INNOVATION IN PAIN MANAGEMENT

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 12 December 2002

Edited by L A Reynolds and E M Tansey

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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 • Making the Human Body Transparent: The impact of NMR and MRI; Research in General Practice; Drugs in Psychiatric Practice; The MRC Common Cold Unit • Early Heart Transplant Surgery in the UK • Haemophilia: Recent history of clinical management • Looking at the Unborn: Historical aspects of obstetric ultrasound • Post Penicillin Antibiotics: From acceptance to resistance? • Clinical Research in Britain, 1950–1980 • Intestinal Absorption • Origins of Neonatal Intensive Care in the UK • British Contributions to Medical Research and Education in Africa after the Second World War • Childhood Asthma and Beyond • Maternal Care • Population-based Research in South Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit • Peptic Ulcer: Rise and fall • Leukaemia • The MRC Applied Psychology Unit • Genetic Testing • Foot and Mouth Disease: The 1967 outbreak and its aftermath • Environmental Toxicology: The legacy of *Silent Spring* • Cystic Fibrosis

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WITNESS SEMINARS:
MEETINGS AND PUBLICATIONS[1]

In 1990 the Wellcome Trust created a History of Twentieth Century Medicine Group, as part of the Academic Unit of the Wellcome Institute for the History of Medicine, to bring together clinicians, scientists, historians and others interested in contemporary medical history. Among a number of other initiatives the format of Witness Seminars, used by the Institute of Contemporary British History to address issues of recent political history, was adopted, to promote interaction between these different groups, to emphasize the potential 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 University College London from 1 October 2000. The Wellcome Trust continues to fund the Witness Seminar programme via its support for the Centre.

The Witness Seminar is a particularly specialized form of oral history, where several people associated with a particular set of circumstances or events are invited to come together to discuss, debate, and agree or disagree about their memories. To date, the History of Twentieth Century Medicine Group has held nearly 40 such meetings, most of which have been published, as listed on pages xi–xviii.

Subjects are usually proposed by, or through, members of the Programme Committee of the Group, and once an appropriate topic has been agreed, suitable participants are identified and invited. 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.

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

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

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.

ACKNOWLEDGEMENTS

‘Innovation in Pain Management’ was suggested as a suitable topic for a Witness Seminar by Dr Marcia Meldrum, who provided many of the names of individuals to be invited, and helped decide on the topics to be discussed. We are very grateful to her for her input. We also thank Dr Christina Faull for writing the Introduction to these published proceedings, and Professor David Clark for his excellent chairing of the occasion, and who read through earlier drafts of the transcript, and offered us helpful comments and advice. For additional help, we thank Professor Duncan Vere, Mr David Joranson and Professor Jan Stjernswärd.

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 and Mrs Tracy Tillotson of the Wellcome Library; Ms Julie Wood, who has supervised the design and production of this volume; our indexer, Ms Liza Furnival, and our readers, Ms Kathryn Merritt and Mr Simon Reynolds. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Dr Daphne Christie assist us in running the meetings. Finally we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

Lois Reynolds

Wellcome Trust Centre for the History of Medicine at UCL

HISTORY OF TWENTIETH CENTURY MEDICINE WITNESS SEMINARS, 1993–2005

1993 Monoclonal antibodies
Organizers: Dr E M Tansey and Dr Peter Catterall

1994 The early history of renal transplantation
Organizer: Dr Stephen Lock

Pneumoconiosis of coal workers
Organizer: Dr E M Tansey

1995 Self and non-self: A history of autoimmunity
Organizers: Sir Christopher Booth and Dr E M Tansey

Ashes to ashes: The history of smoking and health
Organizers: Dr Stephen Lock and Dr E M Tansey

Oral contraceptives
Organizers: Dr Lara Marks and Dr E M Tansey

Endogenous opiates
Organizer: Dr E M Tansey

1996 Committee on Safety of Drugs
Organizers: Dr Stephen Lock and Dr E M Tansey

Making the body more transparent: The impact of nuclear magnetic resonance and magnetic resonance imaging
Organizer: Sir Christopher Booth

1997 Research in General Practice
Organizers: Dr Ian Tait and Dr E M Tansey

Drugs in psychiatric practice
Organizers: Dr David Healy and Dr E M Tansey

The MRC Common Cold Unit
Organizers: Dr David Tyrrell and Dr E M Tansey

The first heart transplant in the UK
Organizer: Professor Tom Treasure

1998 Haemophilia: Recent history of clinical management
Organizers: Professor Christine Lee and Dr E M Tansey

Obstetric ultrasound: Historical perspectives
Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey

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

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

1999 Intestinal absorption
Organizers: Sir Christopher Booth and Dr E M Tansey

The MRC Epidemiology Unit (South Wales)
Organizers: Dr Andy Ness and Dr E M Tansey

Neonatal intensive care
Organizers: Professor Osmund Reynolds and Dr E M Tansey

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

2000 Childhood asthma, and beyond
Organizers: Dr Chris O'Callaghan and Dr Daphne Christie

Peptic ulcer: Rise and fall
Organizers: Sir Christopher Booth, Professor Roy Pounder and Dr E M Tansey

Maternal care
Organizers: Dr Irvine Loudon and Dr Daphne Christie

2001 Leukaemia
Organizers: Professor Sir David Weatherall, Professor John Goldman, Sir Christopher Booth and Dr Daphne Christie

The MRC Applied Psychology Unit
Organizers: Dr Geoff Bunn and Dr Daphne Christie

Genetic testing
Organizers: Professor Doris Zallen and Dr Daphne Christie

	Foot and mouth disease: the 1967 outbreak and its aftermath Organizers: Dr Abigail Woods, Dr Daphne Christie and Dr David Aickin
2002	Environmental toxicology: The legacy of *Silent Spring* Organizers: Dr Robert Flanagan and Dr Daphne Christie
	Cystic fibrosis Organizers: Dr James Littlewood and Dr Daphne Christie
	Innovation in pain management Organizers: Professor David Clark and Dr Daphne Christie
2003	Thrombolysis Organizers: Mr Robert Arnott and Dr Daphne Christie
	Beyond the asylum: Anti-psychiatry and care in the community Organizers: Dr Mark Jackson and Dr Daphne Christie
	The Rhesus factor and disease prevention Organizers: Professor Doris Zallen and Dr Daphne Christie
	Platelets in thrombosis and other disorders Organizers: Professor Gustav Born and Dr Daphne Christie
2004	Short course chemotherapy for tuberculosis Organizers: Dr Owen McCarthy and Dr Daphne Christie
	Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth Organizers: Sir Iain Chalmers and Dr Daphne Christie
	Public health in the 1980s and 1990s: Decline and rise? Organizers: Professor Virginia Berridge, Dr Niki Ellis and Dr Daphne Christie
2005	The history of cholesterol, atherosclerosis and coronary disease Organizers: Professor Michael Oliver and Dr Daphne Christie
	Development of physics applied to medicine Organizers: Professor John Clifton and Dr Daphne Christie

PUBLISHED MEETINGS

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

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

Technology transfer in Britain: The case of monoclonal antibodies
Self and non-self: A history of autoimmunity
Endogenous opiates
The Committee on Safety of Drugs
In: Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds) (1997) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 1. London: The Wellcome Trust, 135pp. ISBN 1 869835 79 4

Making the human body transparent: The impact of NMR and MRI
Research in General Practice
Drugs in psychiatric practice
The MRC Common Cold Unit
In: Tansey E M, Christie D A, Reynolds L A. (eds) (1998) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 2. London: The Wellcome Trust, 282pp. ISBN 1 869835 39 5

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

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

Looking at the unborn: Historical aspects of obstetric ultrasound
In: Tansey E M, Christie D A. (eds) (2000) *Wellcome Witnesses to Twentieth*

Century Medicine. Volume 5. London: The Wellcome Trust, 80pp.
ISBN 1 841290 11 4

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

Clinical research in Britain, 1950–1980
In: Reynolds L A, Tansey E M. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 7. London: The Wellcome Trust, 74pp.
ISBN 1 841290 16 5

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

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

British contributions to medical research and education in Africa after the Second World War
In: Reynolds L A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 10. London: The Wellcome Trust Centre for the History of Medicine at UCL, 93pp. ISBN 0 854840 77 X

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

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

Population-based research in south Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit
In: Ness A R, Reynolds L A, Tansey E M. (eds) (2002) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 13. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp. ISBN 0 854840 81 8

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

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

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

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

Foot and mouth disease: The 1967 outbreak and its aftermath
In: Reynolds L A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 18. London: The Wellcome Trust Centre for the History of Medicine at UCL, 114pp. ISBN 0 85484 096 6

Environmental toxicology: The legacy of *Silent Spring*
In: Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 19. London: The Wellcome Trust Centre for the History of Medicine at UCL, 132pp. ISBN 0 85484 091 5

Cystic fibrosis
In: Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 20. London: The Wellcome Trust Centre for the History of Medicine at UCL, 120pp. ISBN 0 85484 086 9

Innovation in pain management
In: Reynolds L A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 21. London: The Wellcome Trust Centre for the History of Medicine at UCL, 125 pp, this volume. ISBN 0 85484 097 4

The Rhesus factor and disease prevention
In: Zallen D T, Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 22. London: The Wellcome Trust Centre for the History of Medicine at UCL, 98pp. ISBN 0 85484 099 0

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

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

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Volumes 21–22 are available at www.ucl.ac.uk/histmed/witnesses.html
A paperback copy can be ordered from www.amazon.co.uk

Other publications

Technology transfer in Britain: The case of monoclonal antibodies
In: Tansey E M, Catterall P P. (1993) *Contemporary Record* 9: 409–44.

Monoclonal antibodies: A witness seminar on contemporary medical history
In: Tansey E M, Catterall P P. (1994) *Medical History* 38: 322–7.

Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–42)
In: P D'Arcy Hart, edited and annotated by E M Tansey. (1998) *Social History of Medicine* 11: 459–68.

Ashes to Ashes – The history of smoking and health
In: Lock S P, Reynolds L A, Tansey E M. (eds) (1998) Amsterdam: Rodopi BV, 228pp. ISBN 90420 0396 0 (Hfl 125) (hardback). Reprinted 2003.

Witnessing medical history. An interview with Dr Rosemary Biggs
Professor Christine Lee and Dr Charles Rizza (interviewers). (1998) *Haemophilia* 4: 769–77.

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

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

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

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

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

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

Professor Hal Cook – Director, Wellcome Trust Centre at UCL

Professor Mark Jackson – Centre for Medical History, Exeter

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

INTRODUCTION

It is a great privilege to have been asked to provide an introduction to this important and interesting Witness Seminar on innovation in pain management. In 1999 I spent a three-month sabbatical, awarded by the Wellcome Trust, at the Wellcome Institute for the History of Medicine [the forerunner of the Wellcome Trust's Centre for the History of Medicine, UCL]. My focus was to explore the influence of the discovery of the opioid receptors on the management of cancer-related pain.[1,2] I entered the work from a biomedical perspective and was soon immersed additionally in a world of beliefs and myths, psychology and the influence of personality, spirituality and religion, politics and law. I am delighted that this witness seminar has brought out flavours of all of these aspects of pain and its management and, indeed, has been honest enough to mention others such as human and corporate greed.

Pain management in the second half of the twentieth century was influenced, of course, by a wide variety of factors. Opium[3] had been utilized for pain relief for centuries and in 1805 morphine was isolated.[4] Salicylate as an anodyne (in the form of willow bark)[5] had been known about for nearly 300 years and its synthesized form was launched as aspirin by Bayer in 1899.[6] Bayer had just put diamorphine, its 'heroic' drug, on the market, thought to be superior to morphine, in that it was more effective, non-sedating and non-addictive.[7] Addiction was an ever-present issue. The invention of the hypodermic syringe in the mid-nineteenth century was in large part targeted at effective administration of narcotics, with the suggestion that this might avoid addiction. Florence Nightingale remarked:

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[1] Faull and Nicholson (2003).

[2] Faull (1999).

[3] Booth (1996).

[4] Huxtable and Schwarz (2001).

[5] Weatherall (1993).

[6] See www.aspirin.com/world_of_aspirin_en.html (visited 3 June 2004).

[7] Daly (1900).

> Nothing did me any good but a curious little new-fangled operation of putting opium under the skin which relieved one for 24 hours.[8]

However, addictive behaviour could not be avoided by this route of administration of narcotics, which lead to the coining of the word 'morphinism' for this new form of intoxication.[9] By the mid-1950s diamorphine had proved that it too could lead to addiction and there was great international debate about its continued medicinal use.[10]

Alongside these factors, Roselyne Rey discusses the innovations in science and explorations of anatomy and physiology in the nineteenth century, the tensions between the anatomical and physiological, the mental and the moral experiences of pain and the evolution of the conceptualization of pain within the framework of specificity theory.[11] The specificity theory dominated the approach to medicine in general, and pain in particular at the beginning of the twentieth century. By the 1940s this approach to pain was beginning to be challenged on the basis of both laboratory and clinical evidence. Sir Thomas Lewis's *Pain* was key in providing a rigorous exploration of clinical observations and experiments in pain in human beings.[12] The American surgeon William Livingston, in *Pain Mechanisms*[13] and the posthumously published *Pain and Suffering*,[14] subjected such evidence and the predominant framework for the understanding of pain, to clinical observational critique. He found that the experiences of his patients with nerve injury did not fit well with the specificity theory and he looked for other frameworks for pain, exploring concepts of neuromodulation, inhibition and gating, and temporal, spatial and summation patterning of stimuli. He was key to the field of pain research, theory and clinical practice that suddenly came alive in the second half of the twentieth century.

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[8] Porter (1997): 663. Florence Nightingale was bedridden for much of her adult life. Brucellosis has recently been proposed as the cause, see McDonald (ed.) (2001), 33–60.

[9] Arnold *et al*. (organizers) (1998).

[10] Faull and Nicholson (2003). Virginia Berridge has written extensively on opium use and addiction. See, for example, Berridge (1982).

[11] Rey (1995).

[12] Lewis (1942).

[13] Livingston (1943).

[14] Livingston (1998).

It is perhaps worthy of note that in the USA, innovations in pain in the 1940s and 1950s were fuelled by the work of clinicians with injured veterans of the war, especially the experiences of phantom limb pain and causalgia. Most notable of these were William Livingston and anaesthetists Henry Beecher and John Bonica.[15] In the UK, the stimulus to innovation in pain management has to a large extent been the plight of people with cancer.[16] As Dr Marcia Meldrum identifies in her overview to the Witness Seminar (pages 3–5), what united these people, with different backgrounds, different patient groups and different approaches, was a recognition that pain was more than a somatosensory phenomenon. The witness seminar takes the story on from this point in time.

The seminar explores evidence about innovations in the treatment of both cancer- and non-cancer-related pain – the use of drugs, cognitive behavioural approaches and nerve blockage. It also looks at global public health innovations in relation to cancer pain management, specifically the development and implementation of the WHO analgesic ladder and the worldwide use of morphine. It is an eclectic range and mix of evidence and oral history.

For me, some points of fascinating commonality emerge. The first is the role of serendipity in the development of innovation. For example, when Cicely Saunders went to work as a nurse at St Luke's Home for the Dying Poor, she noticed that the nurses ignored the prescription instruction of 'PRN'[17] and were administering morphine four-hourly, regularly.[18] This lack of compliance with or misinterpretation of doctors' instructions provoked the most important innovation in cancer pain management. When Cicely had her first major opportunity to share this innovation she had investigated the regular giving of morphine with more than 900 patients.[19] Another example, humorously portrayed by psychologist Chris Main, who coincidently worked

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[15] Baszanger (1998). See www.library.ucla.edu/libraries/biomed/his/bonica/index.html (visited 2 June 2004).

[16] Saunders' personal experiences were her major drive, but perhaps two key reports contributed to more global endorsement and provided the fertile ground for the hospice movement to grow, including the provision of research funds for pain research. See Joint National Cancer Survey Committee (1952); Glyn Hughes (1960); Clark (1999).

[17] See note 11, on page 6.

[18] Dame Cicely Saunders, pages 6–7. RSM (1963).

[19] Saunders (1963).

just down the corridor from orthopaedic surgeon Gordon Waddell, is the serendipitous failure of Main's initial research project, which lead to a highly creative innovation in pain management programmes in chronic back pain.[20]

Secondly, there are the examples scattered throughout the seminar of attitudes to pain and its management by the seminar participants' professional colleagues:

> It was a matter of patients being rendered so that they didn't know what they were doing, by doctors who certainly didn't know what they were doing.[21]
>
> You can't control pain without killing the patient.[22]
>
> Despite…awareness of palliative care…staff had very low expectations of what could be achieved in their own area of care...there was neither the knowledge nor the vigour to address the problem.[23]
>
> I enquired why narcotics were not available to men and was told that men don't need powerful drugs like that.[24]
>
> I could smell the fear of addiction in America.[25]

Medical textbooks and papers in the 1960s and 1970s additionally convey the enormous extent of misperceptions about pain and fear of narcotic analgesics.[26]

The third point is the oft-repeated statement that pain is a sensory and emotional experience. Despite the audience being in full agreement, there is still a clear challenge to the perspectives that each disciplinary branch has taken. For example, Saunders refers to her anaesthetist colleagues as 'blockers' and this is mildly rebuffed by Jan Stjernswärd.[27] Although they were using this term in two different senses, the interchange seems to me to be revealing. Main

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[20] Professor Main, page 31.

[21] Professor Vere, page 15.

[22] Professor Vere, page 15.

[23] Mrs Raiman, page 18.

[24] Professor Bond, page 21.

[25] Mr Joranson quoting Dr Twycross, page 49.

[26] See Faull and Nicholson (2003); Faull (2000).

[27] Dame Cicely Saunders, page 11, and Professor Stjernswärd, page 43, who refers to a person who inhibits progress.

indicates his concern that the cancer pain management movement has paid little attention to integration of the science and techniques of cognitive behavioural approaches to pain, using instead a predominantly pharmaceutical approach.[28] On several occasions David Clark endeavoured to deepen discussion about connectivity and division between the parallel worlds.[29]

Fourthly, consider the insight into the manner in which individuals played their roles in the achievement of innovation. Obviously there is the factual report of what happened, but the personal style of operation is also revealed to some extent. For example, Robert Twycross (page 26) ensures that he gets across points he thinks are of particular importance even if unrelated to the question the question under discussion; Main recounts very colourful and reflective pictures of how things came about;[30] Saunders and Jennifer Raiman relate their thoughts to the patients' experiences;[31] Saunders' innovations have been enabled by social contacts and other networking;[32] Sir Michael Bond has followed a path dictated by his health;[33] Mark Swerdlow, David Joranson and Stjernswärd have worked to bring people together to improve effectiveness and dissemination of innovation.[34]

The interrelationships, the geneology of innovations in pain management, if you like, between the witnesses and others involved is fascinating – who worked with whom; who met whom where and the impact it had. Small world networks is a modern science, but one that has greatly influenced the development of the world of pain management. One example is the battle,[35] briefly alluded to in the seminar, between the UK and the USA with respect to the evidence that morphine given orally was effective:

> They were all certainly very polite to me but I think they were fairly unconvinced.[36]

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[28] Professor Main, pages 1, 34–35.

