pretty nice escalation. We got to 3 mg/kg per dose, at which point the sponsor came by and said, 'Stop. OK, what have you done here? We cannot give doses like this; we are going to take away the drug'. I asked, 'Don't you want to see the results?' To our great surprise, at 2–3 mg/kg we were getting complete control of emesis in about 40 per cent of patients. Just about the same as with 5HT<sub>3</sub> antagonists. This was just something amazing to us, we were just scratching our heads, we couldn't understand it; we had gone up stepwise: we looked at infusions, and we looked at intermittent aspects. But there were problems: one, it was inconvenient. Our first protocol had five doses of metoclopramide at the high doses, which meant that it was very difficult to give it on an outpatient basis. We later refined that to two doses. It did have dystonic reactions, and these really weren't so bad in most adults, but for younger people below age 30, and for children, this was difficult. We did a study in children and we said you could use it for one day but not beyond.<sup>114</sup> We also then started to notice delayed emesis. This was a real shocker, because we had never seen anybody who hadn't had emesis on the day of chemotherapy, and then we had some patients who had complete control in the first 24 hours, and thereafter started to have emesis. This just came out of nowhere and so we just did not understand what was going on, but knew that we had to do more. And, of course, 60 per cent of patients still had emesis.

Another parallel observation at that time, and I am sorry that Matti Aapro from Geneva can't be here, because Matti did a lot of work with corticosteroids, and we still don't know how they worked in emesis, but simply by adding a single dose

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<sup>114</sup> See, for example, Allen *et al.* (1985).

of dexamethasone, the control went up from 40 to 60 per cent.<sup>115</sup> So suddenly we were approaching having two-thirds of the patients with no acute emesis, and some advantages in delayed emesis, especially with the corticosteroids, but a little bit with metoclopramide. We asked ourselves the same question that Wes Miner and I were talking about: why the high dose? Why do you need the high dose of metoclopramide? We thought it was probably working by blocking another receptor, but which one, and we really didn't know which one. This led, then, to putting these observations together, to further work that led to the discovery and synthesis of the serotonin [5-hydroxytryptamine, 5HT] receptor antagonists, which so many people in this room contributed to and will tell that story. Then later on for the NK<sub>1</sub> receptor antagonists, to the point that we now have 80–90 per cent of patients completely protected against acute emesis with cisplatin and 60–70 per cent with the delayed emesis. It's been quite a surprise to many of us. Again, the contributions are to the control of emesis with cisplatin, but later to other chemotherapeutic drugs as well, and to the way in which we administer antiemetics, and the way we administer chemotherapy.

**Calman:** Thank you very much. Who wants to continue the story? I am looking at my colleagues, particularly in the drug industry.

**Dr Gareth Sanger:** You can tell I am from industry. I am the only non-clinician not wearing a suit here. I would like to draw together perhaps four different strands of research, one beautifully told by Richard Gralla. Back in the early 1980s he published his paper to show that a relatively high dose of metoclopramide could take out cisplatin-induced vomiting.<sup>116</sup> Certainly not an industrial dose because there is no way you would get away with that, more an heroic clinical dose.

But at that time there were other strands of research. I will take you back to some work done by Dr John Fozard who, when I was a PhD student in Manchester, was working upstairs in the pharmacology department, characterizing what was then known as the 5HT<sub>M</sub> receptor; M for morphine – that was the classification that predated 5HT<sub>3</sub> – as defined by Gaddum.<sup>117</sup>

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<sup>115</sup> Aapro and Alberts (1981); Kris *et al.* (1989).

<sup>116</sup> Gralla *et al.* (1981).

<sup>117</sup> Gaddum and Picarelli (1957) suggested that 5HT-induced contractions of the guinea-pig isolated ileum were mediated by a morphine-sensitive 'M' receptor located on the parasympathetic ganglion and a dibenzylamine-sensitive 'D' receptor located on the smooth muscle. See also Bradley *et al.* (1986).

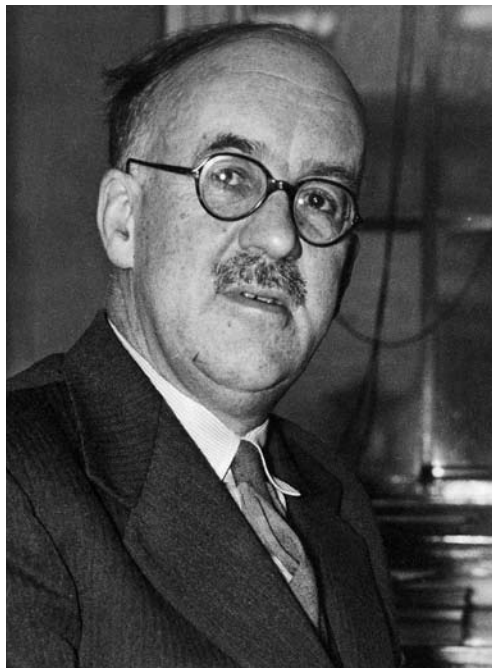


Figure 9: Sir John Gaddum, Department of Pharmacology, University of Edinburgh, 1957. Wellcome Library, London.<sup>118</sup>

Fozard was interested in the 5HT<sub>M</sub> receptor<sup>119</sup> and was developing quite beautiful models of characterizing this receptor, with everybody wondering where his next research grant was going to come from, because there wasn't much interest in that area of research. He eventually left the University of Manchester, and moved to Merrell Dow in France and persuaded that organization to identify selective 5HT<sub>3</sub> receptor antagonists. They were the first published compounds. There was one whose number I can't remember, but one in particular, MDL 72222, was published and eventually went into clinical trials for the treatment of migraine, where there was some encouragement, but it was never developed and you could say that line of research failed.<sup>120</sup> However, John [Fozard] identified certain animal models: the isolated rabbit heart, which could be used to characterize the pharmacology of the 5HT<sub>3</sub> receptor; the von Bezold–Jarisch rat reflex, which is a reflex evoked in anaesthetized or

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<sup>118</sup> Archives and Manuscripts, Wellcome Library, London, L0025591.

<sup>119</sup> Fozard (1984a); Bradley *et al.* (1986). See also the International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin), Hoyer *et al.* (1994).

<sup>120</sup> Loisy *et al.* (1985).

conscious rats, following intravenous injection of 5HT.<sup>121</sup> Effectively, in this model, he was activating the 5HT<sub>3</sub> receptors on the vagal afferents projecting from the heart to the brain stem and then projecting back down again, to cause a whole sequelae of reflex functions. But von Bezold–Jarisch, in particular, focused on the rapid bradycardia that was evoked by that reflex. You could use that as a tool for examining the pharmacodynamic characteristics of any new 5HT<sub>3</sub> receptor antagonist; John was doing that kind of work.

The other line of research, and perhaps the third after Richard's [Gralla] and John's [Fozard] work, was that carried out by ourselves and by our competitors, who are now also my friends, because of various industrial mergers. In particular, work going on in two different companies, one directed by Brian Richardson at the then Sandoz (now a part of Novartis) company in Switzerland.<sup>122</sup> They were identifying a new 5HT<sub>3</sub> receptor antagonist, known as tropisetron. He identified that compound, took it to clinical trials, primarily for the treatment of pain, developing a nice pharmacodynamic model in man, called the 'blister-base pain', where you form a little blister on the hand and you can then take out the pain sensation with 5HT<sub>3</sub> receptor antagonists.<sup>123</sup> A lot of us then speculated about the role of 5HT<sub>3</sub> in bee stings, nettle stings and all sorts of things developed from that. Sandoz took that compound for the treatment of migraine. Again, it didn't work. However, tropisetron is now launched and registered for the treatment of nausea and vomiting. Another company involved was the then Glaxo company, now GlaxoSmithKline, in which I currently work.<sup>124</sup> They took a different approach. They took the different 5HT receptors and said, 'Let's sort this out, let's identify novel receptor agonists and antagonists for the different receptors'. And even though they were competitors to Sandoz at the time, I have to admit that was a tremendously brave approach, because it meant that they identified the ligand and then went fishing for the disease. That's difficult-to-sustain financial backing, even within a company. But they did that, and they identified a compound known as ondansetron. That team, led by Mike Tyers, eventually went into various CNS animal-based behavioural models, and Bob Naylor will tell you a lot more about that, because they worked closely

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<sup>121</sup> Aviado and Guevara Aviado (2001).

<sup>122</sup> Novartis was created in 1996 from the merger of the Swiss-based companies, Ciba-Geigy and Sandoz. For a history see [www.novartis.com/about\\_novartis/en/history.shtml](http://www.novartis.com/about_novartis/en/history.shtml) (visited 30 November 2006).

<sup>123</sup> Richardson *et al.* (1985). See Appendix 2 for structural formulae of some 5HT<sub>3</sub> receptor antagonists.

<sup>124</sup> Glaxo Wellcome plc and SmithKline Beecham plc merged in 2001 to become GlaxoSmithKline plc (GSK). For a history see [www.gsk.com/about/history.htm](http://www.gsk.com/about/history.htm) (visited 30 November 2006).

together. They then took the compound into migraine, following John Fozard's and Brian Richardson's idea, and showed that it didn't work very well, but it did take out the nausea or vomiting.<sup>125</sup> From there they took that into cancer chemotherapy. I haven't been able to speak to Mike Tyers or any of the people who were involved in that work, but Mike and I were lucky enough to receive the 1998 Discoverers Award from the Pharmaceutical Research and Manufacturers of America Association (PhRMA), in which the history of these two different discoveries are laid out. There's quite a lot of documentary stuff in the books that I have brought with me.<sup>126</sup>

The final line of research was conducted in the then Beecham Research Laboratories (now part of GlaxoSmithKline).<sup>127</sup> We were, effectively, trying to take metoclopramide apart to develop novel gastric prokinetics and novel antiemetics that didn't have the CNS side-effects, such as the extrapyramidal reactions evoked by metoclopramide and certain other dopamine D<sub>2</sub> receptor antagonists.<sup>128</sup> It was done using a kind of classical biological research, which you would almost regard as unethical today. It was, 'Let's take a molecule, and let's screen it in conscious animals'. You would never ever do that now. Nevertheless, using that kind of process, they were able to identify certain molecules that appeared to have a selective action. I got hired somewhere in the middle of that, put down at a desk in a spare room and told to find something to do, literally. I eventually developed my own job description, which was to figure out how metoclopramide worked. To cut a very long story short, out of that work came the identification of what we call the myenteric 5HT-like receptor, now known as the 5HT<sub>4</sub> receptor.<sup>129</sup> So, we set the foundations for that discovery and we linked the 5HT<sub>4</sub> receptor to the gastric prokinetic activity of metoclopramide. In making this link, we also said that metoclopramide did not act as a gastric prokinetic because it antagonized at the D<sub>2</sub> receptor. At the time, this was a novel argument. As part of this investigation, we looked at the entire pharmacology of metoclopramide and identified a rank order of activity of metoclopramide at a range of different receptors, recognizing that very low doses or low concentrations of the drug activated what became known as the

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<sup>125</sup> See, for example, Stables *et al.* (1987).

<sup>126</sup> PhRMA (Pharmaceutical Research and Manufacturers of America) (1998). See also page 103.

<sup>127</sup> For a history see <http://search.gsk.com/cgi-bin/RS.cgi> (visited 30 November 2006).

<sup>128</sup> Kris *et al.* (1983).

<sup>129</sup> Dumuis *et al.* (1989).