[29] Professor Clark, page 11 and page 34.

[30] See page 31.

[31] See pages 6 and 18.

[32] A further exploration of this theme can be found in Clark (1998).

[33] See page 11.

[34] See, for example, pages 10, 39–48 and 52–59.

[35] This is discussed in more depth in Faull and Nicholson (2003) and Meldrum (2003a).

[36] Dame Cicely Saunders, page 7.

As Meldrum's overview identified the coming together of those working in the pain field did far more than reduce the sense of isolation for practitioners. The growing understanding of all involved of the complexity of pain demanded integrated research and practice from a range of specialities. It was upon this basis that Wall and Bonica founded the International Association for the Study of Pain in 1973 and the multiprofessional journal *Pain* in 1976.[37]

Of course, the seminar is not comprehensive in its discussion of pain innovations in this period, nor in the witnesses that were present. One facet that is particularly underexplored is that of the neurosciences. The lack of exploration of the innovations in models of pain and analgesia, the placebo response, the identification of opioid and other receptors and ligands and neuromodulatory techniques, such as transcutaneous nerve and dorsal column stimulation and acupuncture, leave a notable gap. This can be usefully investigated separately, but I think it its absence indicates what little influence that laboratory innovation has had on clinical innovation. For instance the celebrated discovery of the endogenous opioid receptors and ligands[38] had resoundingly little impact on clinicians at the time, nor has it lead to innovation in pain management in the subsequent 25 years.[39] Or is it that it is too subtle to be overtly recognized? A clear example of how neuroscience has directly influenced pain management is in spinal analgesia where, subsequent to the discovery of opioid receptors in the spinal cord, the spinal infusion incorporated opioid drugs in addition to the traditional local anaesthetic.[40] The gate theory of pain[41] and the enormous body of work of Patrick Wall influenced and challenged both professional and public understanding of the physical and somatosensory experience of pain, and this is mentioned in this seminar (pages 23, 37 and 68) and an informative interview with Wall is attached as Appendix 1. However, exploitation of the context and impact is not detailed in a way that usefully explores its historical positioning in influencing innovation in pain management from the breadth of perspectives of the witnesses.

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[37] Natas (1996); Wall (1986). See also Wall interview on pages 73–82.

[38] Tansey and Christie (1997).

[39] See also Faull and Nicholson (2003); Faull (1999).

[40] Cousins (2003).

[41] Melzack and Wall (1965). See www.library.ucla.edu/libraries/biomed/his/painexhibit/panel6.htm (visited 3 June 2004).

It is my hope that this introduction will excite readers to learn more about development and change in pain management through the format of oral history and debate among key players in that history. An unexpected gain for me was that the seminar made me laugh out loud at more than one point! Professor Main's statement that psychologists would rather use each other's toothbrushes than each other's questionnaires[42] helps me to understand my colleagues and their culture just a little, but more important, to reflect on the complexity of developing an effective evidence base and tool kit that is most helpful for clinicians and patients.

Christina Faull

Consultant in Palliative Medicine, Leicestershire and Rutland Hospice and University Hospitals of Leicester.

[42] Professor Main, page 32.

INNOVATION IN PAIN MANAGEMENT

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 12 December 2002

Edited by L A Reynolds and E M Tansey

INNOVATION IN PAIN MANAGEMENT

Participants

Professor Sir Michael Bond
Professor David Clark (Chair)
Dr Niki Ellis
Dr Peter Hunter
Dr Jeremy Johnson
Mr David Joranson
Dr Leon Kaufman
Dr Suresh Kumar
Professor Chris Main
Dr Alex Nicholson
Dr Colin Murray Parkes
Mrs Jennifer Raiman
Dame Cicely Saunders
Professor Jan Stjernswärd
Dr Mark Swerdlow†
Dr Robert Twycross
Professor Duncan Vere
Professor John Walker-Smith

Among those attending the meeting: Sir Christopher Booth, Mrs Rachel Gibson, Dr Eva Kidd, Dr Beth Murinson, Dr Bill Noble, Dr Silvia Paz, Dr Jane Seymour, Dr Michael Wilkinson, Dr Michelle Winslow

Apologies include: Dr J Edward Charlton, Professor Tony Dickenson, Dr Christina Faull, Dr Kathleen Foley, Professor Geoff Hanks, Dr Douglas Justins, Professor Desmond Laurence, Professor Henry McQuay, Professor Peter Nathan,‡ Dr Doug Robbie, Dr Ada Rogers, Professor Vittorio Ventafridda, Dr Chris Wells

† Died 26 February 2003

‡ Died 5 December 2002

Professor David Clark: It's a great pleasure to be here as your Chair for the afternoon. Like many of you, I have not been to one of these events before and I think we are all coming to it with a little trepidation. I am going to first of all invite Dr Marcia Meldrum, who is a historian of medicine at the University of California, Los Angeles (UCLA), to start the afternoon off for us with a brief overview of the entire field that we then hope to explore in more detail as the discussion progresses.

Dr Marcia Meldrum: Thank you, David. Well, I think the one thing we need to start off by saying is that, indeed, physicians didn't start working to relieve and manage pain in 1945, but that they have always done so. But in the late 1940s and the 1950s, there was a group of innovators in several specialities and several different countries, who redefined pain in the clinical setting, as more than a somatosensory phenomenon, more than a symptom of underlying disease. And with their recognition that human pain had to be understood in the individual patient, with all the complexity of factors that entailed, they laid the groundwork for our present understanding. Just to mention a few of these, all these names are well known to you, I am sure: Henry Beecher[1] and John Bonica[2] in the US, Cicely Saunders and Mark Swerdlow in the UK, Willem Noordenbos in the Netherlands, Paolo Procacci in Italy.

Initially I think, and particularly for the individuals themselves, it seemed as if they were isolated voices in the wilderness, but over time people began to learn of each other's work, they began to write to each other and to visit. I believe the first formal organization of clinicians interested in pain was brought together in 1967 here in the UK by Dr Mark Swerdlow.[3] As I am sure you all know, John Bonica had the vision of an interdisciplinary pain organization to bring together scientists and physicians. The necessity of such a group appeared to him to be two fold. First, that pain was so complex a phenomenon, involving the patient's sensory, cognitive, affective, and behavioural systems that demanded research from virtually every speciality, and certainly from both basic researchers and clinical researchers, utilizing both types of skills and expertise.

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[1] Beecher (1946, 1959).

[2] Bonica (1953).

[3] The Pain Society, founded in 1967 as the Intractable Pain Society, is the representative body for all healthcare professionals and basic scientists involved in the management and understanding of pain in the UK. For further details of its formation, which is also the the British chapter of the International Association for the Study of Pain (IASP), see www.painsociety.org/pain_what_is.html#form (visited 13 May 2004). See also page 10.

But second, pain seemed, at this point in the early 1950s when Bonica began his work, so neglected and marginalized as a problem within medicine, that he saw it as a political necessity to build a critical mass with the collaboration of workers from many fields. It was also part of Bonica's vision that this be an international field, and he worked consistently not only in the US, his adopted country, but also in Italy (which was his homeland), as well as contacting and working with other clinicians and scientists around the world. In the late 1960s, I think, he formed probably his most crucial alliance with the British physiologist Patrick Wall, who is also, I think, known to everyone here.

As you probably know, the founding meeting of the International Association for the Study of Pain (IASP) took place in May 1973, in the small community of Issaquah, near Bonica's hometown, Seattle, Washington. But you may not know that there was a series of meetings leading up to this where Bonica met with colleagues in a number of countries; and probably the most crucial of these took place in April 1973, only a month before Issaquah, at a meeting organized by Dr Wall in Jerusalem. It was called the Bat-Sheva Seminar on Pain Mechanisms and Therapy. And John Bonica, Ronald Melzack, and Willem Noordenbos all travelled to Israel for that meeting, as did Harold Merskey. In the correspondence[4] planning that trip, we also see Wall and Bonica planning their strategy for the foundation of the IASP at the Issaquah meeting to follow a month later.

There seem to have been three main trends or developments in pain relief. In the 1950s Bonica and a number of colleagues would refine the techniques of the anaesthetic block, originally introduced by René Leriche in the First World War,[5] a less drastic alternative to neurosurgery, but the principle was the same, to disable the sensory pathways and prevent pain information from reaching the brain. In the 1960s a number of psychologists and psychiatrists – here I only mention a couple of names, Bill (Wilbert) Fordyce at the University of Washington and Richard Sternbach in San Diego – began to develop behavioural methods of pain management, ways to try to utilize the body's own, the mind's own defence mechanisms to help manage pain and to help the

[4] The correspondence concerning the Bat-Sheva Seminar (Box 21, Folder 28) and the planning of the Issaquah meeting (Box 6, Folder 129) can be found in the John J Bonica Papers, held in the John C Liebeskind History of Pain Collection, Louise M Darling Biomedical Library, University of California, Los Angeles. The collection also includes oral history interviews with John Bonica, Kathleen Foley, Ainsley Iggo, Ronald Melzack, Cicely Saunders, Richard Sternbach and Patrick Wall.

[5] Leriche (1939).

patient to function effectively despite his pain.[6] But the chief hope of patients and clinicians remained a better analgesic, a drug that would free the patient from subjection to pain, without altering his life.

At the start of this period in the late 1940s there was much hope placed on the development of a non-narcotic analgesic, a variant of the morphine molecule which would control pain without its well-known gastro-intestinal, respiratory and cognitive effects.[7] Many, many such compounds were isolated and tested, but by the 1970s, however, it became clear that none of the new drugs was superior to morphine, and that quite a few were indeed worse; and as a number of people in this room have shown, what was needed was not to replace morphine, but to come to know it much better and more intimately than we had.[8] And although there are a number of new pharmaceuticals, we haven't solved the problem of pain for all patients, but today at least we hope to learn more about how much has been done in the last 50 years.

Clark: I am going to invite Dame Cicely Saunders to begin the discussion and perhaps with a reminder of that famous phrase, 'There's so much more to be learned about pain'.[9]

Dame Cicely Saunders: I am very honoured to start and, of course, I must begin by saluting John Bonica, whose ground-breaking, multiprofessional approach really goes back to 1947, according to his obituary,[10] when he involved a nurse and a neurosurgeon to join his team in Washington state. And his career after that is an epic. I expect we will hear more about his books, his lectures, his conferences and everything else. But it is a wonderful story.

At about the same time, in March 1948, I was impelled by the stories of my patients that I had experienced first as a nurse, but most of all as a social worker. I knew I had to do something about end-of-life pain and I went, as a State Registered Nurse (SRN) volunteer, to one of the early homes. There I found that the nurses seeing the prescriptions of morphine four-hourly

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[6] For example, Fordyce *et al.* (1968).

[7] Constipation, respiratory depression, cough suppression, urinary retention, nausea, vomiting and tolerance, along with drowsiness, are adverse effects associated with opioid analgesics.

[8] Twycross (1977); Clark (2002): 252.

[9] Professor David Clark wrote: 'It was said to Dame Cicely by the surgeon Mr Barrett when encouraging her to go and read medicine in 1951.' E-mail to Mrs Lois Reynolds, 24 June 2004.

[10] Loeser (1994).

'PRN'[11] by the doctors, quite quietly took 'PRN' off and gave the drug four-hourly, so as to prevent pain ever happening. This regular oral four-hourly giving of morphine dates back to 1935, fairly soon after the Brompton cocktail was put together.[12]

Now I was very impressed by this, because the patients were so much better with the pain control than the ones I had seen in hospital before then. During that time I took Mr Norman Barrett, the surgeon I was working for, to see this, and to visit a patient at home and so on. When I said to him, 'I am going to have to go back and nurse the dying somehow,' he said, 'Go and read medicine. So many doctors desert the dying, and there's so much more to be learnt about pain, and you will only be frustrated if you don't do it properly, and they won't listen to you.'[13] So I did read medicine and eventually arrived in 1958 at St Mary's Hospital Medical School in the department of pharmacology under Professor Harold Stewart, who had found a grant for me to look at St Joseph's Hospice on the nature and management of terminal pain.[14]

Going there, which was virtually untouched by medical advance, I was able to introduce records and the regular giving [of morphine] which they hadn't started, and according to one of the sisters of the ward that I was first in, it was the change from painful to pain-free. Having been given four patients to look after, I was soon looking after every admission into those 45 beds. So I began keeping records in detail, pre-computer, on a punch card system, and making tape recordings of patients talking about their pain from 1960, and I realized that what we were looking at was what I described later, in 1964, as total pain.[15] And I will quote from one patient, when I said to her, 'Tell me about your pain, Mrs H.' She just said,

> Well, doctor, it began in my back, but now it seems that all of me is wrong. I could have cried for the pills and the injections, but I knew that I mustn't. Nobody seemed to understand how I felt, and

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[11] PRN [*pro re nata*] indicates analgesic drugs to be administered as needed or as requested.

[12] The Brompton cocktail, a mixture of morphine and cocaine, is used to relieve pain in terminal cancer patients, originally developed at the Brompton Chest Hospital, London, in the 1920s. The formulations vary, but typically it contains 15mg of morphine hydrochloride and 10mg of cocaine hydrochloride per 10ml of the cocktail. See also Robert Twycross on page xx.

[13] du Boulay (1984): 60–8.

[14] For a selection of Dame Cecily's letters from 1959 to 1999, see Clark (2002).

[15] Saunders (1964).

> it seemed as if the whole world was against me. My husband and son were marvellous, but they would have to stay off work and lose their money, but it's so wonderful to begin to feel safe again.

And so she has really talked about the physical, the psychological, the social, and her spiritual need for security to look at who she was, coming to the end of her life. And for another patient it was, 'All pain and now it's gone, and I am free'.

So I spent a lot of time in the Royal Society of Medicine library, looking up everything I could find about pain, and found one of the very important books, by F J J Buytendijk, a Professor of Psychology from the Netherlands on pain,[16] but very little in the textbooks, as Bonica has frequently told us,[17] nothing except for anecdotes about avoiding strong drugs as long as you can, and the problems of tolerance and addiction. But I knew from the work that we were doing that that need not be a clinical problem, and when I presented this in a paper to the Royal Society of Medicine (RSM) in 1962, I had 900 patients that I could refer to and talk about the doses that they had taken and shown no tolerance, no drug dependence, alert and cheerful patients, and I quote from what was in the *Proceedings* the next year: 'It is not possible to treat pain in isolation. We have to consider the whole person'.[18] I could state very firmly that oral morphine works, that is if it is given regularly, balance the need and with the many adjuvants that came on board during the 1950s.

And after this I went over to the US in 1963 and met Dr Beecher, Dr Lasagna, and Houde and Wallenstein who were doing their own clinical trials, but mainly by injection and mainly single-dose studies,[19] and also in Boston I met D E Weissman who was looking at end-of-life psychological pain. They were all certainly very polite to me, but I think they were fairly unconvinced. But as Patrick Wall wrote in 1986,

> The old methods of care and caring had to be rediscovered and the best of modern medicine had to be turned to the task of new study and therapy specifically directed at pain.[20]

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[16] Buytendijk (1961).

[17] Bonica (1953).

[18] Saunders (1963); RSM (1963).

[19] Houde and Wallenstein (1956).

[20] Wall (1986): 1.

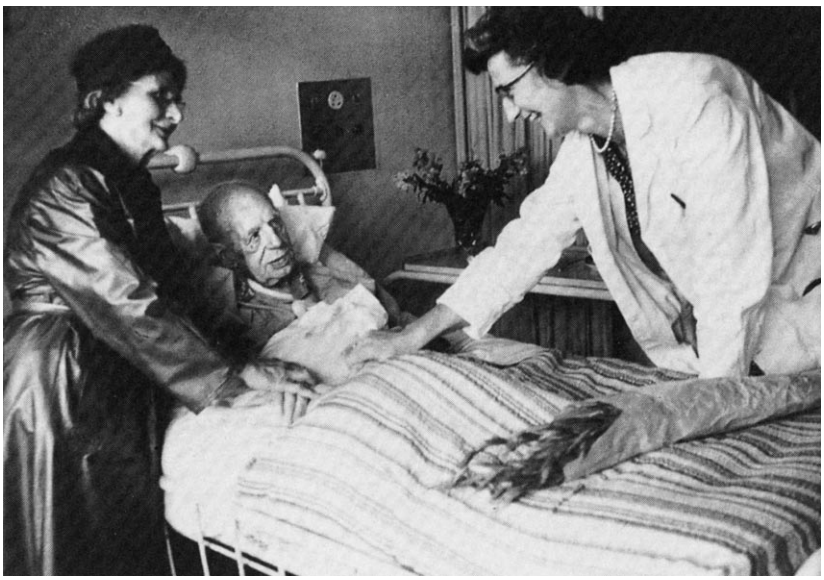

Figure 1: Dr Cicely Saunders and two patients at St Joseph's on their golden wedding anniversary, 1960.

And I was very glad to have links with him from the 1970s. He spent five days going round our wards, as if it were bird-watching. It was absolutely fascinating to see how he spotted the one patient who had the chronic pain syndrome and how different he was from nearly everybody else. But he was certainly another giant figure.[21]

In 1967 St Christopher's Hospice was opened in Sydenham, London, as the first research and teaching hospice. Later we welcomed Robert Twycross, and I had a grant waiting from the Department of Health and Social Security (DHSS) to compare morphine and diamorphine. Robert [Twycross] came to us in 1970 and did the extensive trials in great detail,[22] which I hope he will be able to talk about later, and reaffirmed that tolerance and addiction were simply not clinical problems with practically every patient. But I did know that your enthusiasms have to be tested and also that we were getting better at everything so that the controls with in-patient study were really important, because you were then able to say, 'It's not the drug that you use, it's the way

[21] See Appendix 1 for an extract from a Physiological Society interview with Pat Wall by Martin Rosenberg and Steve McMahon on 5 February 1999.

[22] Twycross (1977).

that you use it that really matters'. And my aim had been to establish a simple transferable regime that could be translated with well-known drugs across the world, and used with the simplicity which we had shown can be handed on, and this was of course picked up by the World Health Organization (WHO), which I am sure we will hear about later.[23]

But I have to say that this crusade is simply not over. The drugs are withheld and other manoeuvres are not always considered and, as Patrick Wall wrote in his introduction to the fourth edition of the *Textbook of Pain*, 'Pain, for me, arrives as a complete package,'[24] and that demands a team approach. Bonica pioneered it, and I did write to him in 1966, which was when I first got in touch, saying that I wanted to learn more about what he was doing. But we both wanted what we knew to be made available to everybody in need. There is plenty still to do. I would like to finish by saluting Peter Nathan, who died last week and whom I tracked down and who in 1952 had an article in the *British Medical Journal*, which I have dug out of my records.[25] He showed that most patients with severe pain can take large amounts of these drugs without becoming addicts, and if their pain is relieved surgically, they will not ask for these analgesic drugs. And pain can be relieved not just surgically, but by a whole-team approach and by listening to their story. 'It was all pain, but now it has gone' is one of the best things you can hear.

Clark: Peter Nathan sadly had given his apologies for this meeting and, as we have heard, died just last week. Could I ask Dr Mark Swerdlow to continue on from there, with some reflections from around that same period, in the late 1960s in particular.

Dr Mark Swerdlow: If I may go back a bit further to 1884 when Carl Koller demonstrated that injecting cocaine would produce local anaesthesia. For a patient with severe pain to have an injection and for the pain to magically disappear is such a conjuring trick, except of course that in no time at all the pain was back, because local anaesthetics don't last very long. So we then move on to 1901 when Rudolf Schlosser injected alcohol on to nerves and that gave a rather more lasting relief. Following from that surgeons, particularly in

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[23] See page 43.

[24] Wall and Melzack (eds) (1999): 3.

[25] Nathan (1952): 907. Morphine was compared with pethidine, amidone, phenadoxone and Höchst 10581 (hexanone) in 75 patients for equianalgesic dosage, duration of effect, toxicity and adverse effects.

Germany and the US, set up clinics where they injected alcohol on to nerves to relieve pain. For quite a little while they were busy doing that, until they found that there were all sorts of surgical operations that were far more interesting and remunerative and they gave up that practice. Anaesthetists became the ones who injected solutions on to nerves for pain relief.

But it's not surprising, then, that in the US in 1936 Emery Rovenstine opened the first pain clinic ever and this was purely a nerve block clinic.[26] In 1948 John Bonica opened one and quite a few other anaesthetists in America opened this style of pain-relief clinic. Now because of the Second World War, the idea of a pain-relief clinic [was widespread] and most of us used the principle of it, [although its practice] didn't spread outside the US; in fact, you might be interested to know that in 1947 the first pain clinic in Europe was opened here in London at University College Hospital (UCH). Later, a few more were opened in various parts of England.

In 1954 I had a year's experience of this new phenomenon in a pain clinic in Pennsylvania. I found it quite fascinating and went back home to England and opened my own pain clinic as a regular session in 1959. There were quite a few clinics opened here and there in England, and by 1960 I wished that there was some way in which one could meet colleagues and discover what they were doing, what sort of complications they were getting, what sort of patients they were treating in their pain clinics, to get some joint information going.

So in 1967 I invited everyone I knew in the pain field in England – there were 29 pain clinics in all – to the University of Manchester at Salford Hospital to a discussion meeting. Seventeen of the 29 actually came and we had a splendid day's discussion which everyone thoroughly enjoyed and, I think, benefited from. At the end of the day they unanimously voted that we should repeat this process the following year and in fact each year thereafter, and that was the start of the Intractable Pain Society of Great Britain. At first it was simply a sort of club, and then in 1974 we formally made it into the Intractable Pain Society, which was, in fact, the first national pain society in the world.[27] I think we all learned a great deal from it, and, of course, not so many years later the International Association for the Study of Pain (IASP) opened on an infinitely bigger scale and it has proved to be enormously beneficial to all those in pain

[26] Nacht (1993).

[27] See note 3.

relief. I think the multidisciplinary idea, which John Bonica started, improved the whole system very much and the pain clinic movement has been extremely valuable. I am glad we are having this meeting today where we can discuss this.

Clark: Could I ask if there were connections between these two worlds of hospice and pain?

Swerdlow: Well, certainly we were informed and perfectly well aware of both of them and there was a lot of intercourse between people who worked in both. Some people, of course, literally worked in both but, yes, there was an enormous amount of throughput between the two.

Clark: Dame Cicely, would you like to add to that?

Saunders: Peter Gautier-Smith from the National Hospital for Neurology and Neurosurgery in Queen Square, London, came and did injections for a few of my patients at St Joseph's [Hospice, Hackney, London]. And when we opened St Christopher's in 1967 Dr Robbie came from the Royal Marsden, London, so we have always had a blocker, as it were, around. What we found was that we used them better, but less often.

Clark: Would Sir Michael Bond like to offer us some thoughts at this stage?

Professor Sir Michael Bond: My beginnings were different again and were driven, strangely, by my health. I set out in life to become a general surgeon and I was only into the training about 18 months when I developed eye problems and had to cease. But during that 18 months at the University of Sheffield my research project concerned the use of cancer chemotherapy agents of various kinds, and I did my work on wards for both women and men and noticed, in passing, the poor way in which people were treated for their pain. It wasn't my duty to deal with that side of things at all, I was collecting information about the effects of the chemotherapy, but I did notice this. When I had to leave surgery and do something in which my eyesight would not be important, relatively speaking, I went into psychiatry. You can work in psychiatry without actually seeing people, can look at them, but you don't have to see them. I didn't reach that point thankfully, but I was very anxious to find a bridging project between what I had been doing and the new world that I had entered.

It so happened that the Professor of Psychiatry in Sheffield at the time was a man called Erwin Stengel, who was Viennese and who, in his early days of training, had connected with Freud. So in a strange kind of way I had this tenuous link to Freud that goes back to the late nineteenth century. Stengel

came to the Maudsley Hospital, London, and eventually became Professor of Psychiatry in Sheffield.[28] In the same department there were two people who are now major figures in the world of pain seen from a psychiatric perspective, Harold Merskey and Issy Pilowsky. When I said that I would like to study pain in women with carcinoma, they were a great help.

Now, I realize in retrospect that all of us were at the tail end of what you might call the 'psychosomatic movement' which in itself had connections with the Freudian psychodynamic world, because Merskey was studying hysteria, Pilowsky was studying hypochondriasis and I wanted to study the relationship between certain personality characteristics and pain in the women with cancer.[29] The selected vehicle was a personality construct known as the Eysenck construct of personality, which has three dimensions. The two that were important were neurotic–normal and extrovert–introvert. The studies on the women showed that there were differences in the way in which they behaved when in pain, and indeed whether they had pain or not, and the two constructs. This prompted Merskey and Pilowsky to start thinking about pain in relation to their own work.

Pilowsky, who was looking at hypochondriasis, developed what was called the Whitely Index of hypochondriasis and you can still come across that in the literature today.[30] And from that he went on to develop the Illness Behaviour Questionnaire, linking up in due time with the work of Bill Fordyce and others.[31] We have heard about Bill Fordyce earlier. He was, I think, an occupational psychologist who worked in Seattle [Washington] and was roped into the pain circuit there and put forward the notion that behaviour theory could be applied to people with chronic pain disorders. In fact, it wasn't long after that that it was appreciated that people are not just behaving animals, they have thoughts as well, and of course that led on to the incorporation of cognitive theory and so we came to cognitive behavioural therapy eventually.

But going back to the days in Sheffield, Harold Merskey became interested in pain and wrote his MD thesis and a book on the subject of hysteria,[32] [and later] became interested in other psychiatric abnormalities and pain. He wrote

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[28] See biographical note on page 110.

[29] Bond and Pilowsky (1966).

[30] Bond (1971).

[31] Fordyce (1982).

[32] Merskey (1964, 1967).

at some length about depression and pain and the occurrence of psychiatric disorders in neurological clinics and in general practice, and the presence of pain. At that time Sheffield produced three people[33] who went on for the rest of their working lives in the pain field. Pilowsky is now retired and he had become Professor of Psychiatry in Adelaide, and now lives in Sydney. Merskey went to Canada and became Professor of Psychiatry in London, Ontario.

Merskey has been, I have to say, by far the most productive, because he is the person who was responsible for leading the group within IASP that defined pain. I am sure everybody here is familiar with the IASP definition of pain.[34] He was also the driving force behind the taxonomy of pain that IASP produced, and he has contributed significantly in a scholarly way to our understanding of pain and the history of pain.[35] Harold is a figure of great significance. That's where it started and I think we realized back in the 1960s, because in general psychiatry there was an interest in behaviour therapy that emerged at about that time, that the future of pain management by psychological means lay in this particular methodology. It was taken up quite rapidly and it was appreciated particularly when Bill Fordyce came along slightly later, that the technique had promise for the management of certain pain problems.

I think that's where my interest in pain started. I did eventually link up with St Christopher's Hospice through a chap called Ken Calman (now Sir Kenneth, the Vice-Chancellor of Durham University and until not long ago was a high 'heedjun', as they say in Scotland), in the Department of Health in England. He was Professor of Oncology in Glasgow at one time.[36] I went with him to St Christopher's on a number of occasions and that proved very fruitful. I set up a clinic for the treatment of patients with chronic pain that appeared to be driven more by psychological than physical factors, I think, in the late 1970s–early 1980s. There may have been one other like it in Manchester about that time or even before, but I couldn't say for sure whether that's the case, but it was certainly one of the first clinics of that kind.

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[33] The third person is the speaker, Professor Sir Michael Bond.

[34] Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is always subjective. Further details can be found at www.iasp-pain.org/terms-p.html (visited 19 January 2004).

[35] The definition of pain appears in Merskey (1979), later classified by the IASP Subcommittee on Taxonomy in Merskey (ed.) (1986), updated in 1990.

[36] See biographical note on page 103.

One of the students we had in the department was Professor Chris Main, who is sitting just here in front of me. He has carried out a great deal of work on pain and in particular with an orthopaedic surgeon, Gordon Waddell.[37] I am sure he will tell you all about it in due course. It was an unusual pairing to have an orthopaedic surgeon and a psychologist working together, as their languages are by and large totally different. Like speaking to an Eskimo I should think. They had a very fruitful union over the years with respect to problems associated with back pain.

Clark: Thank you. We have got three lovely vignettes there all in the 1950s and 1960s. I wonder if I could broaden it out and invite one or two others to comment on that period or perhaps to ask a question. But can we just stay in that general territory of the 1950s and 1960s and reflect a little bit more on what was happening then. Would somebody like to say a little bit more?

Dr Leon Kaufman: I came to University College Hospital (UCH) in 1954 and I want to endorse the comment made by Dr Swerdlow that there was really a pain clinic in existence then, but it was a very half-hearted event. It was a block once a month, because there was no demand for it, and patients were just sent there as a last resort. There was an interest at that time in phantom limb pain. We are actually talking about pain as if there's only one kind of pain. There's acute pain, chronic pain, there's reflex sympathetic dystrophy and so forth. It's a very wide field. But they were also looking at trying to prevent phantom limb after amputation and the question was discussed whether in fact it was better to do the amputation under spinal analgesia rather than general anaesthesia. Some people felt that if you anaesthetized someone for, say, three or four hours after the operation, the phantom limb wouldn't appear. That was discredited when further studies were undertaken.

At the pain clinic, we had Professor Wall who got interested, we had a neurologist and an anaesthetist and that went very well, and now in fact it is run by an anaesthetist, Dr Baranowski [Andrew Baranowski, Head of Non Acute Pain Research of University College London Hospitals], between UCH and the Middlesex. I can emphasize one thing about Peter Nathan, who was a great man on injecting phenol. And he wrote a very interesting paper, nothing to do with pain. It appeared in the *Lancet* in 1967 and was prompted by the fact that after his mother had an operation on her hip performed by an orthopaedic surgeon, she developed avascular necrosis. He was told it was a

[37] See, for example, Waddell *et al.* (1984, 2003).

very unusual complication and he was very inquisitive and researched information from a lot of orthopaedic surgeons and found that each often had at least one or two cases, so it wasn't such a rare complication. That's why the paper was entitled, 'When is an anecdote?'[38]

Professor Duncan Vere: I think you [David Clark, Chair] asked me to comment on concepts and management. I suppose I saw the thing particularly from the general hospital and general practice standpoint. I will say that until about 1965 in hospitals – general hospitals and general practice – there was entrenched ignorance, a tremendous amount of severe pain. Patients who were in severe pain, or dying with pain, were often given the Brompton cocktail (or *Mist. Obliterans*, as it was politely known), and it was a matter of patients being rendered so that they didn't know what they were doing, by doctors who certainly didn't know what they were doing. They were using medicines with actions that they couldn't understand, because they had this complex mixture of cocaine, morphine, gin, sometimes with phenothiazine added.[39]

Parsimony was the order of the day, which rendered control impossible. Pain breakthrough was frequent and intermittent control of course is disastrous, if only for the reason of the self-augmentation of pain. Hospice care had of course begun, and all that Dame Cicely has said was known in principle, but somehow it didn't seem to have come across into the general medical and surgical field in hospitals and general practice. And we wrote a paper on 'The hospital as a place of pain' at that time.[40] Well, the hospice concepts were continuous effective pain control, without blotting out the patient necessarily, and driven very much by a Christian ethical concept of care for persons without denial of their personality. But we had the lawyers continually barking in the wings. One particular professor from Cambridge used to preach that you can't control pain without killing the patient;[41] and, [that is especially true]

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[38] Nathan (1967).

[39] On the Brompton cocktail, see Clark (2003); also note 12. On the use of phenothiazine, see Clark (2002): 206–8.

[40] Vere (1980).

[41] Professor Duncan Vere wrote: 'The professor was Professor Glanville Williams (1911–97), Rouse Ball Professor of English Law in the University of Cambridge from 1968 to 1978, later Professor Emeritus. He suggested that death was inevitable if pain control were to be gained, and that this would probably be seen by the courts as an offence in law; this was one reason for the parsimony in opiate medication to which I had just alluded. Glanville Williams was also Vice-President of the Voluntary Euthanasia Society.' Letter to Mrs Lois Reynolds, 20 February 2004.

of course, if you use mixtures in the way that we did, it was the partial truth; but it need not have been so.

So – mechanisms for continuous pain control: I think there were four key concepts. The first was the reduction of the problem to its simplest elements, and this is where I think Robert Twycross made such a tremendous contribution, he came as a research fellow in our department and realized that it was impossible to control pain sensibly with mixtures. He set about asking the simple questions: What is the relative potency of morphine and of diamorphine? What may be done to use these drugs so that cumulation[42] can occur without intoxication?, and so on. He will no doubt say more about this.

The second important idea was separating drug actions by accurate dosage. Respiratory depression is not a problem if you keep the dose range within that for pain control.

The third important concept was how to gain cumulation of a short-acting drug like morphine. Morphine and diamorphine were then the only effective drugs against severe pain apart from methadone, but more of methadone in a minute. It was important to titrate the use of the drug so that you could reach adequate cumulation and then keep that as a threshold level.[43]

And the fourth important thing, as has already been pointed out, was the recognition of the different modalities of pain and that different drugs could act upon the different modalities in different ways. Some were effective against some forms of pain, others against others, and the tricyclic antidepressants soon began to be used in neuropathic pain. The other important thing, as has already been said, is the whole question of the mind in relation to pain, the amplification of pain by the mind, the importance of the sympathetic nervous system in the modulation of pain and so on, all of this was being considered then.

And lastly on the question of management. It seems to me that the important thing was the use of clinical trials to discover efficacy, potency and the pharmaceutics of drug therapy. St Christopher's was very much to the fore here, and the various research fellows were very busy with the clinical trial work. It was quite a time before folk would feel sure about the ethics of clinical

[42] Professor Duncan Vere wrote: 'Cumulation is the term for the balanced equilibrium where drug concentration rises till input equals output.' Note on draft transcript, 10 November 2003.

[43] Professor Duncan Vere wrote: 'Though the pharmacokinetics of morphine, and the half times of effective action for the opiates were known, many doctors were using them without understanding, often on an "as required" basis.' Note on draft transcript, 10 November 2003.

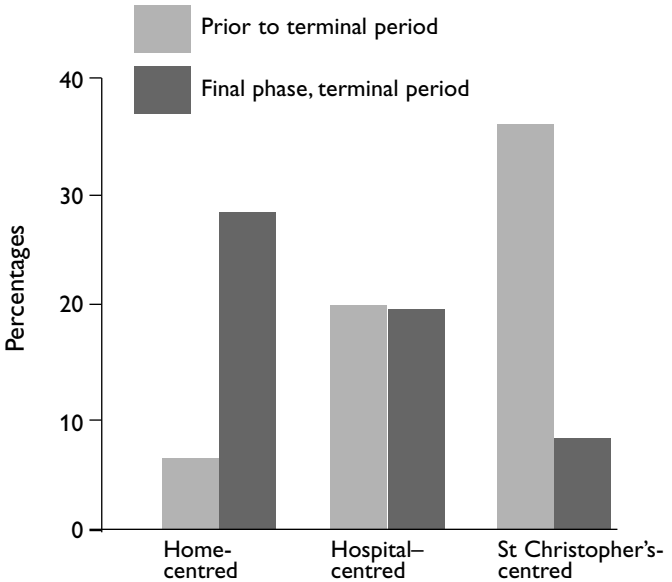


Figure 2: Proportions of patients with severe and mostly continuous pain. Parkes (1978): 22.

trials in this field and there was a lot of debate about that early on, but it was realized that of course there were ways to conduct effective clinical trials as measures in this field without breaching ethical principles. So those are really the main points that occur to me about that period of time, 1965 to 1970, when I think Robert came to join us.

Clark: We will give Robert Twycross the floor in a few minutes, but I would just like to stay in that slightly earlier period if we can and invite any further questions or comments.

Dr Colin Murray Parkes: I have been a consultant psychiatrist at St Christopher's since the outset in 1967 and although my primary interest has never been pain, it was brought home to me very clearly in the early days at St Christopher's how important a determinant of psychological distress pain could be, and equally how psychological distress often seemed to aggravate pain. I directed the first evaluation of the quality of care at St Christopher's as seen through the eyes of surviving family members.[44] We started collecting

[44] Parkes (1978).

information in 1969 to 1971 and we showed, for instance, that patients at St Christopher's were said by their families to have suffered severe unrelieved pain in 8 per cent of patients, whereas at other hospitals in the area, it was closer to 20 per cent, and in those dying at home, nearly 30 per cent. When we repeated that study, in identical form, ten years later, we found that by this time the news had got about how to give decent pain relief in the area, partly because of the teaching programme at St Christopher's, and other hospitals were now doing almost as well in administering pain relief as St Christopher's.[45]

Mrs Jennifer Raiman: I would like to pick up the story, if I may. I was in Professor Duncan Vere's department in 1978 and undertook a descriptive study looking at intractable pain, working with patients, staff and carers, at the Royal London Hospital, London. The study led us to the work of Dr Colin Murray Parkes at St Christopher's Hospice, who also held an appointment at the Royal London at the time. I think the key to the initiation of the study was that the work of the hospice movement was certainly becoming appreciated in the general areas, and its impact was beginning to be felt in the health service, particularly in the areas of pain and symptom control.