5HT<sub>4</sub> receptor, and also antagonized at the D<sub>2</sub> receptor.<sup>130</sup> If you bumped the concentrations up, you can show that it then antagonizes at the 5HT<sub>3</sub> receptor (and we drew heavily from John Fozard's work there [Manchester, and then at Merrell Dow]) and also antagonized the alpha-2 adrenoceptor and, at even higher concentrations, inhibited cholinesterase activity. So it was a really dirty compound. But we took that kind of biology, analysed it, and we then took selected molecules that we were generating to test out ideas. We had identified what was a pure gastric prokinetic compound that stimulated gastric motility in rats and that did not block apomorphine-induced vomiting. In other words, it didn't appear to be a dopamine receptor antagonist, so, based on the knowledge at the time, it should not have been an antiemetic.<sup>131</sup>

By then, we knew that this molecule also antagonized at the 5HT M receptor (5HT<sub>3</sub>). Simultaneously, Wes Miner at Beecham Pharmaceuticals was developing the conscious ferret model to test new D<sub>2</sub> receptor antagonists and antiemetic compounds. I gave this molecule to Wes for testing. As you will hear later from Wes, he tested that molecule, came back and said, 'Look guys, this has got antiemetic activity'. To us, it became difficult to believe that a pure gastric prokinetic would have that kind of activity against such severe nausea and vomiting. By that time, we had access to John Fozard's compound, MDL 72222, a selective 5HT<sub>3</sub> receptor antagonist.<sup>132</sup> We could then go back to the ferret emesis model and say, 'Look, let's do the study. I will predict that this selective 5HT<sub>3</sub> receptor antagonist will take out this type of vomiting. The mechanism has nothing to do with D<sub>2</sub>, and nothing to do with what then became known as the 5HT<sub>4</sub> receptor'.<sup>133</sup> I gave the compound to Wes. There are lots of little anecdotes in that little book that I brought with me, but the one I like is that that study was done late on a Friday afternoon. Wes came back from the animal house, which was then a little shack round the back of the building, and said, 'Look, these guys did not vomit'. He looked at four animals: three didn't vomit at all, and one started to vomit near the end of the observation period. At that time, this was an utterly unprecedented result, and none of us could tell anybody

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<sup>130</sup> See, for example, Sanger (1993): 186.

<sup>131</sup> Dr Gareth Sanger wrote: 'At this time, the main drugs marketed as antiemetics, acted as dopamine D<sub>2</sub> receptor antagonists. Therefore to prevent emesis via a different receptor would have immediately raised the possibility of a "new" biology. See McRitchie *et al.* (1984): 287–301.' Note on draft transcript, 31 May 2007.

<sup>132</sup> Fozard (1984b).

<sup>133</sup> Dumuis *et al.* (1989).



until Monday. So it was a kind of nice exciting result, which we kept to ourselves all weekend. We then took that information, and knowing that we had all the competitors around us, developed our own 5HT<sub>3</sub> receptor antagonist, which is granisetron or Kytril® now.<sup>134</sup> I guess that cuts a long story short.

During the history of that development, we had to face questions about whether or not 5HT<sub>3</sub> receptor antagonists blocked the antitumour effect of cisplatin. I knew Beverley Weston, who then worked for Beecham, and luckily she was married to Ken [Harrap], and so we came along to you, Ken, and you did those studies to show we had no impairment of cisplatin's antitumour activity; at that time a really serious issue.<sup>135</sup> I then took the show around various oncology departments. I heard people say, 'Do you believe this 5HT stuff?' You knew there was no understanding of the science. We called in people to help us with the science, in particular Paul Andrews. I remember him coming into the labs saying, 'Look, I have just been given this white powder from Glaxo to test, I have no idea what it is, but they want me to test it'. I took him in the lab and said, 'Well, we know what it is, here is its structure and here's our data on the compound'. That was ondansetron. So a lot of different, emotional stories; the kids who vomited their hearts out with cisplatin, everybody in tears; and then the doctors, on their own responsibility giving BRL 43694 (granisetron) [5HT<sub>3</sub> receptor antagonist] as it was then known, which stopped vomiting in its tracks and thus allowed chemotherapy to be effective. And then many more tears and emotions. These things came back to the lab as we were doing the work. We heard that in Japan, certain patients on the oncology ward were given Kytril®. They were protected and the rest of patients on the wards who hadn't been given Kytril® rioted. They wanted that drug. And it was that kind of information that was fed back to us in the lab, 'Look fellows, this thing does work'.

**Calman:** Absolutely fascinating. Are there any other comments on this developmental area?

**Mr Wesley Miner:** I would like to expand a little bit on what Gareth has said, because it was a very exciting time for us. It is one of the things that put me on

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<sup>134</sup> Granisetron, trade name Kytril®. See PhRMA (Pharmaceutical Research and Manufacturers of America) (1998). See also Kytril® [[www.rocheusa.com/products/kytril/](http://www.rocheusa.com/products/kytril/)] (visited 14 June 2007)].

<sup>135</sup> Professor Ken Harrap wrote: 'During the Beecham development of granisetron, we did some work in my department at the Institute of Cancer Research [Sutton], that demonstrated unequivocally that, when co-administered with cisplatin to tumour-bearing mice, the antitumour properties of cisplatin were not affected by granisetron.' Letter to Dr Daphne Christie, 26 August 2006.

an adrenaline high for about four or five years afterwards. It was that exciting. The reason it was so exciting – because I came into the whole story in the early 1980s – is that we were hit with this huge clinical problem which Dick [Gralla] has alluded to, and other people have alluded to, the very severe vomiting and nausea. I was very naive back at that time, and said, ‘OK, here we go. Let’s do something about this,’ thinking we were going to solve it. We didn’t know quite how at that point. But everything pretty much followed how Gareth described it. We certainly went on with Dick’s [Gralla] work with high-dose metoclopramide.

The other big thing was John Schurig’s publication on cisplatin-induced emesis in the ferret, and I have to give all the credit to the little ferret.<sup>136</sup> I think ferrets have been alluded to as these little vomiting animals, but without the ferret, none of this would have got anywhere. I think this is important in this day and age, because we are [now] facing so many problems with [limits to] animal experimentation. Well, this is one area that would never have gone forward; you couldn’t have done it without the ferret and the animal experimentation. We certainly looked at the dopamine antagonist, and that actually made the emesis worse in the ferret. We looked at metoclopramide, and then put together what was happening with 5HT<sub>3</sub> receptors.

One other thing I would like to tell you about is with respect to the excitement and what I saw when I was working with the animal models. We had a period where we knew we were looking at 5HT<sub>3</sub> receptors. We knew what was going on; we knew these drugs were good. Up until that time, the way I had conducted the experiments was that I dosed the animal with cisplatin and if you have a control animal dosed with cisplatin it takes 60 minutes before the cisplatin will begin to cause the animal to vomit. So I would do that, but prior to that I would dose with a 5HT<sub>3</sub> antagonist, and with the 5HT<sub>3</sub> antagonist, essentially the animals just would not vomit. So you wouldn’t see any vomiting with the animals at all. Well, while I was running these experiments, I figured, ‘Well, I have to run a control experiment with this; I have to make sure the cisplatin is getting on board’. So I decided what I would do is with every four animals that I would be dosing, I would dose all of them with cisplatin, but one wouldn’t get the 5HT<sub>3</sub> antagonist. And I would watch them all. I did this a couple of times and by about the third time I was getting complete inhibition with the 5HT<sub>3</sub> antagonist, the animals were just not vomiting at all, but this poor little control animal, right on 60 minutes, bingo, right off and he began

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<sup>136</sup> Florczyk *et al.* (1982).

vomiting. This began to concern me, because I figured, ‘Well, okay, I do know the cisplatin is on board, but I am going to have to do something. I can’t just let this poor little guy go away and vomit the whole time’. At that time we had actually surgically prepared the animals. You cannot dose a ferret easily. They just will not let you do it. So I had to surgically prepare the animal with a little intravenous cannula and it used to be exteriorized right at the back of the neck. I was working on my own with the ferrets at this time, which Gareth alluded to. They wouldn’t even let me in the experimental areas with the ferrets, because nobody liked them.

So I was in a little back ‘kitchen’, in my cell, with my four ferrets, and I had to think of a way of putting the little connector on the little valve at the back of the neck of the animal, so that I could actually get the 5HT<sub>3</sub> antagonist on board while the animal was vomiting. The only way I could think of doing this, once the other animals had been dosed with the 5HT<sub>3</sub> antagonist, and this animal had actually started vomiting, is to wait until the animal is vomiting, he is not going to be paying attention to my fingers. I am not going to lose fingers this way. So this is exactly what happened. I waited until the animal started vomiting. I knew the cisplatin was working at that point, and I just very nimbly and very quickly fastened this little connector and while the animal was actually right in the middle of the emetic response, I whacked in the 5HT<sub>3</sub> antagonist, and within five seconds the animal was normal, completely normal. This was one of the most exciting things I have ever seen, and it really gave me confidence then that we had something big.

Then, of course, I was stuck with the situation, how am I going to get this little connector off the animal, because it was now completely normal. So I decided what I would do. Ferrets absolutely love milk, and so I prepared a small bowl of milk and I put it in his pen, and the ferret ran over and I got the little connector off and that was it. We went on to do this on several occasions, and we videoed this result and it got shown to quite a number of people. But that result was that dramatic, and I do remember calling Paul [Andrews], and I said, ‘Paul, I think we really have got something here’, and he said, ‘Yes, I think you have got it’. And we were very pleased with that. So that’s pretty much the Beecham side of it, and as Gareth [Sanger] said, there’s a lot of other little tales.

**Sanger:** I will slightly embellish Wes’ story, because that animal experiment Wes described was videoed; it became known as the ‘ferret video’ within our industry. I think that was the single most powerful message we could deliver

to our upper management to say, 'Look guys, we have something here that's exciting and works'. We showed that ferret video and they came on board.

But the other very interesting point I want to make, alluding to Wes' comments on the necessity of animal experimentation to do this kind of work, relates to a seminar I gave at our local hospital on this kind of biology. It's kind of nice to start off with this video, because it gets them excited, and then they start listening to the science (otherwise they go to sleep). You start off with the video, and as I showed it, half the oncology nursing staff walked out in disgust. This was an animal experiment – you can do it to patients, but not to animals. They walked out. It was quite extraordinary.

**Miner:** One little comment, Gareth said at the end of that first day, the first time we did those experiments, that I came back to the lab and it was a Friday and all that, if truth be known he actually came over to the little place that I was in, popped his head around the door, and asked, 'Did it work?' It worked.

**Professor Robert Naylor:** Just to add to some of these experiences, recollections and reminiscences. What I have found today that is really interesting is that all the experiments, clinical or otherwise, which have been done by chance or design, or could perhaps have been done in different ways, have dramatically affected the outcome.<sup>137</sup> And to do many of the experiments these days would be difficult indeed.

Briefly, at Bradford we have had a serious interest in neuropharmacological research since 1968. The Neuropharmacology Research Group was set up initially to investigate the actions of antischizophrenic drugs and drugs useful in the treatment of neurological disease. By the mid-1970s we had built strong collaborative research programmes with many pharmaceutical companies. A H Robins in Richmond, Virginia, was one such company who were investigating dopamine receptor antagonists, which has already been discussed.<sup>138</sup>

Dr Lawrence (Larry) Sancilio and colleagues at A H Robins Company, were attempting to dissociate the dopamine receptor blockade from extrapyramidal side-effects and antiemetic potential. It was clear to them that you could block

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<sup>137</sup> This is a recurrent theme that has come up in other Witness Seminars. See, for example, Zallen *et al.* (2004): 30; Tovey (1992).

<sup>138</sup> See pages 52–3.

emesis induced by cisplatin in dogs without dopamine receptor blockade; zacopride and dazopride were two such agents.<sup>139</sup>

We determined that zacopride was a particularly potent antiemetic agent against cisplatin in the ferret model of emesis. But neither we nor colleagues at A H Robins were aware of the antiemetic mechanism of action of zacopride.<sup>140</sup>

In Bradford we were following a similar hypothesis. Using a recently discovered 5HT<sub>3</sub> receptor antagonist, ICS 205-930 (tropisetron), obtained from Sandoz, we investigated the ability of this agent to facilitate gastric emptying following injection into the guinea-pig hypothalamus. The importance of this observation was our additional finding that ICS 205-930 potently blocked cisplatin-induced emesis in the ferret.<sup>141</sup>

I reasoned that if this hypothesis (the facilitation of gastric emptying) was correct, then zacopride and ICS 205-930 might facilitate intestinal transit in man. In the noble tradition of a nineteenth century physician,<sup>142</sup> I took the drugs, but neither appeared to facilitate gut activity. Indeed, with  $n=1$ , the trial suggested a reduced gut movement. The hypothesis looked less hopeful.