As anticipated from the body of work that Duncan has referred to, and the knowledge from what was happening on the wards, it was found that the majority of the patients referred had carcinoma, many of whom had secondary disease. They were nearly all found to be experiencing unrelenting, unrelieved pain.

For each patient in the study I interviewed a doctor and a nurse significant in their care, and if possible a family member. We found that despite staff awareness of palliative care and the success in the hospice movement, as it was called then, pain relief was not an aim: 'Oh, yes, they can do it, but we don't do it here'. It was salutary, and of great concern to find that hospital staff had very low expectations of what could be achieved in their own area of care at that time. It was an enormous worry and one that we tried to address with some urgency. We used the body outlines with observation and assessment of the patient, but it was totally patient-focused,[46] so it brought both staff and patients

[45] Parkes and Parkes (1984). See Figure 2 on page 17.

[46] Mrs Jennifer Raiman wrote: 'Patients liked and used the body outlines in the study easily and they ultimately became the focus for the development of a chart to observe and assess pain control. The body outlines were used by patients to regularly record their pain sites, together with their own written observations and assessment ratings on the severity of pain experienced and the level of pain relief achieved.' Note on draft transcript, 12 December 2003.

The London Hospital
PAIN OBSERVATION CHART

This chart records where a patient's pain is and how bad it is, by the nurse asking the patient at regular intervals. If analgesics are being given regularly, make an observation with *each* dose and another *half-way between* each dose. If analgesics are given only 'as required', observe two-hourly. When the observations are stable and the patient is comfortable, any regular time interval between observations may be chosen.

To use this chart, ask the patient to mark all his or her pains on the body diagram below. Label each site of pain with a letter (i.e. A, B, C, etc).

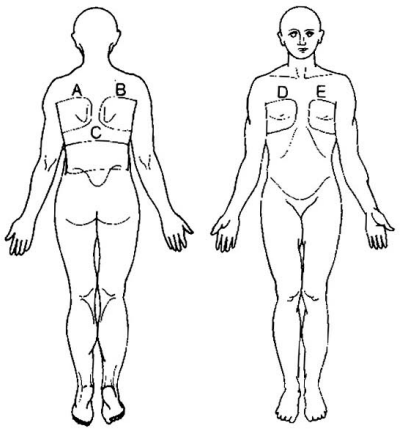
Then at each observation time ask the patient to assess:

1. The *pain in each separate site* since the last observation. Use the scale above the body diagram, and enter the number or letter in the appropriate column.
2. The *pain overall* since the last observation. Use the same scale and enter in column marked *overall.*

Next, record what has been done to relieve pain. In particular:

3. Note any *analgesic* given since the last observation. stating name, dose, route and time given.
4. Tick any other *nursing care* or *action taken* to ease pain.

Finally note any *comment on pain* from patient or nurse (use the back of the chart as well, if necessary) and initial the record.



Date . . . . . **Sheet number** . . . . . **Patient identification label**

Time	Pain rating									Measures to relieve pain (specify where starred)									Initials
	By sites																		
	A	B	C	D	E	F	G	H	Overall	Analgesic given (Name, dose, route, time)	Lifting	Turning	Massage	Distracting activities	Position change*	Additional aids*	Other*	Comments from patients and/or staff	

5 – excruciating	1 – just noticeable
4 – very severe	0 – no pain at all
3 – severe	S – patient sleeping
2 – moderate	

Figure 3: The London Hospital Pain Observation Chart.

together, looking at the pain, trying to break this dreadful cycle where people would give analgesics and go away and not go back to check that it did work.

There was neither the knowledge nor the vigour to address the problem, and to be frank, I became quite haunted by what I heard. And as a result of the study we developed the London Hospital Pain Chart, which was accepted by the hospital and the medical college, and in various ways it was adopted and adapted in the wider health service. It may be still winging its way round various acute wards in some form, I hope. Patients are still involved in that way. What actually spurred us on from that was becoming linked to a cancer charity called Macmillan Cancer Relief, who came to the London Hospital Medical College in 1982 and asked if it was possible to set up a Macmillan Education Unit within Duncan Vere's department [of pharmacology and therapeutics].

Professor Sir Ken Calman was a founder member of this and we had meetings with a variety of people, looking at the ways that education and training in palliative care for professionals could be taken forward, as it was then becoming known as a speciality.[47]

I was seconded to Macmillan in 1983, and later set up Macmillan's Medical Services Programme for the charity, which had concentrated up to that time on the development of Macmillan Nurses. Aided by grants from Macmillan, 300 medical posts in cancer and palliative care, including training posts, have been established since then. I am very pleased to say that there are more training posts being developed, for specialist registrars, senior house officers.[48]

To link back to what Duncan was saying, in relation to the community it has been possible for GP advisors and GP facilitators to be developed with a particular interest in palliative care, obviously with the developments in the whole department. The teaching of palliative care and cancer care is now on everybody's schedule, and the diploma in palliative medicine was established in

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[47] Mrs Jennifer Raiman wrote: 'Professor Sir Kenneth Calman was also chairman of this multidisciplinary group, whose members included representatives from the Department of Health.' Note on draft transcript, 12 December 2003.

[48] Mrs Jennifer Raiman wrote: 'Macmillan GP advisors and facilitators in cancer and palliative care have been developed in association with the Royal College of General Practitioners. In addition, the teaching and practice of palliative and cancer care has been recognized by the establishment of diplomas at the University of Cardiff and elsewhere in the past few years.' Note on draft transcript, 12 December 2003.

Cardiff, which I think has actually linked the community, the GPs, the community nurses, with cancer care, and we hope this will continue to develop.

Bond: I want just to emphasize how awful it was for people in the early 1960s and prior to that, and before the time when the work of the hospice movement, as it was called, became generally known and accepted. Cultural attitudes to pain were very obvious amongst the nursing staff. I was concerned by the extent to which the patients seemed distressed by the poor control of pain, and decided that I would conduct a small study. That would have been about 1961 or 1962. I asked patients to estimate their pain levels, and incidentally the analogue scale for measurement of pain first appeared in Sheffield at about that time, and linked them to the nature of the analgesic that was prescribed for them. I did a study on the male oncology ward and the female oncology ward. The results were amazing, because there wasn't any correlation at all between the type of analgesic given and the level of pain recorded, either before and after the analgesic had been given.[49]

So you could have had a bucket of analgesics in the middle of the ward and said, 'Take one of these. It might work'.

The second observation was that on the ward for women all types of analgesics were available, including narcotic analgesics, but on the men's ward narcotics were not available. I enquired why narcotics were not available to men and was told that men don't need powerful drugs like that. It is hard to believe that such attitudes existed, but they did, and I think nowadays perhaps people forget how much we owe to some of those in this room, to Robert [Twycross] and Cicely [Saunders] and others, for the work they did to break down the sort of barriers that existed, the fear that nurses had that people would become addicted, and so forth. I think it is worth recording that life was very bad sometimes for people with severe pain.

Mr David Joranson: I just have a brief question for Dr Swerdlow. Recognizing the importance of language to the understanding of history, could you tell us a little bit more if there was a story behind the choice of the word intractable, in naming the society the Intractable Pain Society?

Swerdlow: No, there was not.

Vere: I only wanted to add one brief comment to Sir Michael's comments about the prevailing atmosphere. I shall never forget going to one ward, a

[49] Bond and Pilowsky (1966).

gynaecology ward, to ask whether Mrs Raiman might visit it to do some research, and the sister on the ward said to me, 'I want you to understand, Dr Vere, we do not have pain on this ward'.

Dr Alex Nicholson: I am a specialist registrar from the West Midlands. Professor Vere mentioned that tricyclic antidepressants had started to be used and recognized for their role in pain, and I wonder if the clinicians here, who were active at the time when those observations were first made, could perhaps embellish upon that recognition and let some of the younger members know how it started.

Vere: My records seem to indicate that it was about 1977 when the relationship between the sympathetic nervous system and pain was really beginning to be understood with animal experiments, and tricyclic drugs were found to be effective in that area. But there was also anecdotal evidence that in man amitriptyline, I think it was, was effective against some forms of neuropathic pain. I can remember being enormously impressed by the fact that a nurse research assistant joined our department, who had had a nerve entrapment injury some years before and had found that only amitriptyline with nefopam relieved her pain enough to enable her to work.[50] I think there was a lot of anecdote in that area, but I don't know more than that.

Dr Robert Twycross: Could I come in on this particular point? I really think it should be the persons on my left [Mark Swerdlow] and my right [Sir Michael Bond], and I think you should insist, Mr Chairman, that they do say something after me. But as Duncan mentioned 1977, I think it was the professor of clinical pharmacology in Cardiff, I forget his name, who wrote a very important paper around about then, which talked about all the ways which tricyclics might have benefit in terms of pain control. But it was clearly known before that, and I am sure Mark will take us back into the 1960s. But I went to St Christopher's as Research Fellow in Therapeutics in early 1971. Doug Robbie, the anaesthesiologist from the Royal Marsden who dealt with the chronic pain management, introduced me to the Intractable Pain Society, and I started attending the society's annual meetings.

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[50] Amitriptyline hydrochloride (*Trypitizol*: Morson) is one of the earliest tricyclic drugs effective for moderate to severe depression. *Lentizol* is the slow-release version. See Tansey and Christie (1998). Nefopam hydrochloride (*Acupan*: Riker) can be used for persistent pain unresponsive to other non-opioid analgesics. See McQuay *et al*. (1993) and McQuay (1988).

I think in those days I was the only non-anaesthesiologist, but the person who I think within that small group who taught me, and I am talking about 1972, possibly Doug Robbie himself, but Hugh Raftery in Dublin published a paper round about then on the management of post-herpetic neuralgia using amitriptyline and sodium valproate.[51] That particular paper, which I still regard as a landmark paper for me, changed my clinical understanding, it changed my clinical practice, plus personal discussions at the annual meeting. That certainly dates the use of tricyclics and antiepileptics for nerve injury pain.[52] It must date it back to the late 1960s, so with those few personal comments, I think we should ask Mark to take it back into the 1960s.

Swerdlow: Yes, I would like to say that during the 1960s and 1970s something new came up in so far as there was quite an expansion of knowledge and interest in neurophysiology and neuropharmacology. We have heard a lot about psychology and psychiatry as well. And obviously the publication of the gate theory[53] by Ronald Melzack and Patrick Wall in 1965 had a very big impact on this and ever since.

Twycross: Can I ask whether were you using amitriptyline and an anti-epileptic before the 1970s?

Swerdlow: Yes, and then later on of course I was using the antiepileptics in that type of causation of pain, quite a lot actually. But obviously it's not absolutely infallible, unfortunately.

Twycross: Sure, but probably the early choice, the early use of those drugs would have come about because of serendipity. It was probably serendipity and not science originally.

Swerdlow: Yes, I think that's a fair comment.

Meldrum: I just wanted to touch back on a couple of things that were said earlier. We have heard a couple of comments on the resistance of staff in certain hospitals to the use of narcotics. And I am just wondering if this was true of patients as well, if in fact patients wind up with intractable pain problems in your experience

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[51] Raftery (1979).

[52] Tricyclic antidepressants include, for example, amitriptyline, clomipramine, desipramine, doxepin, imipramine, and nortriptyline.

[53] Melzack and Wall (1965). See also Appendix 1, page 78, where Wall describes the background to the gate theory.

Drug type	analgesic	anti-depressant	anxiety reliever (anxiolytic)	muscle relaxant	antiemetic	anti-confusional
anticonvulsants						
carbamazepine	•[a]					
phenytoin	•[a]					
psychotropics						
prochlorperazine			•		•	
chlorpromazine			•	•	•	
haloperidol			•		•	•
hydroxyzine	•		•		•	
diazepam			•	•		
amitriptyline	•[b]	•	•			
corticosteroids						
prednisolone	•[c]	•				
dexamethasone	•[c]	•				

Table 1: Adjuvant drugs used in 1986 to treat specific types or pain or to ameliorate other symptoms that often occur in cancer patients, which were originally developed for clinical indications other than pain.

[a] shooting or stabbing pain

[b] superficial, burning pain

[c] nerve compression, spinal cord compression or raised intracranial pressure.

Adapted from WHO (1986), Table 6, 66.

and are still reluctant to take morphine or another narcotic? Or did you find that in fact that the narcotics did not work for some types of pain problems?

Twycross: I am second generation in all this. And of course it's the historian's responsibility to pigeonhole each of us in this room as to where we fit into the total jigsaw, but I should state that in my opinion I am very definitely the disciple of Cicely Saunders. On the pharmacological side I suppose my main guru was Duncan Vere, so it's great to have them both here today. But having said that, let's get back to the present point: the responsiveness of pain to morphine. Like Cicely and Duncan and many others – probably all the people involved in chronic pain management of one kind or another – we believed not only in looking after patients, we believed in trying to disseminate knowledge because the only way you could get good across-the-board pain control would be to have the basic understanding and the application of those basic principles about pain management inbred into the whole of the medical profession.

However, I think all of us who began to seek to disseminate knowledge learned very quickly that imparting information is not enough. The challenge was, and still is, how to change clinical behaviour. Now for me, in the 1980s, if not

earlier, I was having to bring in a counterbalance, in other words you had convinced people about the use of morphine, particularly for chronic cancer pain, you had convinced them about the regular prophylactic prescription and the use of adjuvant medication, but then some people went overboard and it was morphine, morphine, morphine all the way.

In my teaching, certainly by 1980, I had deliberately classified pain from a teaching point of view into morphine or opioid responsive, morphine partially responsive, and morphine non-responsive. And a lot of people also used the same teaching model during the 1980s and I think it was a very interesting and necessary counterbalance to people's blind over-enthusiasm. And I remember one doyen of chronic pain management and a leading light in the Intractable Pain Society saying to me, 'Robert, do you really believe that there are pains which don't respond to morphine?' And I said, 'Yes, I do'. Now, of course, he knew that, but wasn't it interesting that you can get this divorce between what you know, if you really sit down and reflect, and what you actually do in clinic?

I think that was a necessary period when we had to popularize, in particular, the use of what is called by the WHO the adjuvant analgesics,[54] particularly the antidepressants and the antiepileptics for nerve-injury pain. We had to get across this, as always, oversimplified message. And then that went too far, so in the 1990s we had to unscramble that particular simplistic teaching model. But practically speaking, I think we can still say that there are some pains that will not be relieved by an opioid unless the patient is 'drugged' into drowsiness, asleep. Perhaps a classic would be the pain of somatic muscle cramp. There's another approach to that.

Then there are pains where you may be able to do a good job with morphine, but only at the cost of unacceptable adverse effects in terms of drowsiness and confusion in particular. And in those, from a practical point of view, it is best to regard them as partially responsive and approaching them with a multidrug approach rather than relying totally on morphine. Compared with 20 years ago, there are probably fewer pains that I would regard as essentially totally resistant to morphine. People might want to disagree with that, but, in practice, there are still quite a lot of pains I would urge people to think about as clinicians as only partially responsive and to approach in a multimodality way.

Clark: Robert, will you hold on to the microphone, because I would like you to take us back again if you would, because we sometimes think of you – and

[54] WHO (1986). See Table 1 on page 24 opposite.

I think I have heard you use the phrase – as the man who destroyed the Brompton cocktail. Can you tell us how that came about? And how you found yourself drawn into that area of research and how you conducted those studies?

Twycross: I am going to say something else before I answer your question. We were combating misinformation – that was the big challenge. It wasn't just giving the right information, we had to undo a lot of bad learning, and a lot of that bad learning (I think, Duncan, you may want to comment on this), came from the basic pharmacologists in their teaching of pre-clinical medical students and nursing students. And this of course would carry over into the medical profession and the medical profession would repeat the same misinformation. A lot of that misinformation came because people were making unwarranted extrapolations from one area of research or experience into another area of research or experience.

I have jotted down six areas where people did not make distinctions when they should have:

- acute vs chronic pain
- single dose vs multiple dose
- parenteral vs oral
- addict vs the non-addict or patient world
- human vs animal
- volunteer studies vs studies on patients in pain.

So there was this tremendous misinformation, because of confounding these various dichotomous situations.

So you want to move on to the Brompton cocktail? Marcia started off by talking about various strands. Was it two strands or three strands? It should have been three strands if you had included the hospice/palliative care strand. But quite clearly, there are lots of strands coming through history, and I was pleased that Mark went back to 1884. And, in the UK, whatever the majority of people were doing in terms of non-practice or bad practice, there's probably been continuing good practice for hundreds of years, right from Thomas Sydenham, who said that,

> among the remedies which it has pleased the Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.[55]

In the eighteenth century opium was often given as an alcoholic extract called laudanum. We can assume that, after Friedrich Wilhelm Sertürner isolated morphine from opium, we progressed to solutions of morphine. Certainly, at the end of the nineteenth century we have two communications in the *British Medical Journal* from Herbert Snow, a surgeon at the Royal Cancer Hospital (later the Royal Marsden Hospital), in which he wrote about morphine and cocaine solutions delaying the progression of advanced cancer pain.[56] Others were using morphine solutions either for chronic cough and breathlessness in terminal tuberculosis. So we have this continuing strand, the faithful few handing on the torch from one generation to another.

Now, it's interesting to ask why was it not more widely disseminated? And I am not sure that we can put the historic clock back and find that out. Anyway, I came on the scene when I moved to St Christopher's in March 1971 as Research Fellow in Therapeutics. Amazingly, despite being post-MRCP [Member of the Royal College of Physicians], five years after qualifying, I thought that diamorphine was two molecules of morphine linked together. It was only during my first or second week at St Christopher's that I learnt that it was diacetyl morphine. I have come a long way.

What was this Brompton cocktail? Generally speaking, it was a mixture of morphine and cocaine in honey or syrup plus alcohol. It was probably used as a post-thoracotomy analgesic at the Brompton Chest Hospital, and as a cough and respiratory sedative in terminal tuberculosis. So probably the Royal Marsden and the Brompton Chest Hospitals were using the cocktail, even though they weren't disseminating its use. When was this formula published? It was sometime in the 1950s in a supplement to the hospital formulary, either at the Royal Marsden or the Brompton Chest Hospital.[57] In 1958 it first appeared in *Martindale's Extra Pharmacopoeia*, and then the *British National*

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[55] Porter (1999): 194.

[56] Snow (1890, 1896).

[57] Kerrane (1975).

Formulary (*BNF*) and then eventually in the 1970s it was being published in four formulations and I think again it was in the *BNF*.[58]

Going back to Duncan's point about mixtures, he wasn't talking about using several drugs in a rational way, he was talking about a magic mixture. There were four formulations side by side in the *BNF*, one was morphine and cocaine plus the vehicle (including the preservative, chloroform water), and another was diamorphine and cocaine plus the vehicle, and then there were two with chlorpromazine added. In these latter two, there was a cerebral stimulant – cocaine – and a cerebral sedative – chlorpromazine. One of the things I realized early on was that for some reason people committed intellectual pharmacological suicide when it came to treating the dying. I mean how could people prescribe morphine or diamorphine, plus cocaine, plus a phenathiazine? But that was how it was, and it was this particular situation that Cicely was particularly keen to investigate. We first looked at morphine versus diamorphine, because, on the basis of what she had been taught, Cicely had developed the clinical impression that diamorphine had certain advantages, but she wanted to put it to the test. And that's what she asked me to do, and it was a great privilege to have undertaken that particular trial, with Duncan and with others' help.

When the results came out in the now time-honoured four-hourly way, individual titration to effect, there was no difference in efficacy between diamorphine and morphine given by mouth. This of course was a tremendous step forward, because no longer could people in other countries say, 'Well, you can do it because you have got diamorphine, but we've only got morphine'. So that immediately made it more directly exportable, though the more perceptive had already started exporting it, particularly Balfour Mount and others in North America,[59] having made the obvious step, 'Well, if we haven't got diamorphine, we had better do our best with morphine'.

And then we went on, while working out the results on the first trial, to look at morphine/diamorphine, plus or minus cocaine. Balfour Mount in Montreal investigated cocaine too. We concluded that cocaine might be of benefit for a

[58] Martindale (1958). The 1989 edition of the *British National Formulary* notes that the four compound elixirs, the traditional Brompton cocktail, are no longer recommended (*BNF* No. 17, page 177), and preference is given to a simple oral solution of morphine hydrocholoride 5mg and chloroform water to 5ml.

[59] Mount *et al*. (1976); Melzack *et al*. (1976).

few days, but there was no lasting benefit. So, if it was just relieving some of the initial drowsiness, why complicate the issue by putting in a drug which had potential adverse effects? Certainly people didn't use it in the carefully controlled way as at St Christopher's, with a very modest dose of 10 milligrams every four hours. In contrast, at some centres (notably in the USA) when the dose of morphine went up, the dose of cocaine went up too, so much so that at one hospice, they told their patients that the price of pain relief could well be hallucinations – induced by increasing doses of cocaine.

Anyway, there were all sorts of reasons for trying to simplify [the regimen]. We got rid of cocaine and, perhaps once in a blue moon, a patient would be specifically prescribed a cerebral stimulant (in those days, dexamphetamine), but generally patients were advised to work through the initial drowsiness. Cicely, when was the regular admixture of prochlorperazine syrup[60] dropped? We dropped it in Oxford in about 1979, when we changed to the much less sedative, once-a-day, small dose haloperidol. We certainly simplified right down during the 1970s. We started with what Cicely had inherited and had used very very well. But by the end of the decade we had simplified right down and that's where we remain, and that's where the WHO comes in – and the further popularization of morphine by mouth as the standard strong opioid of choice, particularly for chronic cancer pain.

Saunders: I can't give the date of when we changed. I must make a short salute to Sir George Godber, because when I was getting a clinical impression at St Joseph's that diamorphine was the better drug, I did realize then that you had to test your own enthusiasms and also, as I said before, we were getting better at everything, and it was Sir George leaning on the research department of the DHSS that enabled a totally unknown hospice to have the money waiting to do drug trials by the time we opened, as well, incidentally, as doing a study on what could be done at home as a research and development project, which also started in 1969,[61] and it enabled us to show that people tend to think that a hospice is just a building, whereas a hospice works in the community and what has been shown is that treatment of pain in in-patients can actually be done at home and I think that's enormously important. As far as the introduction of slow-action, obviously at my advanced age of 84, I haven't been in clinical work for some while and I couldn't possibly give you a date.

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[60] Tanner (1978).

[61] Twycross (1972).

Dr Peter Hunter: I would like to make an historical point about how the innovation of cocaine as a corneal and conjunctival anaesthetic came about in 1884. Dr Carl Koller was within six months of having qualified and was working as a trainee ophthalmologist in Vienna. One of the interesting aspects is that Koller had understood what Freud had failed to recognize, that the single most important action of cocaine was that it is a very powerful local anaesthetic and the experiments that established this were completed in a single day.[62]

I am puzzled about serendipity and why *Tegretol*, an anticonvulsant, came to be used to control the pain of trigeminal neuralgia. *Tegretol* was originally synthesized in 1953,[63] but it was 12 years before anybody thought of something to do with it, which was as an anticonvulsant. How does *Tegretol* affect the pathophysiology of pain?

Twycross: One very brief comment on cocaine, and then I am going to hand the microphone to Mark [Swerdlow] to deal with *Tegretol* alias carbamazepine. Just for the record, we have talked about cocaine in two different ways. Mark and Peter Hunter have referred to it as a local anaesthetic. I was referring to it as an orally administered drug absorbed systemically, acting as a cerebral stimulant, and not as a local anaesthetic.

Swerdlow: Like Dr Saunders, I have been retired now for many years and not in practical clinical practice, so although I used *Tegretol* many times in patients with this particular type of pain, I never discovered just how or why it does what it sometimes does.

Vere: I think *Tegretol*, carbamazepine, came to be used because it was an anticonvulsant, a known anticonvulsant, and *tic douloureux*, or trigeminal neuralgia,[64] resembled a miniature convulsion. People used it for that reason

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[62] Dr Peter Hunter wrote: 'Koller (1857–1944) was told by a volunteer that cocaine numbed his mouth. He knew that this had happened before. At the Vienna General Hospital, he and his professor's assistant Dr Gaertner, set out to investigate this. In a single day they produced corneal and conjunctival anaesthesia with cocaine in a frog, a rabbit, a dog and themselves.' Note on draft transcript, 30 January 2004. See Freud (1884); Robinson (1946); Sneader (1996): 152–4. Koller's article was translated into English, see Koller (1884).

[63] Dr Peter Hunter wrote: '*Tegretol* was synthesized by Schindler at Geigy Laboratories, Basle, Switzerland, in 1953.The first clinical trial was in 1963.' Note on draft transcript, 30 January 2004. See Sneader (1996).

[64] Trigeminal neuralgia, or *tic douloureux*, is facial pain that may occur as severe, sudden bursts, sometimes caused by trigger points in or about the mouth.

and then found that it was effective against a variety of neuropathic pain. I can't give you a date for that, but it was pretty early on in the period we have been talking about.

Could I just comment on one or two other dates? Amitriptyline was asked about and, in the literature I brought with me, it looks as if Adler reviewed its use in neuropathic pain in 1978. But there was a whole series of papers on the mechanisms of its action and its effectiveness in human disease, going right to 1983 to Declan Walsh and other authors.[65]

Professor Chris Main: As a clinical psychologist, I wonder whether I could move the discussion on to talk about non-pharmacological and non-physiological aspects of pain. As Professor Bond said, I had the great privilege to arrive in his department in 1976, I think, and caused him some trouble for a few years. My interest in the field of pain was purely accidental. The first stage of my career was extremely unfortunate – indeed many of the stages have been thus. I did some studies on psychosomatics; I carried out a study on the outcome of surgery for peptic ulcer the year before *Zantac* was introduced and the surgical rate dropped to a tenth. So that was the end of that set of studies. I then moved to Glasgow, but I had become interested in the relationship between people's perception of symptoms and what was actually happening physiologically.

I persuaded Michael Bond against his better judgement to let me embark on a PhD with the aid of an old 16-channel Grass polygraph which had to be hand-scored and was maintained by an ex-naval technician who was rather too fond of the whisky. Eventually, having gathered all sorts of information on a study on anxiety that I was doing, the equipment failed, and so did the technician, who was sacked one Monday morning because he still hadn't sobered up from the Saturday night. Coincidentally, around this time I was based in clinical psychology just down the road from Michael Bond, and an orthopaedic surgeon called Gordon Waddell turned up. He had been in Canada working with the Workman's Compensation Board there and had seen what they called a 'Back School', in which four different professionals got a group of back pain patients together to try to help them understand the nature of their problem and perhaps do something about it. In discussion with Gordon, it seemed that there was a clear opportunity to gather some systematic data, since he is very careful about data, and he offered me the opportunity of an attachment to his orthopaedic clinic. As Michael Bond has just said, I think it was probably the

[65] Adler (1978); Walsh (1983).

first opportunity in the UK for a psychologist and an orthopaedic surgeon to work closely together.

We studied a great number of patients with chronic pain of various sorts, and many of them were surgical failures. At that time there was still a high rate of surgery for low back pain, and we saw people who had had three, four or five operations. It became clear that the major issue usually was not whether to offer yet more surgery, but whether we could actually manage them a little bit better. So we started off with a whole series of statistical studies, measuring a wide range of variables, using all sorts of questionnaires. As you probably know, psychologists would rather use each other's toothbrushes than each other's questionnaires, and perhaps that is why there are so many questionnaires on the market. In any event we gave a large number of questionnaires to patients and computerized their answers. This was a painful exercise, because in those days we had to punch cards. My entire PhD consisted of punch cards and, on at least one occasion, I dropped the whole damn lot.

We carried out a series of statistical studies, tried to disentangle physical and psychological factors, and began to construct models of pain and disability. Our efforts were probably among the earliest attempts to quantify accurately what people believed intuitively to be true, that is, how disabled people were wasn't only explained by the underlying physical factors, but by the patients' reaction to their pain. We produced what we called the Glasgow Illness Model, which was the basis of the biopsychosocial model of back pain disability.[66] On this occasion Michael Bond drew my attention to the fact that one of my colleagues and myself had, in a single year, used the entire Medical School budget for computing.

I was then privileged to get a Winston Churchill Travelling Fellowship and this was a landmark occasion for me. I had been encouraged to put my name forward on the basis of the work that Gordon and I had been doing, so I filled the form and to my astonishment was invited to Kensington Palace Gate, where I was interviewed by a distinguished committee, chaired by Lord Flowers, with Baroness Masham, a member of the Parliamentary Disablement Committee, and the Queen's surgeon and gynaecologist, Mr Pinker,[67] and a

[66] Waddell *et al*. (1994); Waddell (1987).

[67] Sir George Pinker KCVO FRCS FRCOG, Surgeon Gynaecologist to The Queen, 1973–90.

most astonishing discussion then took place, because I knew as little about the House of Lords as they did about the field that I was in. But they were charming and courteous, and to my astonishment I was awarded one of these scholarships. There were five of us from the UK, including Henry McQuay who is not here today, who were offered the chance to go to North America in 1982 to look at new approaches to the treatment of pain.[68]

The important thing was that we set up a meeting on the new approaches when we came back. We tried, as part of the mission of the Winston Churchill Trust, to disseminate information.

During the Fellowship I spent eight weeks sitting in pain clinics, participating in what were called pain management programmes, which I had never heard about. The highlight of my trip was a visit to Seattle, Washington, where I met Bill Fordyce, a very kind man whose legacy is immense. He remains my friend and I am one of his greatest admirers.

On my return to the UK, I was determined to set up a Pain Management Programme, but I had a major problem. The North American clinics were set up with between 20 and 30 members of staff, and, in 1983, you can imagine trying to persuade the hospital administrators, as they then were, that you needed a pain programme with this number of staff. So I decided therefore to try to construct a honed-down version, which consisted of a physiotherapist, one of the medical staff, and myself (as a clinical psychologist). The initial pain management programme was for only four patients, and we were absolutely terrified. Nonetheless we succeeded in establishing the first pain management programme in the UK specifically for back pain in Salford.[69] Unfortunately by that time Mark Swerdlow had left the NHS, so I didn't have the opportunity of working with him, but I am proud to say that Salford has forged the way in more than one era.

Since then, the importance of learning how to live with pain and manage it has been recognized, because we simply don't have cures for all pain, and we can no longer assume that for all pain there will be a pharmacological answer to what really is part of the human condition.

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[68] See, for example, McQuay (1999).

[69] Professor Chris Main wrote: 'Since an important part of the mission of the Winston Churchill Trust was to disseminate information, we set up a meeting in Manchester [in 1983], particularly in association with the Pain Society [see note 3], the field of pain management has blossomed.' Note on draft transcript, 16 February 2004.

In conclusion, I would just like to consider what really has happened over the last 40 years. The early studies by Michael Bond and colleagues did try to disentangle psychological and physical factors, and were landmark studies, but many of the early studies were carried out on psychiatric patients who reported pain. We soon came to realize that general hospital patients with chronic pain problems were different from psychiatric patients who reported pain. We embarked on the development and validation of a whole new set of assessment instruments to try to improve our assessment and clinical decision making.[70] 'What is it that's stopping this person from obtaining maximum function?' Some of this can be helped by pharmacology, of course. In my view we need to embrace much wider perspectives on pain and disability, as signposted by the biopsychosocial model of pain and disability.

And finally I would just like to mention that this whole area has developed from healthcare outcomes to occupational outcomes, and the current Green Paper which is just out at the minute on vocational rehabilitation[71] is very, very much designed from a psychosocial perspective and I think there's some optimism that even if we can't cure pain perhaps we can learn to manage it better.

Dr Niki Ellis: I am a public health practitioner. Just to add that Gordon Waddell was extremely influential with these ideas in Australia. He came to Australia in the 1980s with the repetitive strain injury (RSI) epidemic and has had a big impact on back pain management.

Clark: Is there something of a divide, I sensed it in what you were saying, between those people who deal with pain which is malignant in its underlying causation and pain which isn't. You are adopting this rather positive view of what can be done about it.

Main: I think there is an interesting interface. I have done some work in hospices, not a lot, and I am not an expert in cancer pain, but it does seem to me that until relatively recently, perhaps, it was assumed that adequate pharmacological control obviated the need for a more careful look at psychological factors. Now this is not the case in the best of hospices, but

[70] Professor Chris Main wrote: 'More recently, in terms of psychosocial perspectives, we have been trying to move away from older concepts of psychopathology to studies of the psychological and psychosocial obstacles to recovery, with an increasing focus on secondary prevention and work retention and attempting to help prevent people from becoming unnecessarily incapacitated at home and at work.' Note on draft transcript, 16 February 2004. See also Main and Spanswick (2000).

[71] Department for Work and Pensions (2002).

sometimes the whole treatment regime is so pharmacologically driven that psychological factors perhaps have been neglected.

Kaufman: May I just make one or two points. The first recorded death from cocaine occurred at UCH in about 1889 in a young boy who had a convulsion accompanied by opisthotonos.[72] I was concerned about the derogatory remarks made about diamorphine, diacetyl morphine to be correct. I have been using this intrathecally and I think the references made before have been about the oral administration, but if you give it intrathecally, and I have been doing this for a few patients with carcinoma, the pain is relieved immediately. Now it's very difficult to explain this pharmacologically, because before diacetyl morphine (diamorphine) can act it has to be converted to morphine and patients will get immediate pain relief if this is given intrathecally.

I have taken to anaesthetising patients, giving them diamorphine intrathecally during the course of operations. Interesting studies measuring the endocrine response in surgery by cortisol levels, adrenaline, and antidiuretic factors, have shown these are all suppressed by the use of intrathecal diamorphine.[73] Now going on from that, listening to the psychological path of pain relief, one of the research workers working on a thesis at St Mark's Hospital (specializing in abdominal surgery), where I was a consultant, we had three or four major operations a day on patients with cancer. We had a psychologist come into the theatre and watch what we were doing, and he counselled patients prior to operations, hoping in fact that he was able to suppress the endocrine response to surgery. To our surprise, we got the reverse. Those patients who were counselled, who we thought would have had lower levels of adrenaline, cortisol, and antidiuretic hormone, had high levels.[74]

Vere: Can I respond just very briefly to Dr Kaufman's comments on diamorphine, diacetyl morphine. The point is that diacetyl morphine is much more liposoluble and able to cross the blood brain barrier and if it is de-acetylated it does so in two stages: first to 6-monoacetyl morphine, which enters the brain very readily, and so of course it works quickly. Every addict knows this, this is why they prefer it strongly to morphine, because they get a rapid 'buzz' as they call it when they inject intravenously.

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[72] Anon. (1889).

[73] Kaufman (1988).

[74] Salmon and Kaufman (1990).

Kaufman: Point taken, but that conversion takes place in the liver and that takes time. This is an immediate response.

Vere: No. Diamorphine is already diacetyl morphine and so it crosses the barrier. It is very soluble.

Kaufman: I agree, but the fact is that the conversion to morphine doesn't take place at the spinal cord level.

Vere: No, agreed.

Kaufman: But this comes on immediately. The patients are unaware when an injection is being given and they say, 'Doctor, my pain has gone'.

Vere: You inject diamorphine dissolved in saline; this is changed very quickly in solution to 6-monoacetyl morphine which enters the nervous system very rapidly. Then it is rapidly broken further to morphine, though no one knows where. But the result is an extremely rapid analgesia.

Kaufman: That's correct.[75]

Clark: We have been concentrating very much on the clinic and on the laboratory and after tea we are going to widen out and look much more at pain in a public health context, but with just a few minutes left, I am anxious to give anyone who has not yet spoken an opportunity to speak, or indeed anyone who has a question to put to our distinguished audience today to take that opportunity. First of all, of those who have not yet spoken, would anybody like to speak or ask a question?

Hunter: I come under the question category. I would like to ask two brief questions. First, could Jennifer Raiman tell us a little bit more about the London Hospital pain chart, how it's used, and who uses it? And second I would like to ask any pharmacologist in the audience if there are any drugs that are active on the spinal wind-up mechanisms of pain?