On informing Sandoz of the antiemetic action of ICS 205-930, the company remained unimpressed or disinterested. But during this period, Professor Brenda

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<sup>139</sup> Dr David Tattersall wrote: 'At the time the 5HT<sub>3</sub> receptor antagonists were being examined at Bradford it was felt that these agents would be clinically useful for treating a variety of psychiatric and neurological diseases. Unfortunately, the only clinical utility of these compounds proved to be as antiemetics. This was similarly seen with the Substance P (NK<sub>1</sub>) receptor antagonists, which were hailed as treatments for anxiety, depression and pain, as well as antiemetics. Thus far, the only approved use of NK<sub>1</sub> receptor antagonists has been as antiemetics. I think it is important to make this point because the market for antiemetic agents still remains poor. As such, it is a much less attractive target for the pharmaceutical industry than other indications that have a much greater potential market. It has been estimated that a drug costs around \$800 million to develop (not including the cost of compounds that do not make it to the clinic).' Note on draft transcript, 31 August 2006.

<sup>140</sup> Professor Robert Naylor wrote: 'At the Robins Company, David Johnson, Larry Sancilio, Herb Alphin and colleagues were investigating the actions of zacopride and related agents to enhance isolated gut smooth muscle cell contractions. This might be envisaged to facilitate the propulsion of gut contents in the anal direction, to facilitate an "antiemetic" effect.' E-mail to Dr Daphne Christie, 14 October 2006. See, for example, Sancilio *et al.* (1991).

<sup>141</sup> Dr David Tattersall wrote: 'The original finding of antiemetic activity with ICS 205-930 in the Bradford laboratory was published in Costall *et al.* (1986).' Note on draft transcript, 7 February 2007. See also Gamse (1990).

<sup>142</sup> See, for example, Altman (1987); Kerridge (2003). See also Reynolds and Tansey (2001): 27.

Costall and her neuropharmacology team at Bradford had been working with Dr Mike Tyers and Dr Dave Fortune at Glaxo on a series of novel 5HT receptor ligands in behavioural models. One such compound, named GR 38032F (later ondansetron, or Zofran®) and described as a selective 5HT<sub>3</sub> receptor antagonist, was tested in the cisplatin model of emesis in the ferret.<sup>143</sup> It abolished emesis. Glaxo were informed and were interested; the rest is history.<sup>144</sup>

Following its clinical introduction, Dr Gralla and colleagues revealed that ondansetron was a less effective antiemetic in what was described as the ‘delayed phase’. This prompted further ferret studies in both an acute and delayed phase by my colleague Dr John Rudd in Bradford and by others. The 5HT<sub>3</sub> receptor antagonists were shown to be less effective in the delayed phase. The importance of this observation is as follows. Would Glaxo management have developed ondansetron if the drug had been shown to be only moderately effective over a three-day period? It was a good reason not to persevere, as there were many other drugs in the Glaxo pipeline.

Personally, I remained quietly convinced that the 5HT<sub>3</sub> receptor antagonists had genuine benefits, and not just as a result of carefully designed clinical trials. As a laboratory scientist I received letters from cancer patients thanking us for making their treatment more acceptable. This is surely almost unheard of? Their correspondence made for a good day and a very good year. We were all grateful for having the opportunity to make a difference. That is, all except my local health authority. The headlines in my local newspaper the *Bradford Telegraph and Argus* announced that the cost of the new antiemetic drugs had bankrupted the local health authority and that a Professor Naylor working at the local university was to blame.

**Brock:** Moving on from this I want to give a clinical paediatric story. I was part of a group called the Paediatric Oncology Group of Benelux (OPB); I worked in Louvain in Belgium. The only publication that came out of this group was a randomized study on the induction dose of ondansetron; a 5 mg/m<sup>2</sup> or

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<sup>143</sup> Stables *et al.* (1987).

<sup>144</sup> Professor Robert Naylor wrote: ‘But in retrospect, the clinical development of ondansetron to achieve global success in the treatment of emesis in the cancer patient probably retained a modicum of good luck in the preclinical development. In our ferret model of cisplatin-induced emesis the experiment was of four hours duration, believing that authorization by the Home Office to perform the experiments would have been compromised if we had requested a longer exposure of the animal to a moderately severe procedure.’ E-mail to Dr Daphne Christie, 14 October 2006.

10 mg/m<sup>2</sup>, with Glaxo's support, which I then published.<sup>145</sup> One of the reasons that we started this was that we were desperately keen to get this drug for our children on the ward, but it was expensive. And in young children we had a lot of problems. We couldn't increase the dose of metoclopramide; once you go above to 1 mg/kg per dose, or to 1.5, we were getting a lot of dystonic reactions and some of them were in the throat, and really quite frightening and nasty, and the nurses wouldn't let us do it. So we decided to get this study going, a randomized study, where the children would either get 5 mg/m<sup>2</sup>, which we knew worked, or 10 mg/m<sup>2</sup> which we hoped might work a bit better. But what it meant was that all our kids got ondansetron and we got it for free. I had a wonderful time doing the study with Glaxo, because they took me everywhere and we presented the work everywhere. We used to do the ward round every single day with our professor who was very, very strict. At 9 a.m. we would all go round, and every single child would be on their bed – you can't do a ward round like that any more – but they would all be there with their cardboard kidney bowls, vomiting, and we would do every single ward round, every morning, every room, and it would smell bad, and we would feel bad, and the children wouldn't be able to tell us anything because they were just throwing up all over the place. Then once we started with ondansetron nobody was vomiting any more, and then in the cafeteria, because in Belgium the food is good, they would be served steak and fish, and chocolate mousse; but they couldn't even have the food trays in the room before ondansetron. But afterwards, the kitchen staff would come running up to me and they would say, 'Professor Brock, Professor Brock, what's going on? All the oncology patients are ordering food, they want chocolate mousse, we are coming and fetching the trays and the food has been eaten, and it is not the parents who are eating the food, because the parents also get their own tray'. To me, that was a wonderful watershed, when we did ward rounds not only were they not vomiting, but they actually were ordering food and eating it.

I agree entirely about the delayed emesis, because I then did a study on serotonin metabolites in the urine, and serotonin is released in the 24 hours after cisplatin and bang, it goes. I have been trying to tell people for years not to waste the money on ondansetron on days two to five, but use something else. But it is finally getting through because we are so tight for money that they are beginning to cut back.

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<sup>145</sup> Brock *et al.* (1996).

**Naylor:** Cost has always been a real problem with this particular group of drugs.<sup>146</sup> For example, there have been up to 30 people working in Bradford in neuropharmacology research over the last 35 years. You know that many frequently work 12–14 hours a day; thousands and thousands of hours go into their studies.<sup>147</sup>

Yet, following the headline in my local newspaper (the *Bradford Telegraph and Argus*) that I had bankrupted Bradford Health Authority with the expense of the new antiemetic medication, I failed to respond with a rebuttal. And a chance to refute a silly allegation and enhance the scientific enterprise was lost.

**Calman:** My particular incident was with methotrexate, when we were using higher and higher and higher doses, and the drug rep from methotrexate actually won a holiday for selling the most methotrexate. He had a fortnight in Barbados, and our health authority was almost bankrupt.

**Andrews:** Can I make one point about the cost? I agree completely about the food on the wards, which people did start to comment about, but also because when these drugs first came out, they were very expensive, relative to metoclopramide – metoclopramide and dexamethasone were very cheap – and many of the companies were very concerned that the people were not getting the compounds because of the cost. I think it was Glaxo who actually calculated the cost of a vomit for a patient, how much the bowl cost, how much cleaning-up cost, and factored that into these pharmacoeconomic models, and I think the 5HT<sub>3</sub> receptor antagonists were the first examples of drugs where pharmacoeconomics played a major role in the whole marketing package.<sup>148</sup> So I think they really did change the paradigm, because the other point is that at the time when the companies started, if you did a survey on how much the antiemetic market was going to be worth, it was almost nothing, so it wasn't an area to go into for the money, whereas, I think, now worldwide it's over \$1

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<sup>146</sup> Professor Robert Naylor wrote: 'Clearly scientists and clinical staff are not responsible for the setting of the cost of drugs. But I am not sure that as scientists we have fully pulled our weight.' E-mail to Dr Daphne Christie, 14 October 2006.

<sup>147</sup> Professor Robert Naylor wrote: 'For example, one Boxing Day [the day following Christmas Day] a few years ago, the Chancellor of the University of Bradford, an influential business man, was visiting the university to encourage his troops. That he found many research pharmacologists working in the laboratories provided him with dinner table conversation of hard-working staff in his university for years to come.' E-mail to Dr Daphne Christie, 14 October 2006.

<sup>148</sup> pages 67–8.



billion and most of that is in the 5HT<sub>3</sub> antagonists, so that set the basis now for encouraging people to go and look for antiemetics, because they can see that there's a market if you get something better. I think it shifted the paradigm on antiemetic research at the time.

**Professor Ian Judson:** I wanted to add two or three observations in relation to this. Obviously, as a medical oncologist, I can only concur that when we first started to treat patients with these drugs, to see patients eating their breakfast or dinner while doing a ward round, was astonishing, when previously they would simply be sedated and still being sick.

I vividly remember the ferret video we saw [see page 56], when together with Ken [Harrap], we were looking at the possibility of exploring these drugs in a ferret model, and in relation to the platinum development story. But I wanted to extend the observation, after what Ken was saying, in terms of the onward development beyond carboplatin. When we started, when Ken's group started to develop an orally bioavailable platinum complex, that was only possible because of the 5HT<sub>3</sub> antagonists. Not that JM216, the drug that finally went into the clinic via the oral route, was particularly emetic, it was probably comparable with carboplatin, but without these drugs it would have been an idiotic thing to do. As it was, people still said it was a laughable concept, but without these drugs, it would have been an impossible concept.

**Sanger:** I have got one very small point to make. Bob's [Naylor] comments about the letters he received reminded me of this. I only received one letter and that was from the antivivisectionists, and following that I spent three months searching for bombs under my car, following police security advice. Very different experiences.

**Miner:** A real quick comment on what Bob [Naylor] was saying before about the gut motility and prokinetic effects of these drugs. I think it is important when we look back on it now – if anybody ever decides to reinvestigate this whole work – when Gareth [Sanger] and I were looking at the drugs, we certainly looked at renzapride, which is quite a reasonable 5HT<sub>3</sub> antagonist, but it does not completely block the emesis that you see in the ferret. I have always had a feeling, and Paul [Andrews] and I have talked about this before, that the actual prokinetic effects, the 5HT<sub>4</sub> agonist effect, probably detracts a little bit from the 5HT<sub>3</sub> antagonist activity. We just need to clarify that a little bit if we are going forward.

**Grahame-Smith:** Despite what we have heard there is something that still confuses me and that is that we don't have a clear mechanism of action of the 5HT<sub>3</sub> antagonists. By that I mean: where are they working, how are they working and what is the mechanism by which cisplatin causes vomiting? Some people may think they know the answer to those things, but I certainly don't know the answers in terms of precise molecular mechanisms.

I think it is unfair to talk about pure serendipity, because although, looking back, the 5HT<sub>3</sub> antagonists were developed serendipitously, there was the high-dose metoclopramide pointer. Nor was the process entirely intuitive – logical steps were followed, and one can see that with hindsight – but we didn't know the molecular mechanism of action of cisplatin that caused emesis in order to be able to target a molecular event on the way with a compound. We didn't have that, and I don't think we do now.

**Dr David Tattersall:** I was Robert Naylor's PhD student and I think you have brought up a very important point. I was also involved in the Substance P (NK<sub>1</sub>) receptor antagonists, and we spent many years trying to determine molecular interactions for the mechanisms of action of the NK<sub>1</sub> receptor antagonists. If we had done the same with the 5HT<sub>3</sub> receptor antagonists it would have taken ten years, so the original observation, the original published observation for 5HT<sub>3</sub> receptor antagonists was about 1985. The compounds were in the clinic; indeed a number of pharmaceutical companies had compounds in the clinic, very very rapidly. With the NK<sub>1</sub>s we couldn't do that, because we had to show more mechanism of action. I think it was purely serendipitous that we didn't at that time with the 5HT<sub>3</sub> antagonists. So, for instance, we had very little pharmacokinetics. In 1991, approximately 40 per cent of compounds that were taken into the clinic failed due to poor pharmacokinetics in humans. By 2001 that had been reduced to 10 per cent, so we've solved the pharmacokinetics. We had efficacy in a model that we believed to be predictive, and this was an unusual species, it wasn't something that had been used very long, less than 10 years. We didn't obtain toxicity information with the NK<sub>1</sub>s in ferrets. It was felt that it wasn't going to be predictive of what happened in humans, because there was no background data. So I think that it was entirely fortuitous that we didn't pursue too much of a mechanism of action. That was going on, however, in a number of academic institutions at the time.

**Dr John Rudd:** I also came from Bradford where Robert [Naylor] was my supervisor. For me things started off in 1988 and at that time the first information

I read was a review by Paul [Andrews], who hasn't really had that much to say.<sup>149</sup> Everybody was searching for a mechanism of action, and within Bradford, and within other laboratories around the world, we were all looking, and there were new technologies coming along, we had autoradiography, we had high pressure liquid chromatography (HPLC), showing changes in transmitter levels, and we could see where the 5HT<sub>3</sub> receptors were. So it was quite exciting. In those days it was a privilege to be in the laboratory, because in Robert's laboratory you could do anything you wanted. If you wanted to try something, you would go to the cupboard, open it, and it was full of drugs. Today I found out that Robert has taken one or two of them himself.<sup>150</sup> But it was full of drugs, and you were able to do any type of experiment that you wanted, and in a way you had this freedom to do it. When I came along, ondansetron (GR38032), well, it was old news in 1988,<sup>151</sup> and we thought we should look for responses that weren't blocked by ondansetron. And then we started to read about the problem with delayed emesis, and we started to understand the current animal model, this simple cisplatin (10 mg/kg)-induced emesis model wasn't going to produce the answer.<sup>152</sup> And how do you make a step from acute emesis, to an acute and delayed-emesis model? I think it's by talking to the very people that are in this room. So what was I able to do as a student? I was able to go to every British Pharmacological Society meeting I could, I could travel around the world and talk to different people, and basically that's how you make a discovery. So in the early 1990s, a Japanese group was looking at cisplatin in pigeons, and had

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<sup>149</sup> Dr John Rudd wrote: 'In actual fact, Professor Paul Andrews had pulled together many key scientists working in the emesis research field, providing modern ideas for emesis control, many of which appeared in his original review in the 1988 September issue of *Trends in Pharmacological Sciences* [Andrews *et al.* (1988)].' E-mail to Dr Daphne Christie, 16 November 2006.

<sup>150</sup> See page 58.

<sup>151</sup> Dr John Rudd wrote: 'Primarily because 5HT<sub>3</sub> receptor antagonists were already showing promise to reduce cisplatin-induced nausea and emesis in patients.' E-mail to Dr Daphne Christie, 16 November 2006.

<sup>152</sup> Dr John Rudd wrote: 'The original cisplatin (10 mg/kg)-induced emesis 4–6-h ferret model is sensitive to 5HT<sub>3</sub> receptor antagonists, but relatively insensitive to dexamethasone; even their combination fails to produce reliable additive effects to reduce retching and vomiting. However, combinations of glucocorticoids with other antiemetics were effective to reduce nausea and emesis in man. Therefore, we set out to find new emesis models capable of detecting the antiemetic activity of dexamethasone. The key experiments were funded by Glaxo Group Research, with input from Drs KT Bunce and C C Jordan.' E-mail to Dr Daphne Christie, 16 November 2006.

interesting data,<sup>153</sup> so we take note of that. One of the most important things I heard was a conversation from Robert after he came back from a meeting. He had spoken to Gareth [Sanger], talking about a study, again done by a Japanese group, in the dog with cisplatin, whereas in that particular experiment, if you prevented the dogs from being sick, and then you fed them 20 hours later, they would vomit.<sup>154</sup> But the control animals that had vomited at the start of the experiment did not vomit again when subsequently fed at 20 hours. So it seemed to me that somehow our ferrets were really vomiting too much, and we should try to do something about it. And Glaxo were still interested in this at the time, and had a meeting [in Bradford] and they wanted us to go forward at the 10-mg dose over 24 hours and see whether or not we could see a delayed phase.<sup>155</sup> At the time, bringing together all the things from Richard [Gralla] and around the world, and knowing what delayed emesis was, I said to myself, ‘Well, why don’t we just do it properly, do a proper dose–response again (3–10 mg/kg, i.p.), start at the beginning, and use a three-day period. And that’s exactly what we did, and when I think about what I did, and what Wes is talking about, Wes had got a very nice laboratory at the bottom of his building, that was very nice. Robert put me at the top of my building, and I had to go out across the roof, in the snow, in the rain, into my little room, where nobody would come to visit me.

The other thing that I should share with you is that when you do acute and delayed emesis experiments, you are literally sleeping at work. So I spent three days or so at work, and I would sleep on the office floor. Going to work at night I wouldn’t switch on the lights, because I didn’t want anybody to know that I was there, because you would have stories of people literally having their arms

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<sup>153</sup> Dr John Rudd wrote: ‘An abstract showing the temporal profile of emesis induced by cisplatin (3 mg/kg, i.p.) in the pigeon was shown at a Serotonin Club meeting in Houston in 1992 [Uchiyama and Suzuki (1992): 62]. Cisplatin induced a “biphasic” response, but some 5HT<sub>3</sub> receptor antagonists themselves induce emesis in pigeons, making it difficult to rationalize the data with the clinical situation.’ E-mail to Dr Daphne Christie, 16 November 2006.

<sup>154</sup> Dr John Rudd wrote: ‘The original dog study was conducted by Fukuda and co-workers [Fukuda *et al.* (1991)]. A similar study was subsequently performed using an identical protocol with DAT-582 [(6*R*)-(-)-N-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide dihydrochloride] [Yoshida *et al.* (1992)]. We quickly performed our own experiments on the ferret (June 1992), but did not see emesis in ondansetron-protected animals when they were fed at 20 h.’ E-mail to Dr Daphne Christie, 16 November 2006.

<sup>155</sup> Dr John Rudd wrote: ‘Those present at the meeting in Bradford were Drs D J Twissell, C Bountra, J A Rudd and Professor R J Naylor.’ E-mail to Dr Daphne Christie, 16 November 2006.

broken. So I used to have to learn my way around the laboratory, because we didn't have very good security.<sup>156</sup> I think the average age of the security guards was 50-something. These are the types of things that you had to go through. We went on to develop this model of cisplatin-induced emesis with an interest originally in dexamethasone, to try to look for a model that could detect the antiemetic activity of dexamethasone, and from there we went on to look at the NK<sub>1</sub> receptor antagonist.<sup>157</sup>

I remember having big chocolate bars and coffee just to keep me awake and, I guess, listening to your stories has been quite a privilege. So what can I say? I remember seeing Robert. I would be in my laboratory at 11 pm. He would be in his tuxedo, going somewhere nice, and I am still, to this day, doing these types of experiments, and I have still not put on a tuxedo.

**Calman:** I am conscious that we have one other area to cover, so could we make this the last couple of comments.

**Gralla:** We have had some wonderful stories about the controlled emesis, exciting research from the clinical to the lab, and back to the clinical, but I think we may be giving a mis-impression, and I think it's very important that we have heard John Rudd and David Tattersall speak. First of all, there's tremendous advantage and tremendous value to the animal models, but there are major limitations: (1) corticosteroids are excellent in humans, not so good in the animal models; (2) you can completely shut off the emesis with many of these antiemetics in animal models, but you cannot do that in humans. The story is much different in humans than in animals, in terms of the degree of control. We do not have anything approaching 100 per cent control, and we should not walk away saying that we do. We have a wonderful change that all of us like to look on the bright side, from 100 per cent of patients being sick, to a small majority of patients being sick now. In other words, the 5HT<sub>3</sub> antagonists are an advantage over metoclopramide, in terms of fewer side-effects, dystonic reactions and greater convenience, but as far as the antiemetic control is concerned, only a small advantage. That greater convenience contributed to the fact that they

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<sup>156</sup> Dr John Rudd wrote: 'Anti-vivisection activists were a serious concern to most scientists working with animals in the UK in the 1990s.' E-mail to Dr Daphne Christie, 16 November 2006.

<sup>157</sup> Dr John Rudd wrote: 'The new cisplatin (5 mg/kg, i.p.)-induced acute and delayed emesis model was sensitive to 5HT<sub>3</sub> receptor antagonists and glucocorticoids. The model subsequently revealed the potential of NK<sub>1</sub> receptor antagonists to treat delayed emesis [Rudd *et al.* (1996)].' E-mail to Dr Daphne Christie, 16 November 2006.

can be easily used by most physicians, a single dose is as good as multiple, and what we didn't know in the beginning, that they are perfect for paediatrics, because they don't have dystonic reactions. A study published a few months ago, an extraordinarily well-done study, showed that the combination of a 5HT<sub>3</sub> antagonist and dexamethasone after four cycles of chemotherapy in women with breast cancer who were previously untreated, were getting it mainly for adjuvant purposes, only 39 per cent were completely free of emesis during the entire treatment.<sup>158</sup> So we have made enormous progress, but we still have a long way to go.

The problems with industry are a plus and a minus; the plus is that without industry we would not have the 5HT<sub>3</sub> antagonists, so we should be extremely grateful. But then when the marketing department takes over, they wish to believe that serotonin is the only mechanism that causes emesis. This was a grave mistake, at which point I became not too popular in a couple of these companies, by saying, 'OK, this is an important pathway, but not enough'. That is where we have some wonderful studies that David Tattersall has published, looking at NK<sub>1</sub> antagonists, that many others in this room have looked at, and these have helped us go forward.<sup>159</sup> These have helped us understand, as John said, about the delayed emesis and about the NK<sub>1</sub>. So we have to recognize that we have a long way to go. We have taken a big step, but we oncologists need to reach the point where we can face every patient and say, 'Emesis is not likely to be a big problem for you'. We have taken about four steps, and we have three or four more. It is wonderful that 80+ per cent of patients now treated with NK<sub>1</sub> antagonists can be completely protected against acute emesis, and that 60–70 per cent can be completely protected against delayed emesis. What we have are problems that I heard over here before, the fact that in the 1980s, we had patients, all of them, with emesis. That was not necessary, there were drugs that would have done a much better job and that were available at that time, but they were not employed. We have a problem of effectiveness and efficacy. The efficacy and the effectiveness level is less, which is what happens in the real world. Getting the word out is important. Part of this is the smokescreen created by the economic problem. The 5HT<sub>3</sub> antagonists are some of the most cost-effective drugs, or probably *the* most cost-effective drugs in oncology. They prevent hospitalization. You don't have to prevent very many hospitalizations to make them economically sound. They are a dominant strategy for many

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<sup>158</sup> Perez (1998).

<sup>159</sup> See, for example, Tattersall *et al.* (1993).

patients, again because they allow us to de-hospitalize patients. I must say, in the UK people have been slow to de-hospitalize patients. They could save a lot of money, but unfortunately the expense comes from the same pair of pants, but a different pocket in the same pair of pants. So it's necessary to look at all these aspects, because patients should not be prevented from getting these drugs, which are inexpensive, compared with many oncological products that work only marginally, because of incorrect economic evaluation. But we as clinicians, and as basic scientists, should not also rest on our laurels; we have a long way to go yet before everybody is protected. We have made giant steps, but there's still a distance to go.