Raiman: The chart was developed for use by patients and staff working together. Patients draw their pain, noting the level of severity on the body outlines. It comes as a great surprise to many people that there is more than one pain. The intention was that it was patient-focused, and the chart permits the patient to open out so that they could have a better idea of where their pain was. Both medical and nursing staffs use it when talking to the patient about their pain, when administering analgesics, and record the analgesics given on

[75] Some correspondence has ensued on this topic, which will be deposited with the records of this meeting in Archives and Manuscripts, Library, London.

the chart, along with the level of pain present. If the analgestics work, patients receive them four-hourly. The nurses would return between the doses to note and treat unresolved or breakthrough pain. There was room on the chart to record what was affecting the pain, and indeed what was not affecting it, and patients were also asked about other things that relieved their pain. The chart was to be as broad-based as we could get on a manageable piece of paper.[76]

Vere: Could I just comment before answering Dr Hunter's question? One of the first patients who responded using the pain chart, with the body outline, was a patient of mine with carcinoma of the bronchus with secondaries in the cervical spinal and he was a well-known artist; he drew his 'pain' and it extended out beyond his body figure. He drew it very beautifully, and I remember asking him why had he gone outside the outline and he said, 'Well, that's where my pain is, that's where I feel it, that's what it's like'. And this of course was similar to stump neuroma pain that extends beyond the actual physical anatomy of the body, but it's how it is perceived, and that leads directly into Dr Hunter's question.[77]

I think the key paper is by Marshall Devor in 1984, a paper to the Wenner-Gren Symposium[78] where he talks about some delightfully executed experiments, where lesioned paws in animals became imprinted in the spinal cord with the map of the pain-responsive neurons, and echoing circuits set up with transition ultimately up to the thalamus, and this can be blocked early on in the first 24 hours by vincristine/vinblastine-type drugs, the vinca alkaloids derived from the Madagascar periwinkle, which block the physical transmission of the carriers of information from peripheral receptors to the dorsal root entry zone in the spinal cord. But then later you can't block it in that way. You can, of course, gate it also by pain, which was Melzack and Wall's great discovery.[79]

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[76] Mrs Jennifer Raiman wrote: 'The normal size of the chart is A3 [11.7 inches by 16.5 inches] to be clipped [folded] to the patient's boards/notes.' Note on draft transcript, 12 December 2003. See Figure 3, page 19.

[77] Professor Duncan Vere wrote: 'Wind-up pain is another matter; it happens quickly and only when C fibres are actuated at certain frequencies. It involves N-methyl-D-aspartate (NMDA) receptors and has been reviewed by Professor A Dickenson [Dickenson (1997)], but I am not aware of drug actions upon it. Both central imprinting and central hypersensitivity to pain are avoidable once pain is controlled by opiates by maintaining constantly adequate blood levels of these drugs.' Note on draft transcript, 10 November 2003.

[78] Devor (1984).

[79] Melzack and Wall (1965). See also the Physiological Society interview with Pat Wall in Appendix 1, page 73–82.

Clark: I would just like to ask Dame Cicely, if I may, one question in conclusion. Harold Stewart's name was mentioned very, very briefly. Could you tell us a little bit about Harold Stewart[80] and how he drew you into his area of work?

Saunders: I knew him because he used to play tennis with my father. My father happened to meet him at Wimbledon and said that I was coming to the end of my time at medical school and house jobs and wanted to work on pain, and he was at that time, before he had become professor, head of the department of pharmacology at St Mary's, and he was working with animal pain and wanting very much to get access to patients and finding it quite impossible to do that in the hospital. And so he said that there was a family trust that could produce some money and so that's how we got together. And he went on and supported me, because he expected me to do a respectable trial, and after I took him round St Joseph's Hospice, Hackney, London, when I had been there about three months, he said, 'Well, I can see what's happening, do a descriptive study, keep your records,' and with the idea of doing a double-blind which we had looked at, really fell into abeyance. He has only very recently died himself,[81] I think the thing about him was that he was prepared to pick out something that was outside his ordinary experience and let me run with it, and I am terribly grateful to him, because it wouldn't have happened without him.

Clark: We are now going to widen the focus from where we have been, both conceptually and geographically, and turn our attention to the question of pain, not so much seen as a problem in the clinic or in the laboratory, but as a wider problem within society and perhaps particularly within the public health systems of different societies and different countries. I would like to begin by asking Dr Mark Swerdlow to introduce this topic to us, and to speak about his early links with Jan Stjernswärd, who will then talk for five or ten minutes about his work at WHO.

We will move on to David Joranson from Wisconsin to talk about the work that he's doing on the development of pain relieving programmes in the poorer regions of the world. So that's our broad agenda. Others please contribute as we go along, and then about ten minutes from the end, I am going to offer an

[80] See, for example, Wood-Smith *et al*. (1962).

[81] See biographical note on page 110.

opportunity for a kind of mop-up session to pick up on any comments of any kind that people may wish to make and which we have not heard yet.

Swerdlow: I would like to go back to something like 1980. At that time the treatment of patients with cancer pain, which obviously was a kind of pain which urgently needed relief, was by no means satisfactory, and it was very fortunate indeed that Dr Jan Stjernswärd was appointed head of the cancer unit at the WHO. After his appointment he started a programme, one element of which was relief of cancer pain and I was asked to join his department to try to help. We both felt that if patients in the poorer parts of the world, and even in the richer parts of the world, couldn't actually get their cancer cured, relieved and treated, then at least we ought to try to relieve their pain.

We set up a study in three developed countries and three underdeveloped countries to see what the situation was at that time, what sort of treatment patients were receiving and what sort of relief, if any, they received. At that time Jan sent me to two or three very poor countries, to see actual cancer patients in hospital, and it was pathetic to see the worse-than-basic conditions within the hospitals. I remember the women's ward in one hospital in Sri Lanka in particular – there must have been 12 or 14 women there with really advanced cancer – and as I walked round the ward, none of them seemed to be in great pain. I asked the young doctor who was in charge of this ward what treatment they were receiving. He said, 'They get two tablets of aspirin a day', (I think it was) and I just couldn't believe it. I asked, 'Do they not receive anything except two aspirin tablets a day? Don't they get any sort of native herb treatment of any kind?' He said, 'Well, yes, they do get a native medication,' and when I asked, 'What's in the native medication?', he said, 'Oh, I don't know that'. (I have often wondered since then why somebody hasn't gone out there to study those herbs and what's in them, because they looked to be pretty effective.)

Jan and I decided that we should try to get WHO to study the problem of relieving cancer pain, and we enrolled some of the leading clinicians in the cancer pain world – quite a few of whom are here today. We then set up two major meetings at which the problem was studied and where the cancer pain ladder principle was gradually worked out.[82] Several years later this was broadcast by WHO to the medical services in every country in the world. It was of great benefit to cancer sufferers, and WHO did a wonderful thing, and

[82] A small informal group invited by WHO met in Milan in 1982 and developed the WHO analgesic ladder for cancer pain management. See Figure 4.

Figure 4: Some of the 1982 WHO group at the Villa D' Este on Lake Como, Italy.
L to R: John Bonica, Mark Swerdlow, Robert Twycross, Kathleen Foley, Vittorio Ventafridda, and Jan Stjernswärd.

are still doing so. Now I would like Professor Jan Stjernswärd to talk about this, as it was very much his project.

Professor Jan Stjernswärd: What motivated me to make pain and palliative care a priority in the WHO Cancer Programme, when reorienting it as newly appointed Chief of Cancer in 1980, was the suffering I saw in my African patients at the the Kenyatta National Hospital, Nairobi, Kenya, when doing clinical research there in the mid-1960s. Over 50 per cent of the children with Burkitt's lymphoma were cured by mono-chemotherapy. The great majority of the patients, however, were late-stage incurable solid tumours, to whom offering therapies was like peeing in the desert, you go five metres and on looking back you see no trace, no effect. I realized that the most relevant human and pragmatic thing to do would be to offer pain relief as an integrated part of any comprehensive cancer control effort.

Between 1980 and 1996 I formulated an action programme implementing the already accumulated knowledge in cancer control in a pragmatic rational public health way, putting science into practice, especially in developing countries. Together with epidemiological colleagues, we established data showing that two-thirds of cancer patients were in the developing countries and most were incurable due to late diagnosis. Numerous technical manuals including those for cancer pain relief, policy guidelines for implementing the technical methods in a public health way, e.g. for pain relief and palliative care and for the National Cancer Control Programme were done.[83] I established and advocated concepts such as 'one-third preventable, one-third curable, palliative care to two-thirds'; 'cancer is a Third World problem too'; 'freedom from cancer pain'; 'down staging'; and 'National Cancer Control Programme' and 'WHO three-step pain ladder'. Several demonstration projects, collaborating centres and numerous National Pain Relief and Palliative Care Programme/Initiatives around the world were supported by WHO and a worldwide network of achievers in pain relief and palliative care were identified and built up.

Pain as one of the most common symptoms was selected as the symptom to address.[84] For palliative care the philosophy and ethics were simply that the same attention and care given to those entering life, the newborn, should be given to those leaving life, the elderly and chronically ill. The pain relief and care I had seen in hospices only reached a few, often 200–300 patients a year, while many more were in need, perhaps 200 000 getting nothing. However, the hospices served as lighthouses showing the way in an ocean of suffering. As a specialist in radiotherapy/oncology I had not received a single hour of education in pain relief. I therefore decided to contract a pain specialist as temporary adviser to the programme. I found that Mark Swerdlow was available, then 62 years old. He had read an article in the *Lancet* arguing that if you retire when you are 62, you would live longer, especially if you walked rapidly for an hour every day. In his case he also played the violin regularly. You can see that he looks happy and healthy still today.

Mark advised me 'who was who' in the pain-zoo and stressed that 'you must see Vittorio Ventafridda', who also happened to be around the corner in Milan. In the cafeteria in WHO Geneva, Vittorio drew, on a paper serviette, the

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[83] WHO (1986, 1990, 1992, 1996, 1998a, 1998b).

[84] Stjernswärd (1985, 1988) and Stjernswärd *et al*. (1985).

principles for what would later become the 'WHO three-step pain ladder'.[85] The paper serviette is somewhere in one of 46 unpacked boxes in my attic at home. Jointly with the Floriani Foundation, Milan,[86] WHO held an informal meeting[87]outside Milan in an old medieval castle where we locked up some of the feudal lords in pain control. My charges to them were, 'I want a simple, effective, scientifically valid method for pain control, applicable, affordable and maintainable at community level'. That is, the public health approach together with policies and strategies for its implementation, so it could reach everybody in every country, and also in the developing countries were the need is greatest.

In spite of the fact that Cicely just called Mark 'a blocker' he was not blocked totally in his attitudes, for as chairman at the meeting he could accept this simple approach. However he was, and I am afraid still is, very much in favour of the needle and nerve blocks.

A draft guideline for cancer pain relief was produced in 1984.[88] On return to Japan, Dr Takeda immediately tested the method in 154 patients.[89] It was controlling pain in most of the patients. Several other tests, in over 3000 patients,[90] showed the validity of the WHO three-step ladder [see Figure 5].[91] I myself was convinced testing it in Geneva with Henri Rapin, at Centre Soins Continue.[92] I saw a woman, grandmother, full of breast cancer metastases, lying facing the wall in agony, sweating, moaning as the doctor passed the

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[85] See Figure 5, page 43.

[86] The Floriani Foundation was established in 1977 by Vittorio Ventafridda together with Virgilio Floriani to assist and help terminally ill patients, with Ventafridda as Scientific Director. See Ventafridda (2002).

[87] Professor Jan Stjernswärd wrote: 'Participants at the WHO consultation brought together outside Milan in October 1982 were Dr J Birkhan, Haifa; Dr J Bonica, Seattle; Dr P B Desai, Bombay; Dr K Foley, New York; Dr M Martalete, Porto Alegre; Dr A Rane, Stockholm; Dr M Swerdlow (Chair), Salford; Dr F Takeda, Saitama; Nurse F R Tiffany, London; Dr R Twycross, Oxford; Dr V Ventafridda, Milan; Dr F van Dam, Amsterdam; Dr R Gelber, Boston; Dr K Stanley, Geneva; Dr B Wessen, Boston; Miss M C Cone, IFPMA, Geneva; and Dr J Stjernswärd (Convener and Secretary), WHO .' Note on draft transcript, 12 April 2004.

[88] WHO (1984).

[89] Takeda (1986).

[90] Ventafridda *et al*. (1987); Schug *et al*. (1990).

[91] WHO (1986), Annex 1, Figure 1, page 51.

[92] Rappaz *et al*. (1985).

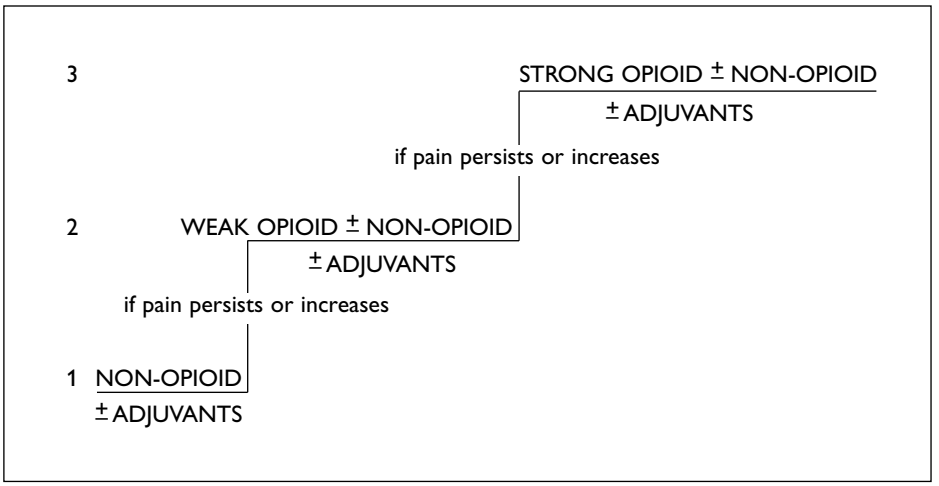

Figure 5: The World Health Organization's three-step pain ladder, which recommends medicines of increasing strength if pain worsens. WHO (1986), see note 91. See also Table 1, page 24.

room – as did the physiotherapist and the family – with the nurse being the only regular visitor. We put her on the 'three-step pain ladder' and after a week she was at home, pain-free, taking care of herself, coming back only two days before dying in hospital three months later. We treated 124 patients and I was convinced that the method worked.

I now needed to have the 'WHO three-step pain ladder' made official. I succeeded in getting extra financial support from the German Ministry of Health, courtesy of Dr Helmet Voigtländer, to hold a WHO meeting to finalize the draft guidelines in December 1984 with experts in cancer pain management, in national and international legislation concerning the regulation of opioid drugs, in healthcare delivery, education, pharmaceutical research and manufacturing as well as representatives of several international non-governmental organizations, altogether 36 persons, geographically balanced. The 'WHO three-step pain ladder' was officially born.[93]

The extent of the problem – reasons for inadequate control of pain and barriers – was addressed and comprehensive cancer pain management outlined in detail. Education and training, legislative factors and substance abuse and organizational aspects were also covered. Robert Twycross was the rapporteur

[93] WHO (1986).

of the meeting. We locked ourselves up for two weeks in WHO and Robert sharpened 100 pencils and we met every day with the mantra of 'simplify, simplify, simplify'. Robert was so successful that a simple guy like me could understand it. I imagined being back in Kenya, having to use the book at Narok District Hospital in Masaai land as *the* only source for practising pain control. The book became the second WHO bestseller, started to appear in English, French, Spanish, German, Italian, Japanese, Russian, Portuguese, Turkish and Arabic and is now translated into over 20 languages. The method is now the standard in most countries. Its rapid acceptance is largely because all the participants took ownership of the book and method. You always know who the mother is, but not always the father. The method was published in the name of WHO, no one author or editor was singled out, so everyone present could claim parenthood to the method. Although I often have been introduced as the father of the 'WHO three-step pain ladder', it is Vittorio Ventafridda who is the real father.

For optimal effect and its implementation as a technique/method I felt it important that priority-setting policies, strategies and managerial needs be addressed as well as proper advocacy. A WHO Expert meeting on Pain Relief and Palliative Care met in July 1989,[94] and the concept of a national cancer control programme where palliative care is incorporated as one of the major building blocks, together with primary prevention, was launched, along with therapy linked to early diagnosis for increased efficiency.[95] Strategies for incorporating pain relief and palliative care into the clinics were outlined, and foundation measures for an effective national programme were outlined. These measures cost little, but will have a big effect. This includes the triangle of education, drug availability and policies. It is important that these activities be coordinated, done simultaneously for effect. Thus, education without the drugs being available and the inability to practise is not very effective and vice versa, drug availability without education guaranteeing confidence in the use of morphines is not very effective. Recommendations to governments on how to establish a national programme were given.

I wanted a guide for outsiders of all unknown steps needed for making opioids available. A grant from the Drug Directorate of the Canadian Department of Health and Welfare permitted a young, brilliant senior consultant and

[94] WHO (1990).

[95] WHO (1995).

pharmacist, N R Donaldson, to be seconded from the Drug Directorate to the Cancer Unit at WHO. Donaldson produced excellent, clear stepwise guidelines that were to be included in the second edition of *Cancer Pain Relief*.[96] Unfortunately he never saw his product published as he died prematurely.

I addressed many international and national meetings around the world while WHO Chief of Cancer, and these offered a good opportunity for advocacy.[97] It was estimated that 24 million people would have read these articles. An indirect indicator of possible impact could be the increase in morphine consumption, as documented by the International Narcotics Control Board (INCB), a UN organization in Vienna.[98] Morphine consumption between 1972 to 1984 was under two tons a year, and since 1984 has it steadily increased and is now up to 25 tons annually. Earlier it was around 1mg per capita, now up to a global mean of 6mg, and in the UK it has reached over 15mg per capita.

WHO launched its programme in 1984. We have, however, failed in India, the greatest producer of opium. In spite of early efforts to make affordable morphine easily available,[99] consumption has gone down recently, approaching zero. We estimate that less than 3 per cent of India's one million cancer patients get adequate pain relief today.

Noreen Theo, a Chinese/Burmese pharmacist in the US, joined the Cancer Unit at WHO. She knocked at my door and said 'I offer my services, I like what I see' and she was the one that made official contact with the INCB, who mainly addressed the regulatory polices for the restrictions of use of opioids,

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[96] WHO (1996).

[97] Professor Jan Stjernswärd wrote: 'See, for example, "Pointers", and "Editorials" on the need for pain relief and palliative care were done, such as Stjernswärd (1989–1990, 1994). A flyer, *Freedom from Cancer Pain*, was produced for the waiting rooms in hospitals, which simplified the "WHO three-step pain ladder". The reoriented WHO cancer control programme, including pain relief and palliative care, was described in a press kit in English, French and Spanish, accompanied by a video, "Why not freedom from pain?" Press conferences were held in Geneva, New York (UN) and Tokyo in 1984. The effect, measured by "pick up" by news clippings and editorials in leading national newspapers around the world and in leading international scientific journals, like *Nature* and the *Lancet*, was analysed and showed extensive coverage. Stanley Englebart, an investigative journalist, had a five-page article in *Readers' Digest* on "Unnecessary pain and WHO pain relief programme" [February 1991, pages 10–18].' Note on draft transcript, 12 April 2004.

[98] See Figures 6 and 7 on page 51.