**Williams:** One of the things that strikes me as a molecular biologist away from the immediate clinical field, is that if you go to a conference on platinum, where there are chemists studying in great detail the action of platinum, there is hardly any paper which does not deal with platinum and DNA. The reason for that is that I don't think it has ever got through to the ordinary biochemist that you have a lot of problems about the toxicity. So they are not interested in this problem of toxicity, which obviously is absolutely critical to the use of the drug. It seems to me that some stimulus is needed from the medical community, down to the research community at the molecular level, because we have techniques now where you should be able to follow platinum atoms, wherever they go, and see what the targets they are hitting are. So why is there such a problem with platinum? Why don't we know the background mechanism? There's nobody that I know working on it. They don't study the protein's interaction in platinum at all any more, and I think that's a great shame because we know there are several other toxic problems, and they are not being tackled by the molecular biologists. If you knew where the platinum went, then you might have a different route to preventing its action in the wrong places, rather than hitting a completely different target which is something to do with emesis. So instead of stopping emesis, find out why it ever started.

**Andrews:** The hypothesis, I think, that most of us accept of how the platinum works, in the acute phase, is that it acts on the enterochromaffin cells in the upper part of the gastrointestinal tract. For some reason, they seem to be particularly sensitive to the effects of cisplatin and indeed other cytotoxic drugs with a different action. One of the hypotheses which has reasonable evidence is that there's a generation of free radicals within those cells. That causes an influx of calcium ions, which then leads to normal exocytosis of 5HT from the granules; it is not the cells being destroyed and breaking open. There are a lot of

mistakes in the literature. It is not the cells that are breaking open, because it is far too quick for that. It is normal exocytosis of 5HT-containing granules that's triggered, and the 5HT then acts on the 5HT<sub>3</sub> receptor, which is located on the vagal terminals peripherally, it's not systemically released 5HT; it's very much locally released. There may be some effect within the central nervous system, but the bulk of the evidence from the ferret studies is for a peripheral effect within the gastrointestinal tract. So I agree with you. In fact a number of us, including Gareth and I, wrote in a 1988 review about why the enterochromaffin cells are so sensitive to the substance.<sup>160</sup>

The other thing that is curious is that 80–90 per cent of the 5HT in the body lines the gastrointestinal tract. It is lining the mucosa, it is not in the neurones. So we have hypothesized that maybe you could predict emetic efficacy for cytotoxics by looking at the ease with which they release 5HT from enterochromaffin cells, but nobody has ever done that, because there's not a very good enterochromaffin cell model around to study. But it is very curious why those cells should be so sensitive.

**Calman:** I think it's really nice to end this session with a question, and that says that this is not resolved, and there are still some very fundamental things to be done.

**Brock:** Although the emesis issue has been terribly important, and I agree entirely that it needs to be taken forward, I wanted to come back to the fact that for us, of course, as paediatric oncologists, the really important toxicity is the permanent toxicity. The real problem there is this battle with the effect of the platinum on the DNA and the efficacy of the platinum on the tumour and the effect of the platinum on the healthy cells, which then causes the toxicity. But I want to be a little bit encouraging, and probably that's true that we do try to look at the good side, but if you are an oncologist you have to. This year the Royal National Institute of the Deaf has really taken on the challenge of trying to get the pharmaceutical firms to search for new chemoprotectants. They had a very big press conference just a few months ago that I was involved in, to try to put forward the fact that there's probably \$1.4 billion worth of industry out there to get the right drug to prevent the toxicity, particularly to the ear. I got involved and was invited out to the USA last year to look at Professor Ed Neuwelt's work, who is a neurosurgeon, an amazing man from Portland, Oregon, who has been doing a lot of work on sodium thiosulphate. Professor Neuwelt has been doing work in animal models,

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<sup>160</sup> Andrews *et al.* (1988). See also Andrews and Sanger (eds) (1993); Racké *et al.* (1995): 18.



xenograph mouse models, and cell lines, in STS [sodium thiosulfate], the antidote for cyanide, which is found in every single hospital in the world, and is cheap. He started looking into this because he uses carboplatin in blood–brain barrier disruption for brain tumours, and when you give carboplatin through blood–brain barrier disruption, you get very severe toxicity.<sup>161</sup> One of his patients was a professor at the university – you don't like to give radiotherapy to a patient over the age of 60, because they develop dementia – she accepted the blood–brain barrier disruption programme, giving intra-arterial carboplatin after mannitol, and she became deaf. It was her husband who discovered the STS, and that triggered the programme into looking at STS, but I think they have got a balance now between the timing of the platinum and the delayed timing of the STS, and are looking at it very carefully in the hope that we will actually prevent the permanent toxicity of platinum, which is so serious, particularly for the children.

**Calman:** It is interesting looking back. I began in 1974, I had no staff, no office, no beds, no telephone, no typewriter, and it really was amazing how we all had to deal with that, and that's the way it was.

I mentioned the issues of sperm storage, and I think that's quite an interesting area for comments.

Maybe we should also mention the issue of support groups, and part of the answer that I found almost immediately, indeed when I went to the Memorial Sloan-Kettering,<sup>162</sup> I noticed just how involved the groups were there. I set up my own little set of groups in Scotland, called 'Tak Tent', which is the old Scots phrase for 'Take Care' and in a sense it predated 'Backup', because Vicky Clement-Jones came to see me in terms of how this might develop.<sup>163</sup> The key was that individual patient groups were able to help other patients. For example, we had someone who worked in a benefit office and who wrote on how to get benefits appropriately, and others, particularly those who had experienced sickness or hair loss, who also wrote for other patients. We wanted to encourage that, and this was quite important for me. We also had some trouble with health and safety because of the amount, and the way in which drugs were being administered. They were generally made up in a small room close to the patient

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<sup>161</sup> Neuwelt *et al.* (1998).

<sup>162</sup> Memorial Sloan-Kettering Cancer Center, NY City, NY. See note 82.

<sup>163</sup> Dr Vicky Clement-Jones founded 'Cancerbackup' in 1985. The charity offers high quality information and support to people with cancer and to their families and friends. See [www.christie.nhs.uk/patients/infocentre/default.aspx](http://www.christie.nhs.uk/patients/infocentre/default.aspx) (visited 3 May 2007).

and in drawing up the correct amount excess drug was occasionally pumped into the air. This could not be seen with platinum, but with adriamycin the red colour was visible on the wall.

Some of the most interesting things happened in a lift. I worked on the seventh floor of Gartnavel General Hospital, Glasgow, and on one occasion someone had been at the outpatient clinic and had been given a fairly large dose of metoclopramide and began to become quite dystonic on the way up in the lift. Fortunately with the aid of a colleague we were able to get him out and deal with it quickly. And the second, and this was a really important one, was when we began to treat young men with testicular teratomas. I went up in the lift from the clinic with a young man and the lift was quite full. He began to ask me what his blood levels were and what his X-rays were like. I had his X-rays in the lift, so we had a look at it, and I could see the horror from the rest of the medical staff in the lift who felt, I think, that this was not the way to talk to patients in this hospital. This was a remarkable way of showing just how powerful it was to involve patients.

These are a few things to get you talking and I hope at some point our colleagues at the back of the room might just say a word or two of what it felt like from the patients' perspective. Comments and other consequences of using cisplatin?

**Mrs Brenda Reynolds.**<sup>164</sup> My daughter, Julie, was taken into hospital on 12 May 1981 – she didn't know, she was poorly the day before, which was the Monday. The local doctor came to visit and said, 'I think your daughter has got a Wilm's tumour'. Well, I stood in my kitchen dumbfounded. Never having heard of a child having tumours, I didn't really associate a tumour with cancer, to be perfectly honest. He came back at night, at 10 pm, and said, 'Can you be at Great Ormond Street, London, at 10 am?' Myself, Julie and a good friend of mine, packed a bag, got in my old car, and drove down from Cambridge. We hadn't a clue where we were going, and we went home eight weeks later. We had no anti-sickness drugs, and I think if I had known or heard what all you have said today, I don't think I would have, you know, all the experiments and how it started, I think I would have been more frightened today than I was then. Really. But I was very lucky.

We went into hospital on the Tuesday, met a Dr Jon Pritchard<sup>165</sup> on that day, they did some tests, they didn't really hold out a lot of hope for her. They

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<sup>164</sup> Mother of Julie [Wenn], a patient aged eight, treated with cisplatin as a child in 1981.

<sup>165</sup> See biographical note on page 102.

didn't think she would be coming home, really. I think it was about a 1 per cent chance at that time, I am not quite sure, but it was very, very small. On the Friday they operated. She had a double ovarian tumour and also she had tumours on her lungs, and at eight-years-old, well, that was quite scary. But they took it out, they didn't know whether she would come back from theatre all right, but she did, she couldn't understand why she had gone into hospital feeling all right, and then felt desperately ill. All she wanted to do was go home. The hospital started her treatment: cisplatin, bleomycin and vinblastine, that was the combination. We had friends that came down to visit, and she used to cry, and I mean *cry*, and say, 'Please don't let them do it to me, please don't let them do it to me'. Neighbours and friends used to say, 'All right, Julie?' I used to say, 'Out. Please go out when they come to do the treatment.' Because you had to be cruel to be kind. Once the drugs went in, she used to watch the clock. Like you were saying with the ferrets, you could time it to exactly when she was going to start to be sick. We used to have to stay in there. I hear about people now who go in for the day for treatment and come home. But you used to have to spend seven days in there. And then we used to come home on the train, spend most of the time in the toilet, because she was still being sick. It's very different now, but she came through it. It is now 25 years ago, 12 May 1981, and she has two beautiful children, which she never thought she would have, because they thought the treatment would cause permanent infertility. But they didn't know what would happen with children, because they hadn't had any that had grown up. But she was told at the age of eight that she more than likely wouldn't have children. I didn't agree with it, but Dr Pritchard was right. She grew up knowing the worst, so she never knew no different.

**Calman:** Thank you very much. I know how very difficult this kind of experience is, and we are very grateful to you for coming.

**Bagshawe:** Can I raise the subject of long-term sequelae to cisplatin? It seems to have two components: one is the possible effects of renal damage which occurs despite the hydration that takes place in its administration, and one generally sees a fall in the creatinine clearance [glomerular filtration rate] in patients receiving platinum.

The other aspect, of course, is the question of secondary tumours. As far as I know, there hasn't been any data published on the development of hypertension in patients who receive cisplatin, at least I don't know of any. But I do know that

there is a high incidence that will be reported in the next year or so, of patients who have had cisplatin and who are developing systemic hypertension.

The secondary tumour situation, of course, is much more difficult, because the drugs are usually given in combination. But it's very important, I think, that where patients who had cisplatin with vinblastine and bleomycin in the testicular tumours, for instance, that those data should continue to be updated, because we found with the gestational tumours when we reviewed them in 1985 that the expected number of tumours in that group, and it covered some 3500 patient years, only two tumours were reported at that time. Ten years later, when the number of patient years was 15 000 odd, the incidence of secondary tumours was higher than expected. I think there were 37 tumours, whereas 24.5 would be expected in that particular group. So it is very important that there should be a collection of data from these patients who have received cisplatin, without the complications introduced by other drugs, particularly of etoposide, which we know has a risk of secondary tumours.<sup>166</sup> With patients who had cisplatin and etoposide for testicular tumours, there was a review of the data from Charing Cross and the London Hospital about 10 years ago, that showed that the relative risk of secondary leukaemias, was 150-fold.<sup>167</sup> There were six acute leukaemias diagnosed, when only two were expected in that group. So the business of collecting data as clean as one can get it, seems to me to be very important.

**Calman:** May I just emphasize that, with another little hat that I wear? The importance of long-term data collection, as sometimes is happening, the fragmentation of a thing called the NHS, may actually limit this, and I hope that particularly in this area, we will be able to continue to collect good data, because that's the kind of information that we actually need.