[99] Stjernswärd *et al*. (1985).

but added a policy to support a more liberal use of morphine in patients with severe pain, as it should be their right to have freedom from pain.[100]

Several WHO collaborating centres covering pain relief and palliative care were established. Three of the most active were in Wisconsin, Oxford and Saitama, Japan. The Wisconsin Centre produced the journal, *Cancer Pain Relief*, with Sophie Colleau as active editor. David Joranson was later appointed as Director and has never disappointed. He speaks the language of the regulators. I also asked him and Robert Twycross, as Director of the WHO collaborating centre in Oxford, to help with morphine availability in India. An outstanding educator, Twycross was asked to address education in India, and since then Robert has given at least two to three weeks twice a year for education on palliative care in India concentrating on supporting the Calicut WHO Demonstration Project, which by now is running itself admirably and conducting the first regular Indian palliative care courses and diplomas. Gilly Burn was the first to respond to my challenges and has been an outstanding advocate for pain relief and palliative care in India over the years.[101]

Eduardo Bruera brilliantly lead and coordinated the introduction of the WHO public health approach for pain relief in Latin America, addressing the need for drug availability, education and policies in coordinated efforts. One outcome was the Florinapolis Declaration.[102] In eastern Europe Jazek Lucak lead the development from Poland reflected in the Poznan Declaration.[103] Several successful WHO demonstration projects were supported, such as the Wisconsin Cancer Pain Initiative in the early 1980s, started by June Dahl[104] and later spread like wildfire to most of the other states in the USA.

The demonstration project in Catalonia, Spain, has successfully shown the importance of a joint governmental and non-governmental approach and the possibility of achieving effective coverage within a ten-year period for the

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[100] INCB (1989); Stjernswärd and Theo (1990).

[101] Burn (1990).

[102] Stjernswärd *et al*. (1994).

[103] The Poznan Declaration 1998 (*European Journal of Palliative Care* 1999 6: 61–3) and Suresh Kumar in India championed the public health approach in the Calicut Declaration (*European Journal of Palliative Care* 1998 5: 78).

[104] Dahl (1980, 1993).

majority of the terminally-ill geriatric, cancer and AIDS patients, including effective home care through a rational, integrated approach.[105]

The Calicut Demonstration Project in the state of Kerala, India is an important model for the world, showing what can be done at community level for the people, with the people and by the people. Suresh Kumar is here today and can give further details. India is made up of over 500 districts, with between 2 to 5 million people in a district and that is where the patients should have their pain relief and palliative care. Calicut district has 4.5 million people and already most of the terminally ill are getting palliative care. The safe handling of opioids at community level has also been demonstrated.[106] Kerala, with 38 million people, was the first state in India to introduce a ten-year state cancer control action plan and it included pain relief.[107] Kerala now produces its own immediate-release morphine (IRM) costing around US$0.01 for 10mg.

Uganda is another success story as a model for Africa and, like Catalonia, shows the importance of an integrated governmental and non-governmental hospice approach using WHO foundation measures.[108] They have introduced IRM solutions manufactured in the country costing less than the price of a loaf of bread for a three-week supply, and have made pain relief and palliative care for the terminally ill a priority in their national health plan.[109] When selecting opioids for a national initiative it is critically important first to establish clear policies, as several initiatives have failed due to a lack of clear targets. Thus, when the country tenders for IRM none of the large international pharmaceutical companies answers. Instead, the companies' aggressive marketing, directed towards doctors, that promotes the use of expensive drugs for routine control of pain makes the programmes non-sustainable.[110] A monthly dose costs up to two-thirds of a nurse's salary or more in many countries instead of the few dollars that IRM should cost for a month's supply. Nor are these drugs better than IRM. The risk of misuse is, on the other hand,

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[105] Gómez-Batiste *et al*. (2002).

[106] Rajagopal *et al*. (2001).

[107] Nair (1989).

[108] Stjernswärd (2002).

[109] Uganda, Ministry of Health (1999, 2000, 2001).

[110] Daher *et al*. (2002).

much greater. Having worked hard on establishing policies for availability of affordable morphine, it is destructive to see how the pharmaceutical companies march in and outsmart us by aggressive, unethical marketing of unaffordable, but not better, drugs. Fentanyl patches in hot countries on hairy people is not recommended and may cost up to two-thirds of a nurse's salary for one month's supply. I just came back from Mongolia a week ago and only MST was available for a selected few, costing US$120 for a week's freedom from pain. This is many times more than the monthly salary for a great part of the population. However, seeing the price of IRM in Kerala and Uganda gives hope that freedom from pain may become a reality also for the great majority of sufferers, who live in developing countries.

When choosing opioids for a national public health policy in which the government will provide affordable or free medications, the criteria outlined in Appendix 2 should be followed.[111]

Clark: I will ask David Joranson to continue in that line.

Joranson: Well, it's really a pleasure to be in the same room with you. I see myself as a student of history, so having a chance to contribute something to this process is really a thrill. I thought I would reflect on how the Cancer Pain Initiative began in Wisconsin at the time that Jan was talking about, which was when the WHO Programme was taking shape for the rest of the world,[112] and how we connected with WHO. I will provide you with some data about what has changed and what hasn't changed since 1980 and I would like to make a few comments about what has happened in India, because I know you are very interested in that, especially since we have Dr Suresh here.

I have to admit that I am a former drug regulator, some people regard me as a 'recovering' regulator. I got my start as the administrator of the state Controlled Substances Board in Wisconsin in the mid-1970s, and later in the 1970s my colleague Dr June Dahl joined the Board. She was and is Professor of Pharmacology and teaches medical students about drugs and pain. In 1984, our enlightened US Congress proposed legislation to make heroin available for the relief of cancer pain in the US. We carefully considered this legislation because the cancer pain problem was serious in the US and in Wisconsin, but we could not understand why physicians in the US who were already afraid to

[111] WHO and Jordan Ministry of Health (2002). See Appendix 2, page 83.

[112] WHO (1986).

prescribe morphine would suddenly embrace heroin. We did not want to do anything that would hold out false hope for cancer patients and their families.

We took the opportunity to meet Dr Robert Twycross at a conference in Rye, New York. As I recall, he announced when he took the chair that when he had left the plane at Kennedy International Airport, 'I could smell the fear of addiction in America'. He reiterated this several times, that if you have morphine, you don't need heroin. So it was on the strength of that kind of thinking that the Controlled Substances Board opposed the heroin legislation, but went to work to develop a positive programme more directly aimed at the problem of cancer pain, the Wisconsin Cancer Pain Initiative (WCPI).[113] This effort involved an interdisciplinary group and a lot of education as well as evaluation of the barriers. As Jan mentioned, he was with us in December 1986, to inaugurate the initiative, and he made the WCPI a demonstration project for WHO. It was a very important moment in our development, as you might imagine, to have the support of someone like Jan as well as people like Dr Twycross and Dr Kathleen Foley.

The WCPI specialized in education aimed at practice change. Dr David Weissman, at the Medical College of Wisconsin, and Dr June Dahl put together an educational programme called the 'role model programme', which was funded by the US National Cancer Institute.[114] It was evaluated and it proved to be an effective way of using a short amount of time and a minimum amount of educational resources to actually make changes in physician practices with respect to pain relief. We studied the barriers to cancer pain relief in Wisconsin and in the US; our first job was to conduct a review of the literature that was available about barriers to cancer pain relief. After reviewing our early articles, I find that the barriers then appear to be the same as they are now. We know some more about them now, and we probably classify them similarly: those that relate to the patients themselves and the family members, to the healthcare providers, the healthcare system, and to regulatory issues.

In the US we found there was great variation in opioid policy among the different states.[115] In the state of Washington, which has been mentioned several times today, we found that the State Medical Board actually

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[113] Dahl *et al*. (2002).

[114] Weissman *et al*. (1993).

[115] Joranson *et al*. (2000).

discouraged the use of narcotic drugs in the treatment of chronic pain. That policy persisted for quite a few years and was finally reversed.[116] Opioids are now seen as part of the medical treatment of pain in the state of Washington. I think that the earlier policy probably expressed the view of the interdisciplinary pain clinic movement, which essentially excluded the use of opioids in the treatment of chronic pain. But now that view has been modified to a large extent.

The state cancer pain initiatives have grown to where there are initiatives in almost every state, managed by the American Alliance of Cancer Pain Initiatives. The Alliance has a website where you can search for cancer pain initiatives.[117]

My next point is the relationship between the international narcotics regulatory system and the decision of WHO to put morphine on the third step and call it an 'essential drug in the relief of cancer pain', which was entirely correct. But this decision also necessitated developing relationships with narcotics authorities at the international and national level, in order to ensure that these drugs are made available, because they are so tightly restricted, in some cases almost like nuclear material. Jan has described to you how WHO made this initial link to the INCB in Vienna. I was at the INCB in Vienna last week and they still remember Jan, and they still advocate the appropriate medical use of opioids. Throughout the world they are even called 'opioids' now, instead of 'narcotics'. But in many countries, the use of narcotic drugs is still a fearsome thing, and they are extremely tightly regulated. For example, Peru recently changed its national law to increase the amount of morphine allowed for an outpatient from a 24-hour supply to a 15-day supply. Opioid prescribing policy has been very strict in Italy and that too has changed recently. [118]

There are a number of other examples. I will use morphine as short-hand for the other appropriate opioids as well, all the full agonists. Their consumption for medical purposes has changed a great deal since the benchmark of 1980. I would like to refer to the two graphs (page 51), which show morphine consumption in milligrams per capita from 1964 through 2000. As Jan mentioned, the consumption of morphine for medical purposes throughout

[116] Joranson *et al*. (2002a).

[117] See www.aacpi.org (visited 23 February 2004).

[118] Blengini *et al*. (2003).

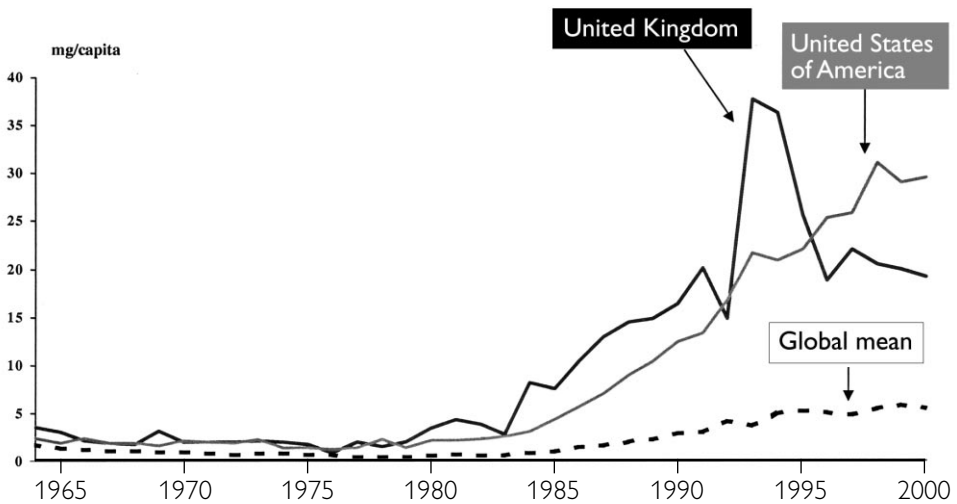

Figure 6: UK and US: Consumption of morphine, 1964–2000.

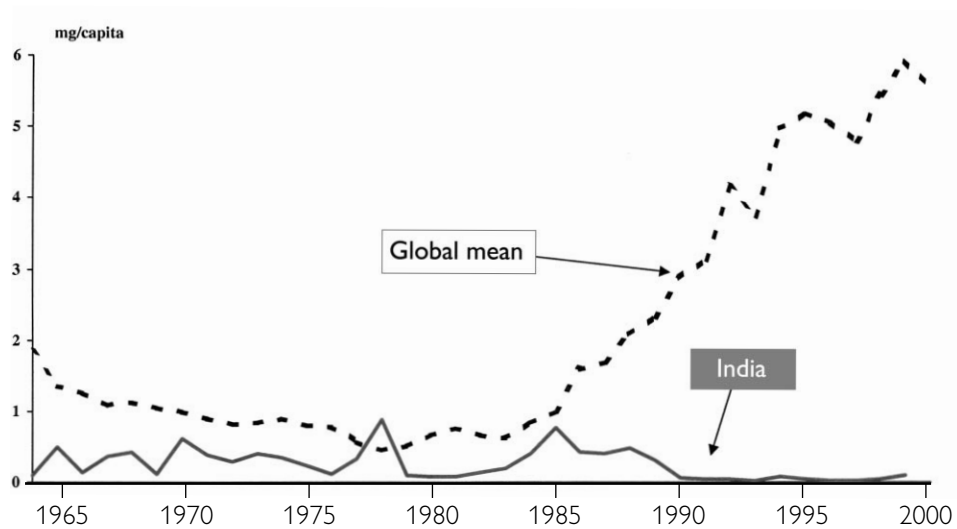

Figure 7: India: Consumption of morphine, 1964–2000

Sources: International Narcotics Control Board; United Nations Demographic Yearbook 1999.

the world stayed relatively low and stable until the time that WHO released its guidelines in the mid-1980s and then began to increase, at least in some countries. The dotted line represents the global mean. The global mean in 1980 was 0.7mg per capita throughout the world, and there were no countries that consumed more than 10mg per capita. By the year 2000 the global mean had jumped to 5½mg per capita and there were more than 14 per cent of the 135 recording countries that were consuming more than 10mg per capita. You can guess which they are: countries in western Europe, North America, Australia, and so forth.

I have to emphasize that even in 2000, 61 per cent of the 139 countries that reported statistics to the INCB still consumed less than 1mg per capita, and it is these countries that represent the vast majority of the world's population. Africa, India, China, and most countries in Latin America, consume still less than 1mg per capita. I am led to conclude, after discussions with Jan and many others around the world, that the progress that has been made to improve the availability of morphine has occurred in the easiest places in the world, that is to say, mainly in industrialized countries that have functioning healthcare systems.[119] Most of the world's population still lacks ready access to opioid analgesics such as morphine.

A few comments about India, then I will subside and turn it back to our Chairman. Many of you are familiar with the pioneers who worked in India and who have visited there frequently.[120] Jan has mentioned their names. My first visit was in 1990. Jan asked me to help set up a project there. It was a dismal failure. For reasons that we both now understand, you can't put morphine in a hospital where there isn't a clear understanding of its value and confidence in its use. So we went back to the drawing board and began to meet the people in India who were making a difference in palliative care, especially those in Kerala, like Dr Rajagopal and Dr Suresh Kumar from Calicut. Later we realized that throughout the 1980s, the same period that WHO was making its big palliative care push in India, the consumption of morphine was decreasing every year. The harder we worked to improve palliative care, the less morphine there was in the country. That is chronicled in Figure 7. You can see that while there had been morphine consumption in India, although well below the global mean, India nevertheless had consumed some morphine prior

[119] Joranson and Gilson (1997).

[120] Burn (1996).

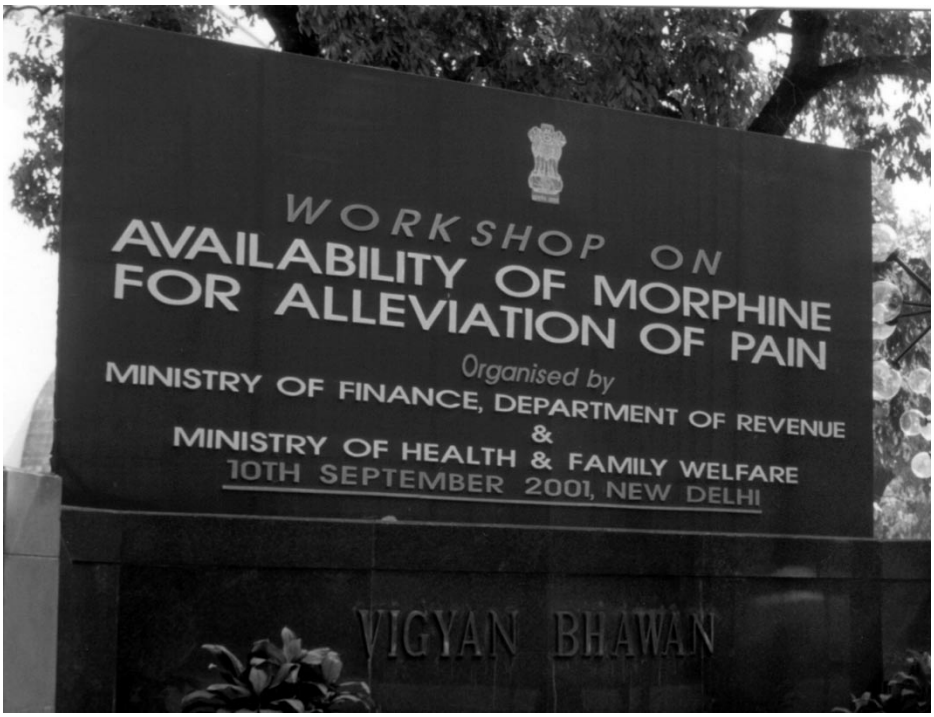

Figure 8: Workshop held in New Delhi.

to 1986. Jan, I think that was injectible, parenteral morphine in ampoules, and I think you are correct that it was not tablets, because tablets were not yet permitted by the Government of India.

No sooner had the tablets become available, than the Indian Government passed a law that imposed extremely tough new regulations and penalties. Historically, the British Government of India had relied on taxation on the cultivation and sale of opium for revenue to purchase tea and silk and other things from the East. The revenue bureaucracy that was established in India under the British Raj collected excise taxes that helped the finances of government in a big way. It was this opium taxation bureaucracy that eventually assumed responsibility for the licensing of medical morphine in India. Under this bureaucracy it was almost impossible for a hospital to obtain all the necessary licences to be able to obtain a shipment of morphine. And then in 1985 the Indian Government became even tougher on narcotics, so tough that several generations of physicians and pharmacists backed away from using the drug any more. That was the reason why morphine consumption

declined through the late 1990s. But as a result of our group's projects with Indian colleagues and with which Jan is familiar, and Dr Suresh as well, a number of workshops were held and changes were made in India's national narcotics policy as well as those in the individual Indian States. The consumption of morphine in India has begun to rise again in direct relationship to its use for palliative care, especially in Kerala, but not only there.[121]

I could conclude with one additional point. For those of you who are interested in a global view about the nature and extent of barriers to the availability of opioids, I would refer you to the report of the INCB for 1995.[122] The report contains the results of a survey of all governments in the world, about what they thought were the impediments to making morphine available for the relief of pain. The highest ranked barrier was fear of addiction. The second was excessive regulatory restriction of narcotic drugs, and that was ranked equal with inadequate education of health professionals. I think this brings us right around to where we are today.