**Brock:** I would like to strongly endorse that and I think that in that sense perhaps paediatrics has led the field. Dr Gill Levitt has very strongly built up the late effects at Great Ormond Street, London, and the average age of follow-up now is about 35 years, so we do have records of the secondary incidences of cancer.<sup>168</sup> In fact, with cisplatin it is pretty low, which is encouraging; it is high in the brain tumours, but is relatively low in the solid tumours. The renal function problems are protein and magnesium loss. But what is encouraging in

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<sup>166</sup> Rustin *et al.* (1996).

<sup>167</sup> Boschhoff *et al.* (1995).

<sup>168</sup> See, for example, Taylor *et al.* (2004). See also Cavalli (1982).

this area is that Gill Levitt has just been chosen as chairman of a group to lead the late effects study also in the adults and try to bring it together, and I think a lot of the international studies are making it mandatory that late effects 10-year follow-up is being done, and further on.

**Calman:** I have no concerns about the clinical staff wanting to do this; I am concerned that systems should be available to allow that to happen. Are there any other general comments about the consequences of the use of cisplatin?

**Calvert:** Just to continue on the theme of the late effects and the possibility of secondary tumours. One thing that has been very surprising over the last 20 years is that there are not nearly so many as we thought there would be, because the use of cancer chemotherapy has extended life so much with a large proportion of patients with breast cancer, for example, getting adjuvant chemotherapy, and then being cured, and available for follow-up for many years. I am not aware of any very significant reported increases in secondary tumours there, although they have had mutagenic agents.

**Calman:** I want to take up another couple of quick points before we finish.

**Thomson:** To follow up that point, I mentioned, 'Haddow's paradox', but I think early on there were some studies done on the mutagenic power of cisplatin using the AMES test.<sup>169</sup> If I remember rightly, it has a very low mutagenicity.

**Calvert:** The other point relates to sperm banking and fertility. And that's another thing that we have learnt, that infertility is less frequent than we thought it would be and the return to fertility is quite common, in men as well as women.

**Gralla:** To echo the point of the long-term follow-up: I think that organized survivor clinics make a lot of sense. Not just to look at the issues of secondary malignancies, to look at long-term toxicities, neural toxicity; to look at issues of fertility, but also to look at psychological difficulties, learning defects, risk-taking behaviours, in different individuals, and to do it in an organized way. This is something that we can all learn from, which will then help us to learn, long-term, to select the best regimes. It is possible that progression-free survival, which can be better, will be worse in certain groups and that overall survival will be better in others, especially if drugs have minor cardiac toxicity as people get older; this sort of thing. So I think a truly organized survivor clinic, not just a

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<sup>169</sup> See, for example, Ames *et al.* (1973); McCann and Ames (1976).

collection of data, can serve the patient with psychological, social and emotional needs, and can serve the medical community with a good way of keeping track of all these aspects. We have to look at it from an institutional point of view, just as you have suggested.

**Calman:** What is interesting is that I chair a little group for Macmillan Cancer Relief here in the UK, looking at questions that patients want answered, to develop the research, and that was one of the ones that came out quite strongly. We want to have an idea about long-term survival and the issues and the problems etc., and that's an area which has been developed.

**Williams:** May I make a general point, which is not on this subject? The general point is that it is very interesting that in the literature on the study of platinum compounds of various kinds, there is a very large number of them in the bioinorganic – or whatever you want to call it – biological inorganic chemistry journals such as the *Journal of Bioinorganic Chemistry*. Many of these compounds are claimed to be active. How on earth are they going to be tested? Meanwhile, we are developing a whole lot of other heavy metal complexes, which are also said to be anticarcinogenic; for example, there are a number of ruthenium compounds that have been tested on what I would call microbiological targets; in other words, they have gone through tests like the phage test,<sup>170</sup> and the AMES test for mutagenicity of compounds. They have been tested to some degree in animal tests, and I don't understand quite how the medical community is going to handle this material that's coming into being. Are the chemists just wasting all their time? Are the chemists just producing 101 different compounds which have some effect, and we will never know if they are useful or not, because these studies are not concentrated or organized in any particular way? A huge amount of money is going into this work.

**Calman:** May I say a few words to wind this up? Some of you probably don't know, but one of my interests is in telling stories and I wrote a little book about three or four years ago about storytelling in medicine, and what we have heard today is a wonderful collection of stories which, in the jargon, illuminate the discovery and development of platinum. Could you, or would you do it again? Now? I suspect the answer is no, as I have listened to the way in which this has been developed. You wouldn't get permission to do it, it would be difficult. Could you plan this? Planning scientific discovery? The answer must be pretty

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<sup>170</sup> See page 19.

close to no, which is quite interesting in terms of the funding of research. You can fund bits of it, but not all of it. So it's quite interesting. Well, that's what you have told us this afternoon. You can't plan this. This is about people. What has also come through is the enormous courage of patients, we have heard that today, but I think the tremendous creativity and courage of staff too, from taking the pills to doing funny things with ferrets late at night. It's an amazing range of things.

I have just finished another little study on medical education,<sup>171</sup> and one of the things that came out for me, was something that I have called medical magnets, or you could call them scientific magnets. That is, people who attract other people to work with them, and we have had a whole series, right at the beginning, with Rosenberg in Michigan, the Chester Beatty and the Marsden group, Ken Bagshawe's group, the groups that were beginning and developed in the USA. They attract people, and they attract them because they have got something new to offer. They are hugely enthusiastic about what they do. People want to work with them. They have a global network. I mean Alex Haddow just flies backwards and forwards making these links, it's amazing. Very hard-working all the time. They love teaching. They love supervising. They love having post-docs and PhD students, because that's what it's all about. And they have enormously open minds. Sir Peter Ustinov was Chancellor at the University of Durham just a year or two back, and he used to say, 'Doubts unify, certitudes divide'. It's a lovely phrase. If we are still prepared to doubt things, we can actually have a dialogue. But if I am sure that drug X really works, we won't have a dialogue. And maybe that's quite a nice way to finish this.

I have had a really good day; I have listened to some wonderful stories. I think this is going to make an excellent volume, and there are some big lessons for science and medicine, and its development. On your behalf, may I thank Tilli and all the staff who have walked about with microphones, and done other things, to make a very interesting afternoon? So, on your behalf, we thank them.

**Tansey:** May I just make a final comment please? I would like to echo something that John Rudd said earlier, that it has been a privilege to be here this afternoon and to hear these stories and accounts. But they are not just stories, these are the building blocks of history and we have a serious purpose in holding these meetings, to record them, to transcribe, edit them, and to make them widely

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<sup>171</sup> Calman (2006). See also Reynolds and Tansey (eds) (2007).

available to people – your colleagues in clinical oncology and pharmacology, my colleagues in the history of medicine. We are extremely grateful to all of you for coming along and contributing your stories and, on your behalf, I would also like to thank Sir Kenneth Calman for his excellent chairing.



## Appendix 1

### In Praise of Methotrexate

by Professor Sir Kenneth Calman

I want to tell a story of some anti-cancer drugs,  
So sit back, charge your glasses, and pin back both your lugs.  
It all began with Ehrlich, of 'magic bullet' fame,  
Back in the 1890s when science was just a game.  
He synthesized an alkylator ethylenimine,  
The first true cytotoxic the world had ever seen.  
A space of 40 years elapsed, until in time of war  
The ship, the John F Harvey sank down in Bari Harbor.  
Aboard this ship was mustard gas – its effects the Bard recites  
Made many of the men right sick and dropped their leucocytes.  
The medic, Alexander, had a flash of inspiration  
That clinical benefit might result when the white count showed elevation.  
So Goodman and Gilman and Dougherty from the field of Academia  
Assessed the use of mustard in childhood and adult leukaemia.  
And so the scene is set, Sidney Farber's on the stage.  
The drug was methotrexate and chemotherapy came of age.  
Aminopterin was first, or so the Bard relates,  
Both compounds being active as synthetic antifolates.  
The drug is given orally or by the intravenous route,  
Intramuscularly, intrathecally, which ever one will suit.  
Its pharmacokinetics fit a three compartment system.  
It has three half-lives in venous blood, but I do not wish to list 'em.

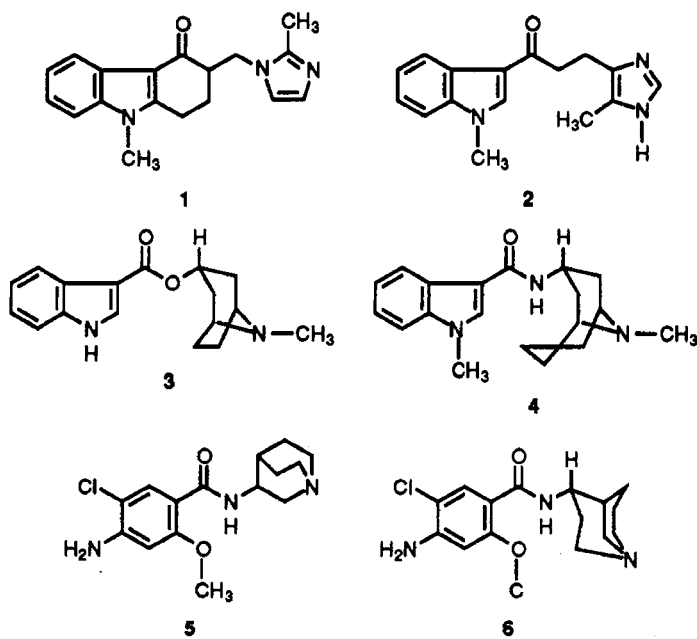
Its mechanism of action, its biochemical pharmacology  
Have been described for many years and are like dogma in oncology.  
Methotrexate acts, or so the Bard oft says  
On a critical enzyme molecule, dihydrofolate reductase.  
It has a very high affinity  $10^{-8}$  or more  
And inhibits the conversion of  $\text{FH}_2$  to  $\text{FH}_4$ .  
Enzyme action is inhibited at micromolar concentration,  
Always of course assuming adequate drug penetration.  
Other enzymes are important like carboxypeptidase,  
Hepatic aldehyde oxidase and thymidylate synthetase.  
Thymidine kinase is another catalyst,  
The others have much longer names I will not even list.  
Its action on the cell cycle is really quite terrific  
Like some other antimetabolites methotrexate is S-phase specific.  
Methotrexate does exist in many different states  
And currently the interest is in polyglutamates.  
There are monoglu's and diglu's and glu's to the power N,  
Their significance, however, is quite beyond my ken.  
To measure methotrexate is not an easy task.  
Which methods are the best ones do I hear you ask?  
Well there's GLC, HPLC and radioimmunoassay,  
And EMIT kits of course which are actually rather classy.  
Some techniques at first were really rather primitive  
And couldn't even measure the 7-hydroxy derivative.

The side-effects of methotrexate must not be forgotten.  
Mucositis is perhaps the worst in fact it's rather rotten.  
Renal damage may result and can accentuate toxicity,  
Hepatic damage can occur when its given with some chronicity.  
Sore eyes can be a problem and reddened conjunctiva,  
Methotrexate is secreted in the tears and in saliva.  
One side-effect, however, which has not been documented  
Is car-cin-o-genesis which makes one quite contented.  
So far the evidence suggests, and the Bard has not heard rumours,  
That methotrexate, given long term, does not cause second tumours.  
Before I bring this rambling verse to a necessary close,  
I must mention methotrexate given in mega dose.  
Instead of 15 mg, we now use 15 g.  
And such dose can be repeated, in fact *ad nauseam*.  
Folinic acid rescue is the secret of success,  
Without old leucovorin we'd be in quite a mess.  
Well I'm getting tired now and on my feet I teeter,  
But before I end this rhyme I should like to change the metre  
Because  
You can flatten 'em with platinum.  
Get big cell kill from fluorouracil  
Be a medicine man with melphalan  
Keep things pristine with vincristine.  
Shout with glee with 6MP.

Quite amaze with asparaginase.  
Be a boss with cyclophos.  
Never be alone with prednisone.  
But don't touch custard after mustard.  
Play to win with doxorubicin.  
But you can fix it with methotrexate.  
My verse it must now terminate.  
I ask you all to celebrate.  
Your glasses raise to participate  
And with one voice expostulate  
IN PRAISE OF METHOTREXATE.

## Appendix 2

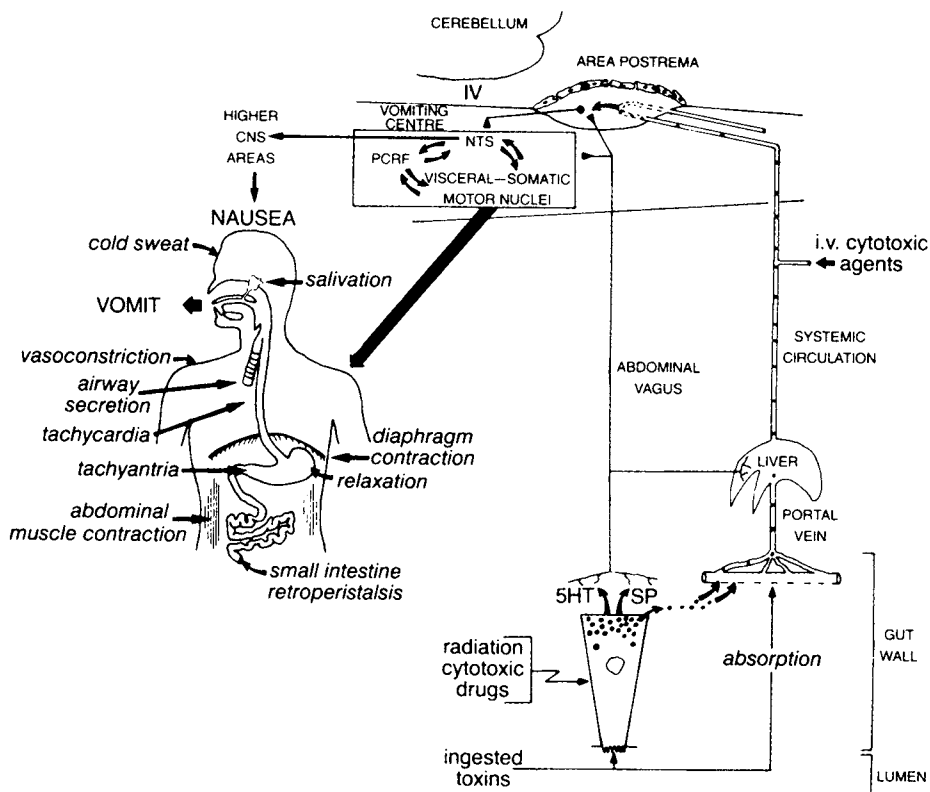
### Structures of some 5HT<sub>3</sub> receptor antagonists



Ondansetron (1), GR 65,630 (2), tropisetron (3), granisetron (4), zacopride (5), and renzapride (6).

## Appendix 3

### Components of the emetic reflex



Major components of the emetic reflex believed to be involved in emesis evoked by cytotoxic therapy or by orally ingested toxins.

Adapted from Andrews *et al.* (1988): 335.

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## Biographical notes\*

### **Professor Paul Andrews**

(b.1953) studied physiology at undergraduate and postgraduate levels at the University of Sheffield prior to obtaining lectureships at the University of Edinburgh and St George's Hospital Medical School, University of London, where he is Professor of Comparative Physiology. His research over the past 25 years has focused on the pre-clinical neuropharmacology of emesis with particular emphasis on anti-cancer chemotherapy and the role of the vagus. He has worked on the site(s) of action of 5HT<sub>3</sub> and NK<sub>1</sub> receptor antagonists in conjunction with colleagues in industry and is currently working on non-animal methodologies to investigate emesis.

### **Professor Kenneth Bagshawe**

CBE FRCP FRCOG FRCR HonDSc FRS (b. 1925), was at St Mary's Hospital Medical School, London (1946–52), Research Fellow at Johns Hopkins, Baltimore, in 1955, Senior Lecturer in Medicine at the Charing Cross Hospital Medical School, London, in 1960, Professor of Medical Oncology (1975–90)

and Chairman of the Cancer Research Campaign Scientific Committee (1983–88).

### **Dr Penelope Brock**

(b. 1954) gained her medical degree in 1981 from Louvain University in Belgium. She is currently Consultant Paediatric Oncologist at Great Ormond Street Hospital, London, and Honorary Senior Lecturer at the Institute of Child Health, London. Her doctoral degree was on cisplatin toxicity in infants and children. She developed the Brock grading system for cisplatin ototoxicity and is UK Chief Investigator for a number of international clinical trials, and International Chairman of the Sixth International Paediatric Liver Tumour Trial (SIOPEL 6) testing, in a prospective randomized study, the chemoprotectant sodium thiosulphate in its prevention of cisplatin ototoxicity.

### **Professor Sir Kenneth Calman**

KCB FRCS FRSE (b. 1941) graduated in medicine in 1967 at the University of Glasgow and proceeded to MD and PhD, being initially involved in medicine as a lecturer in surgery. An MRC

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

Clinical Fellowship took him to the Chester Beatty Research Institute in London in 1973 and he returned to Glasgow to be Professor of Oncology from 1974 to 1984. He became Postgraduate Dean in Glasgow, then Chief Medical Officer for Scotland, Chief Medical Officer for England, and subsequently Vice-Chancellor at the University of Durham. He has been Chancellor at the University of Glasgow since 2006.

**Professor Hilary Calvert** FRCP FMedSci (b. 1947) worked at the Institute for Cancer Research at the Royal Marsden Hospital in London from 1977. He was responsible there for the introduction of carboplatin into clinical practice and its subsequent clinical development in ovarian cancer. Since 1989 he has worked in the University of Newcastle upon Tyne, implementing a program of drug development aimed at using the molecular pathology of human cancers to define targets, developing drugs aimed at those targets and performing preclinical and clinical studies. He also runs a major clinical trials program with up to eight Phase 1 studies of anti-cancer drugs open at any given time in addition to Phase 2 and 3 studies. He is the Clinical Director of the Northern Institute for Cancer Research and Professor of

Medical Oncology at the University of Newcastle upon Tyne, UK.

**Dr Michael (Mike) Cleare** worked for 30 years at Johnson Matthey, UK, before joining Columbia University, Science and Technology Ventures, New York, as executive director in 2000. From 1966 to 1988, he worked in research and development, where he was involved in the discovery and development of platinum-based anti-cancer drugs, in particular carboplatin. From 1990 until 1999, he served as president of several of the company's major divisions, including Pharmaceutical Materials, Chemicals and Metals, Catalytic Systems and Electronic Materials.

**Professor Thomas (Tom) Connors** FIBiol (1934–2002) was Director of the Medical Research Council Toxicology Unit, Carshalton, London, from 1976 until his retirement in 1991. He was the first person to evaluate the anti-tumour potential of cisplatin and later, in collaboration with the late John Roberts, he conducted fundamental studies into its mechanism of actions leading to the development of carboplatin. In association with the Cancer Research Campaign he served as Chairman of the Scientific and Grants Committee, and was instrumental in the

formation of the CRC Phase 1/2 Drug Development Committee. In 1990 he became Chairman of the British Association for Cancer Research Executive Committee and President in 1994, and was Honorary Professor at the School of Pharmacy, University of London.

**Professor Brenda Costall**

(b. 1947) worked at the University of Bradford as Lecturer in Pharmacology (1973–9), Senior Lecturer in Pharmacology (1979–83), Reader in Neuropharmacology (1983–5), Professor of Neuropharmacology since 1985 and Head of the School of Pharmacy (1998–2004).

**Sir John Henry Gaddum**

Kt FRS FRSE (1900–65) went to Trinity College Cambridge in 1919 on an entrance scholarship for mathematics and read medicine. He won a senior scholarship at Trinity in 1922 and obtained second class honours in the Science Tripos (Part II) in Physiology. In 1922 he became a medical student at University College Hospital, London. He worked at the Wellcome Research Laboratories, London, in 1925, at the National Institute for Medical Research, London (1928–34), and was Chair of Pharmacology at the University of Cairo (1934), Professor of Pharmacology at University College, London (1935),

at the Chemical Defence Research Station, Porton (1939–45), and in 1958 was Director of the Institute of Animal Physiology, Cambridge. See Feldberg (1967).

**Professor David Grahame-Smith**

CBE FRCP (b. 1933) was Rhodes Professor of Clinical Pharmacology, University of Oxford (1972–2000), Honorary Director of the Medical Research Council of Clinical Pharmacology, Oxford (1972–92), Honorary Director of the Oxford University Smith Kline Beecham Centre for Applied Neuropsychobiology (1989–99), and Honorary Consultant in Clinical Pharmacology and General Internal Medicine to the Oxford Radcliffe Hospitals (1972–2000).

**Professor Richard Gralla**

(b. 1948) is a medical oncologist, whose practice and research interests have concentrated on lung cancer, new agent development and supportive care in cancer. He has been Chief of the Thoracic Oncology Service at Memorial Sloan-Kettering Cancer Center (New York), Director of the Ochsner Cancer Institute in New Orleans, Louisiana, and Professor of Medicine, Columbia University, in New York. He is President of the New York Lung Cancer Alliance, and is the immediate past president of the Multinational Association of

Supportive Care in Cancer.

**Professor Sir Alexander Haddow** Kt HonFRS HonFRCP 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 (1977).

**Professor Kenneth Harrap** CBE CChem FRSC (b. 1931) joined the Chester Beatty Research Institute, London, in 1956. He became, successively, Head of the Department of Applied Biochemistry in 1970, Head of the Department of Biochemical Pharmacology in 1977, Chairman of the Drug Development Section in 1982, and the first Director of the CRC Centre for Cancer Therapeutics in 1994–97, later Emeritus. Major registered drugs associated with the work of his groups are carboplatin and tomudex. He has been a partner in Weston and Harrap Consulting since 1997, advising on oncology drug discovery and development.

**Dr James D Hoeschele** (b. 1937) joined Professor

Barnett Rosenberg's platinum research group in the Biophysics Department at Michigan State University as his first Post-Doctoral Fellow from 1970 to 1972. He then took successive positions at Engelhard Industries (1972–76), Oak Ridge National Laboratory (1976–83), Parke-Davis Pharmaceutical Company (1983–92), University of Michigan (1992–94) and Michigan State University (1994–present). His research focused predominantly on the development of platinum anti-cancer drugs and, in general, on the use of precious metal complexes as medicinal agents. He has played a role in the development of cisplatin and is a co-discoverer of carboplatin. He continues to do research relating to the use of precious metal complexes as medicinal agents.

**Professor Ian Judson** (b. 1951) has been Consultant Medical Oncologist at the Royal Marsden Hospital and the Institute of Cancer Research, London, since 1989. He has been involved in new anti-cancer drug development for over 20 years and played a role in the early trials with carboplatin and conducted the first Phase 1 trials with satraplatin (JM216), an oral platinum agent, and picoplatin (AMD473), developed to overcome platinum anti-cancer



drug resistance. He also has an interest in the management of soft tissue sarcomas and played a key role in the development of imatinib for the treatment of gastrointestinal stromal tumours.

**Mr Wesley (Wes) Miner**

(b. 1948) is a graduate in Physiology from the University of Edinburgh. From 1982 to 1986 he worked as a Senior Scientist at Beecham Pharmaceuticals (now GlaxoSmithKline) with Gareth Sanger on the discovery and development of the use of 5HT<sub>3</sub> antagonists as antiemetic therapy for treatment and prevention of anti-cancer therapy-induced nausea and vomiting. The culmination of this work resulted in the discovery of granisetron.

**Professor Robert Naylor**

(b. 1943) graduated from Bradford in 1967 and undertook a doctoral neuropharmacology research program under the supervision of J E Olley. With Brenda Costall he subsequently established the Bradford Neuropharmacology Research Group, becoming Lecturer, Senior Lecturer, Reader and Professor of Pharmacology, with a Personal Chair in Neuropharmacology and Head of the School of Pharmacy at Bradford. He investigated the functional role of brain dopamine

systems in motor control and the detection of atypical antipsychotic drug action, and anti-Parkinson treatments. Concomitant investigations of the role of serotonin in central and peripheral systems revealed the antiemetic actions of the 5HT<sub>3</sub> receptor antagonists in animal models.

**Dr Jon Pritchard**

FRCP FRCPCH FRCPEd (1942–2007) was Consultant Paediatric Oncologist at the Hospital for Sick Children, Great Ormond Street, London (1978–98), Bart's (1980–98), South East/South Thames Regional Health Authority (1985–98), Royal Hospital for Sick Children, Glasgow from 2002 and Royal Hospital for Sick Children, Edinburgh, from 2002. Dr Pritchard was the first doctor to give the drug cisplatin to a child (pages 41–42). See Anon (2007).

**Dr Barnett (Barney) Rosenberg**

(b. 1926) obtained his PhD in Physics at New York University (NYU) in 1956, and joined MSU in 1961 until 1997. In 1965, Rosenberg and his colleagues proved that certain platinum-containing compounds, notably cisplatin, inhibited cell division and thereby cured solid tumours. Cisplatin obtained FDA approval in 1978.

### **Dr John A Rudd**

(b. 1967) began working on the mechanisms of emesis control as a focus of PhD studies under the supervision of Professor Robert J Naylor (University of Bradford, UK) and Dr Keith T Bunce (Glaxo Group Research, UK). Research was directed towards investigating emetic responses resistant to 5HT<sub>3</sub> receptor antagonists, the discovery of broad inhibitory antiemetic drugs, and the mechanism of the antiemetic action of dexamethasone. He developed the ferret model of cisplatin-induced acute and delayed emesis and revealed the potential of NK<sub>1</sub> receptor antagonists to reduce delayed emesis. He moved to the Chinese University of Hong Kong in 1995. He currently has an Emesis Research Group that has strong links with industry.

### **Dr Gareth Sanger**

(b. 1953) was Research Fellow at King's College Hospital Medical School, London (1977–90), and scientist and manager within the different companies now represented by GlaxoSmithKline. He was jointly awarded (with Dr M Tyers) the 1998 Pharmaceutical Research and Manufacturers of America (PhRMA) Discoverer's Award for the 5HT<sub>3</sub> receptor/antiemesis research which led to the identification and development of Kytril®. His

current expertise is in the biology of ghrelin, motilin, 5HT, tachykinins and other areas. He is editor and reviews editor for the *British Journal of Pharmacology* and editorial board member for *Drug Discovery Today*.

### **Dr Tilli Tansey**

HonMRCP FMedSci (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 at UCL.

### **Dr David Tattersall**

(b. 1961) has been involved in the development of antiemetic drugs for over 20 years. During his PhD studies he worked in the Neuropharmacology Laboratory of Professors Robert Naylor and Brenda Costall, investigating the control of vomiting. It was during these studies that the 5HT<sub>3</sub> receptor antagonists were shown to inhibit emesis induced by cisplatin [Costall *et al.* (1986)]. He moved to the laboratories of Dr Richard Hargreaves and Professor Ray Hill at Merck Sharp & Dohme in Harlow. The most recent treatments for chemotherapy-induced emesis, the Substance P (NK<sub>1</sub>) receptor antagonists, were developed during this time [Tattersall *et al.* (2000); Hesketh *et al.* (2003)]. He has been head of a

preclinical *in vivo* biomarkers and translational biology group at Pfizer in Kent, since 2006.

**Professor Andrew J Thomson** FRSC FRS (b. 1940) graduated from Oxford in 1965, obtaining his DPhil under the supervision of Professor Robert Williams. In the Department of Biophysics, Michigan State University (MSU), working with Professor Barnett Rosenberg, he discovered the biological effects of cisplatin and also studied models of visual pigments. He joined the School of Chemical Sciences at the University of East Anglia (UEA) in 1967, where he has remained ever since. With Professor Colin Greenwood he established an interdisciplinary unit, the Centre for Metalloprotein Spectroscopy and Biology (CMSB), studying the structures and functions of the proteins of bacterial respiratory chains. He has developed novel magneto-optical techniques to inspect the metal cofactors employed by such proteins. In 1985 he was appointed Professor of Chemistry. From 1998 he served as Head of the School of Chemical Sciences for five years and founded the first new School of Pharmacy in the UK for 30 years, jointly with Chemical Sciences. He became the founding Dean of the Faculty of Science at UEA in 2002.

**Professor Martin Leslie Tobe** (1930–93) was Lecturer (1956–65), Reader (1965–71) and Professor (1971–93) at the Department of Chemistry, UCL. His research centred on the mechanisms of substitution of transition metal complexes. He won the Corday-Morgan Medal of the Chemical Society (now the Royal Society of Chemistry) in 1963.

**Sir Peter Ustinov** Kt CBE FRSA FRSL (1921–2004), British-born actor and writer, was Chancellor at Durham University, from 1992; Rector of the University of Dundee from 1971 to 1973 and goodwill ambassador for UNICEF in 1969.

**Dr Loretta Van Camp** (1948–2006) was co-discoverer with Drs Barnett Rosenberg and Thomas Krigas of the anti-cancer drug, cisplatin [Rosenberg *et al.* (1965)]. She received an Honorary Doctor of Science from MSU in 1999.

**Professor Robert (Bob) Williams** FRSC FRS (b. 1926) worked from 1948 in the Inorganic Chemistry Laboratory at Oxford on the role of metal ions in biological systems. He has been a Fellow of Merton College, Oxford (1951–55) and Wadham College, Oxford (1955–)

and successively Lecturer, Reader (1955–74) and Napier Royal Society Research Professor (1974–91). His work is summarized in Williams and Phillips (1966); Williams and Fraústo da Silva (2001, 2006).

**Dr Eve Wiltshaw**

OBE FRCP FRCOG (b. 1927) qualified in 1952 from the University of Wales and researched clinical haematology in Boston, Massachusetts, USA, from 1953 to 1955. She joined the Institute of Cancer Research and the Royal Marsden Hospital in 1955 to work on drug treatment of cancer patients and was Medical Director there from 1986 to 1994. She is known for the introduction of cisplatin and carboplatin into clinical practice in the UK. See Wiltshaw (1998).

## Glossary\*

### **biomaterial**

Material used to construct artificial organs, rehabilitation devices or prostheses, and to replace natural body tissues.

### **brachytherapy**

A procedure in which radioactive material sealed in needles, seeds, wires or catheters is placed directly into or near a tumour.

### **bradycardia**

A slow heart rate, usually defined as less than 60 beats per minute.

### **cannabinoid**

Any of various organic substances, such as THC (tetrahydrocannabinol), found in cannabis.

### **choriocarcinoma**

A malignant tumour of syncytial trophoblasts and cytotrophoblasts, almost always occurring in the uterus. Also called chorioepithelioma, chorionic epithelioma, trophoblastoma.

### **cisplatin (cisplatin)**

A platinum-containing chemotherapeutic drug used to treat metastatic ovarian or testicular cancers and advanced bladder cancer, and head and neck tumours.

### **creatinine clearance**

A method that estimates the **glomerular filtration rate (GFR)** of the kidneys; the amount of liquid filtered out of the blood that gets processed by the kidneys. Clearance is measured in ml/min. The lower the creatinine clearance, the less effective is the working of the kidneys. Normal values are between 100 and 140 ml/min.

### **cytotoxic**

Of, relating to, or producing a toxic effect on cells.

### **electrolyte**

A chemical compound that ionizes when dissolved or molten to produce an electrically conductive medium.

### **electrophoresis**

A process by which molecules, such as proteins, DNA or RNA fragments, can be separated according to size and electrical charge by applying an electric current to them. Each kind of molecule travels through the medium at a different rate, depending on its electrical charge and molecular size.

\*Terms in bold appear in the Glossary as separate entries

**enterochromaffin (EC) cells**

Cells that occur in the epithelial lining of the lumen of the gastrointestinal tract. They produce and contain about 90 per cent of the body's store of **serotonin (5HT)**.

**etoposide phosphate (Eposin<sup>®</sup>, Etopophos<sup>®</sup>, Vepesid<sup>®</sup>, VP-16<sup>®</sup>)**

An inhibitor of the enzyme topoisomerase II. It is used as a form of chemotherapy for malignancies such as lung cancer, testicular cancer, lymphoma, non-lymphocytic leukaemia and glioblastoma multiforme. It is often given in combination with other drugs, for example, **cisplatin**.

**exocytosis**

A process of cellular secretion or excretion in which substances contained in vesicles are discharged from the cell by fusion of the vesicular membrane with the outer cell membrane.

**filamentation**

Anomal growth of certain bacteria, such as *E. coli*, in which cells continue to elongate but do not divide. Bacterial filamentation is a defect in the completion of replication and is observed in bacteria responding to various stresses, for example, while responding to extensive DNA damage.

**glomerular filtration rate (GFR)**

The quantity of glomerular filtrate formed each minute in the nephrons of both kidneys, usually measured by the rate of **creatinine clearance**.

**half-life**

Measurement of the amount of time it takes for half of the radioactive atoms in an element to decay. For material with a half-life of one week, half of the original amount of activity will remain after one week; half of that (one-quarter of the original amount) will remain after two weeks and so on.

**hepatoblastoma**

A form of liver cancer that usually occurs in infants.

**isomers**

Molecules with the same chemical formula and often with the same kinds of bonds between atoms, but in which the atoms are *arranged* differently; that is, they have different structural formulae.

**lysis**

The dissolution or destruction of cells, such as blood cells or bacteria, by the action of a specific lysine.

**methotrexate (amethopterin)**

A toxic antimetabolite that acts as a folic acid antagonist, used as an antineoplastic agent and in the treatment of rheumatoid arthritis and psoriasis.

### metoclopramide

A potent dopamine receptor antagonist and a 5HT<sub>4</sub> receptor agonist used in treatment of patients with delayed gastric emptying. It is also useful for facilitating small bowel intubation and as an antiemetic. The most common side-effects are somnolence, nervousness and dystonic reactions.

### pro-drug

A drug that enters cells more easily and once there, is converted to the desired active molecule.

### radiotherapy

The treatment of disease with ionizing radiation. Also called radiation therapy.

### seminoma

A malignant tumour of the testis arising from sperm-forming tissue.

### serotonin (5-hydroxytryptamine, or 5HT)

A monoamine neurotransmitter synthesized in serotonergic neurones in the central nervous system and **enterochromaffin cells** in the gastrointestinal tract.

### stereoisomer

An **isomer** whose bond structure is the same but whose atomic arrangement in space is different.

### tubular secretion

Transfer of materials from peritubular capillaries to the renal tubular lumen.

### von Bezold–Jarisch reflex

A cardiovascular decompressor reflex involving a marked increase in vagal (parasympathetic) efferent discharge to the heart, arising from stimulation of chemoreceptors, primarily in the left ventricle. This causes a slowing of the heart beat (**bradycardia**) and a dilatation of the peripheral blood vessels, which results in the lowering of the blood pressure. The concept was originated by von Bezold in 1867, and later revised by Jarisch in 1937.

### Wilm's tumour

A neoplasm of the kidneys that typically occurs in children. It is also known as a nephroblastoma.

### X-rays

Invisible, highly penetrating electromagnetic radiation of a much shorter wavelength than visible light, discovered in 1895 by Wilhelm Röntgen.

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Dr Gareth Sanger

Mr Wesley Miner

Professor Paul Andrews

### **Back cover, top to bottom**

Professor Hilary Calvert

Professor Kenneth Harrap, Dr Eve Wiltshaw

Professor Robert Naylor, Mr Wesley Miner,

Dr David Tattersall

Professor Andrew Thomson