I will just close on a story, one that I remember very fondly. It involves Dame Cicely, whom I met for the first time in Singapore, in the mid-1990s at the Hospice in Asia Conference. I was eager to ask you a question. I wanted to know if you thought that health professionals and patients in the UK were as afraid of addiction when morphine is used for pain as they are in the US. I then got your permission to crawl into the back of this little, tiny car you took on a hospice tour.

You said that in the past doctors and cancer patients hadn't been very concerned about addiction, but recently you had sensed that some of the doctors were getting more concerned because of what they had read in the media about narcotics abuse. I don't know if that still stands at this point or not, but I think that the fear of addiction, and what we have taught people erroneously about addiction and opioids, is the top barrier to making opioids more available for the relief of cancer pain in just about any part of the world, especially developing countries.

Clark: Well, thank you very much indeed to all three of the speakers who have introduced this topic. I am going to throw it open now to the rest of the floor and begin with Dr Suresh Kumar from Kerala in India.

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[121] Rajogopal *et al*. (2001); Joranson *et al*. (2002b).

[122] INCB (1996).

Dr Suresh Kumar: I come from a very different part of the world than most of you. Our situation is quite different from the West, so the major challenge for most of us working on the other side of the world is to evolve a model appropriate to the social ecology. A small group of doctors and social workers in Kerala, the southern state of India, have been experimenting with models of palliative care over the last decade. We started in 1993 with a small outpatient clinic in a teaching hospital in Kerala. Over the last nine years it has expanded to more than 30 clinics spread all over the place, with associated home care programmes. But the problem with this model is that there is no continuity of care. The patient attends the outpatient clinic, or the home care team see the patient at home, but since the patient is at home in the community there's no continuous real access to the clinic and also the coverage is patchy.

We have been trying to work on this and after a lot of deliberations, last year, in August 2001, we started a new programme. It's on a trial run in a small district, one of the poorest districts in Kerala, Malappuram, a district with a population of 4 million. It's called Neighbourhood Network in Palliative Care (NNPC), aimed at training helpers and volunteers in the community and supporting them with trained professionals and with the local palliative care units acting as nodal centres for the activity. It has run for a year now of a three-year project, a very ambitious one, aiming to achieve a coverage of 60 per cent of all the patients in need of palliative care, and not just cancer. We have made some preliminary assessments in this first year. The area now has something like 30 per cent coverage. I am talking about a place where the daily per capita income is something less than 50 pence and all the running expenses for the project are raised locally. The money for training is initially through funding from abroad or another part of India, but it's a sustainable project. We aim to achieve something like 60 per cent coverage in three years. Malappuram is a small district and India has something like 530 districts. It's a small beginning. For the first time in a decade I am feeling that we are on the right track.

Clark: Are there other people in the room who have had experience of cancer pain problems in this global international context and would like to comment on it?

Bond: May I ask a question of the previous speaker? To what extent are local government agencies backing your project and do they put any resources into it? And if so, what do they put into it? Do they give you sufficient, 50 per cent? Just a little, are they interested?

Kumar: The state of Kerala has been supporting us. When you take the state of Kerala as a whole, the Government is not yet involved much financially. But when it comes to the new experiment that I mentioned in Malappuram, the local people themselves raise the money. They are the main supporters financially and also morally. Again, it's true that once the community gets involved it is difficult for the local politicians not to take notice. So the people in Malappuram are getting very active support and part of their funding from the local government.[123]

Twycross: I have enjoyed the comments by Suresh and David [Joranson], and of course Jan before that, but David has underplayed the horrendous task it has been to move things forward in India. David's been a wonderful advocate, badgering away at the Indian Government and badgering away in various states, and just keeping it up has been a tremendous task. India will owe a lot to David when the story is fully told.

I would like to emphasize that it is the united States of India. There are some 30 states, and morphine is produced in tablet form in only four or five of those states. The regulations meant that you not only had to have a licence to hold morphine in your institution, you had to have a licence to transport it from one state to another, because you were crossing a state boundary. If you moved it from Tamil Nadu to Kerala, you needed an export/import licence, and, of course, the bureaucracy (which I am told was bequeathed to India by the British Raj) was so efficient that it made this either impossible or nearly totally impossible.

In the early days, palliative care clinics would perhaps have 100–200 patients receiving morphine and, because of all the red tape, the morphine would run out. What do you do with 200 patients who need morphine, and there is none? That's the sort of problem that Suresh and his colleagues had to cope with. There's a saying that what Kerala does today the rest of India will be doing in 50 years time. So far, only about 3 per cent of the people in India who need good palliative care receive it; there's still 97 per cent to go.

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[123] Dr Suresh Kumar wrote: 'Now, two years after the initiation of the Neighbourhood Network in Palliative Care (NNPC) Project, the district of Malappuram has an exceptionally good coverage of 70 per cent in palliative care. The financial support from the local government is also going steadily up. It is now five to ten times more than the pre-NNPC period. The training programmes in Malappuram has also become locally funded now. Two more districts in Kerala have initiated NNPC programs this year.' Note on draft transcript, 14 November 2003.

Kumar: Thanks to David's efforts, the Government of India sent out a circular to all the states,[124] suggesting that they modify their narcotics regulations to enable the medical use of morphine. Eight states have since modified their rules. My point is that even after these eight states have changed their regulations, morphine is freely available for medical use only in Kerala. Basically, it is one thing to amend the rules, and it is another to create a demand. Even if you have amended the rules, if you don't have the machinery to implement the change, the new rules may not serve much purpose. For you to have the machinery, there should be some demand. If you go on lobbying just with senior bureaucrats, without any demand from the community, the amended rules remain on paper.

Stjernswärd: I think we should remember the three Ts: 'Things Take Time' Although slow, progress is happening in timeless India. It is not only the regulations that must be resolved, but also the price for the painkillers. Uganda,[125] as a model not only for Africa, has demonstrated that pain relief costing hardly anything can be given freely provided you have the will and enlightened political leadership. For most of the world, consideration of cost-effectiveness is essential for covering pain relief to all in need of it. The poor are the most cost-sensitive users of any health services, high cost reduces utilization among the poor. Almost half of the world's population, an estimated 2.8 billion, live on less than US$2 a day, and 1.2 billion live on less than US$1 a day. In India, with one-sixth of the world's population, 89 per cent live on less than US$2 a day and 53 per cent on less than US$1 a day. WHO states that there are affordable methods available for pain control that are maintainable at community level. But when states or governments tender for morphine after we have convinced them to introduce pain relief and palliative care, who pops up? – the large multinational pharmaceutical companies. None offers recommended generic immediate release (IRM) or slow release morphine (SRM). These companies produce attractive didactic educational material for pain relief. If they also would produce affordable generic morphine, like aspirin, we could join forces, and change the world for the better, quicker. The Keralaits solved the problem themselves by buying a used tablet-making

[124] Dr Suresh Kumar wrote: 'The Government of India circular requesting individual states to modify narcotic regulations is contained in a letter from Revenue Secretary to all Chief Secretaries, dated 8 May 1998, F. No 664/63/97–NC, GOI, Ministry of Finance (Department of Revenue).' Note on draft transcript, 17 November 2003.

[125] See Stjernswärd (2002).

machine from Amnedabad for US$12 and produced 10mg IRM tablets costing around one US cent.

Parallel education – of the population and the health professional as done in the Malappuram community approach – and making morphine available is important and serves as a model for what to do for India's 500-plus other districts. Cipla Pharmaceuticals, India, has shaken the large multinational companies by producing generic AIDS drugs accepted by WHO for US$320 instead of over US$10 000, and has created a centre for education in palliative care in Pune, India, with 48 beds, and is also producing and using generic SRM. Introducing palliative care education in the undergraduate curricula of doctors and nurses would cost little but might have a big effect. Unfortunately, there is only one medical college in Bangalore, St John's, that has done it. It will be important that availability of pain drugs is coordinated with the educational efforts. Drug availability without adequate clinical empowering education does not work, as we learnt at a visit to the main hospital in Gwálior, India. Colleagues from the hospital claimed to be offering pain relief at a meeting of the Indian Association of Palliative Care in that city in the mid-1990s. The hospital had morphine donated by WHO and the Ministry of Health. At a later inspection, we found that after one year of having morphine only one patient could have been treated adequately, as the supply of morphine was found intact, unused, except for a few tablets.

Bulgaria serves as an example where the pharmaceutical companies blocked the development of a National Pain Programme achieving adequate pain coverage. After a workshop there, David and I got the Ministry of Health to agree to make pain drugs available as recommended by WHO, and to make palliative care beds/units available in all the 13 cancer centres. Bulgaria had two trained and devoted palliative care doctors, who should be 'trainers of the future trainers and palliative care doctors'. At a follow-up meeting in the capital, Sofia, with representatives of the multinational companies present in the country I pointed out that one month's supply of their drugs would cost an average of US$180 to US$200 a month. This should be seen in relation to a doctor's salary of US$105 per month and that it should be possible to achieve the same pain control for a few dollars, if following WHO recommendations. The Professor of Pharmacology enthusiastically offered to help the Ministry of Health to make generic morphine available as recommended by WHO and I sent him necessary background publications. What happened? A year later I met the two doctors from Bulgaria at a workshop in Poznan [Poland] and they happily informed me that SRM now was available free for the patients. It was

the same preparation [offered earlier] costing US$180 for a month's supply. Pointing out that 'nothing is free' and it probably was paid for by taxpayers' money in a country whose health budget was already in the red, I wondered what had happened with the professor's recommendations? 'Oh yes, he had been in Germany for three months on a study trip paid for by the company that sold the expensive non-generic SRM!' There are still no palliative care units in the 13 cancer centres or pain coverage. Human greed has to be controlled before we can control pain.

Hunter: Briefly, I would like to touch on the issue of how the rate of spread of a reform is often puzzlingly slow. This phenomenon was specifically addressed by Professor Albert Dicey[126] in 1905. He measured the time in years between, say, the date when the fact that six-year olds hauled coal in mines became known, and a law being passed to stop it. He measured this interval for many different problems and established an average time interval of 25 years. This was referred to as Dicey's Law.

I would also like to relate this whole question of pain to a wider social picture. As a consultant physician in the Royal Shrewsbury Hospital, I was very impressed that the Kerala Christian doctors there were good, very good, or downright outstanding. I am intrigued by the fact that Christianity was established in Kerala at an early date.[127] The issue was raised by Professor Vere earlier in this discussion, and I wonder whether there's anything in the mechanism of Christianity that explains why it appears to have these effects?

Clark: I think you have oversimplified it.

Kumar: Just one comment. The district of Malappuram where they are experimenting with the neighbourhood network, with very good success, is 80 per cent Muslim.

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[126] Dr Peter Hunter wrote: 'Professor Albert Venn Dicey (1835–1922) held the Vinerian Chair in Law at Oxford University, where he taught law from 1882–1909. He was also the Principal of the Working Men's College, London, from 1889–1912, as well as being among the first part-time academics at the London School of Economics, lecturing in law there from 1896 to 1899.' Note on draft transcript, 30 January 2004. See Dicey (1905).

[127] Dr Peter Hunter wrote: 'At the Royal Victoria Infirmary, Newcastle-upon-Tyne, I worked with a quite outstanding doctor, Professor Matthew Roy, a Kerala Christian. In 1985 three-quarters of men in Kerala were literate, while 65 per cent of women could read [15th edn of the *Encylopaedia Britannica* 6, 155, 810–11].' Note on draft transcript, 30 January 2004.

Twycross: I was going to make a similar observation. You cannot call Kerala a Christian state. It may have 25 per cent of its population nominally Christian, which is extraordinarily high for a country where the total Christian population may be only 0.5–1.0 per cent. As far as I know there's only one Christian state in India and that's Megalaya, up in the north-east where the majority of the population would claim to be Christian, but certainly not Kerala. Kerala has had a fascinating history. War created it in 1956, and it often has a communist government. So you have to ask what is it in communism that fosters progress, as well as in Christianity and Islam? And, let's not forget the Hindus, of course.

Stjernswärd: West is not always best, nor is Christianity. The communism referred to in Kerala is not of the Russian bureaucratic apparatchik type but more of a true socialistic type, like, I dare say, the original Christian communities. Furthermore, Kerala regularly changes governments, between a more capitalistic and a communistic party, in itself a healthy phenomenon. Kerala's success stories are most likely founded on their high literacy rate, in some districts up to 100 per cent, and that it is a matriarchal society in many aspects. Kerala, like Sri Lanka, has an average life expectancy of 78 years and the two societies are quite similar. Jimmy Grant, deceased Director General of UNICEF, found that 'quality of life' measured by three things: percentage of new born surviving, disease-free time during the time we have life on loan, and adult mortality, how long we live. Sri Lanka beat many countries, including several in the West. This is with an average income per family a year of around US$300. Thus, money alone is not the solution.

What worries me is that palliative care is becoming overmedicalized. Since we became humans in Africa during the Pleistonian time, some 1.8 million years ago, we have died and had rituals and later religions with ceremonies that have helped to cope with pain and suffering. I love Cecily's concept of total pain and have found that Buddhism and Hinduism, not only Christianity, have efficient traditional ways to cope with spiritual and existential pain. They have supportive rituals that they should not lose, like the secular agnostic Swedes have done. 'Inshallah' is a wonderful word for accepting the unavoidable. The Americans do not die, they just underachieve. The SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment) study gives frightening data on a healthcare system that has gone amok, got overmedicalized and commercialized.[128] The cultural and socioeconomic

[128] SUPPORT Principal Investigators (1995).

factors are as important as the medical for what kind of supportive care and death we get.

So, keep an open mind for multiethnic and cultural factors. Palliative care has music therapy and visualizations, many countries that do not have pain relief or palliative care have it too, but call it mantras or other things. We are born and die in hospitals in the West and can spend months in the freezer in Sweden before being buried, when other cultures require more civilized burial or cremation within hours or a few days. We have lost the old rituals while others still have them and find them supportive for bereavement and total pain.[129]

Vere: What I actually said was that I sensed that the aim to investigate and improve the care of dying of patients was driven in part by Christian ethical persuasion about the care of the person without obliterating their personality. May I just ask a question about Figure 6 [see page 51] that is very helpful? Why has the use of morphine declined in the UK? Not horrendously, but about a 50 per cent [decline] over a period which is quite brief [1993 to 1996], at the very time that you might expect it to stay up.

Joranson: First of all, those statistics are reported by individual governments, as to the amounts of each of the drugs that were consumed. Consumed means the amounts that are distributed to the retail level. Over time that typically equals how much is consumed by patients, but it's more a measure of distribution to the retail level, than it is to individual patients. Having said that, I would speculate about why there was a sudden drop and apparently a consistent pattern afterwards for morphine in the UK, and that might have to do with the introduction of other opioids at the time.

Twycross: If you look at it from a distribution point of view, before that strange peak [in 1994] there is a dip. Presumably, for one reason or another, people ran down their stocks and then suddenly built them up again. So you have to iron out those two years. They kept the stocks up for a couple of years and, then again, they found they were overstocked, and there is another consequential dip. I agree with you that since then it may be because of other opioids on the market.

Bond: If I could say, Chairman, that we have concentrated very much until just recently on the white Anglo-Saxon view of life in pain and I think the most recent speakers have brought out the fact that life is not exactly the same in

[129] Parkes (1972).

other parts of the world as it is here. Perhaps the best way of dealing with the pain problem in a country that is not ours is to start at the bottom, and find out what it is that people complain of and what it is they already do, because they might be pretty efficient, not be like the Christian missionaries of the nineteenth century who went in and said, 'This is what you need'. You have to go and find out what they think they need and see what we can do to help them.

A little anecdote might not go amiss, just to show how very difficult it is to understand other cultures sometimes. This is a story about a young man who came from a north African country to Holland and reported to his family doctor with abdominal pain. The family doctor was not able to find any physical cause for it, and asked the young man if he could think of any reason why he should have abdominal pain. The young man said, 'Well, of course, I came over here to earn money to send back to my family and I am afraid I haven't been sending back as much as I should have done'. So the doctor said, 'So, do you think that's why you have got abdominal pain?' He said, 'Well, I know my father's angry with me'. The doctors asked if that was likely to give him abdominal pain. He said, 'Oh yes, that's quite possible, in fact I am sure that's the real reason, because my father has got pain in his knee'. So the doctor then said, 'Well, if your father's got pains in his knee, why should that be?' And the young man replied, 'Well, in my country when girls are born they are of no consequence, compared with boys, so boys always sit on the father's knee as a baby, and if the father later is displeased with the boy, he gets pain in his knee. Symbolic, you see'. So the doctor said to him, 'Well, why don't you go back and make your peace with your father and help to get rid of his pain in his knee and the pain in your stomach?' The boy replied, 'Well, I am a bit loathe to do that, because I will become impotent'. So the doctor asked, 'Well, why will you become impotent?' He said, 'Well, if a father is very angry with a son, the son always becomes impotent'. So there you are, we have to be very careful when dealing with people who are not in their own society.

Clark: Thank you for that anecdote. Sri Lanka has been mentioned by Dr Swerdlow and Professor Stjernswärd, and as some of you here may know I have spent some time to my great pleasure and privilege reading the letters of Dame Cicely Saunders in depth in recent years,[130] and in that correspondence I discovered a relationship between Dr Saunders and Dr K J Rustomjee of what was then Ceylon [now Sri Lanka], who visited you [Saunders] in 1961. Can you tell us a bit about that?

[130] See Clark (2002).

Saunders: This large and splendid gentleman arrived at St Joseph's and said he was interested in starting a home for cancer patients. How he knew about St Joseph's I really don't know, but he had been in the USA and he certainly introduced me to the American Cancer Society, who were a great help when I went over in 1963. But I just remember him as a splendid chap whom I have kept in correspondence with, but we were obviously in some way or other on the same wavelength, although we came from such very different places. What we were aiming to do was something remarkably similar, and he got there first.

Clark: With the Bandaranaike Memorial Home,[131] which opened in 1962. Well, we have had a fascinating international interlude, rather unusual for Anglo-Saxons to look beyond their shores for quite as long as this, more than an hour, indeed. We have a little time now for any final observations or questions of any kind.

Swerdlow: Just a quick one to follow up Sir Michael [Bond]. I went to one of the most extraordinary medical pain congresses I have ever been to in Japan. Half of the speakers were Westerners and the other half were Japanese. The Westerners all talked about their way of relieving pain and then came the Japanese who produced lots of beautiful slides, pictures of herbs growing in the garden,[132] that sort of thing, and then their results. And their results were very different from ours. I am not quite sure why, whether this was a question of their mathematics or whether they were very pleased with themselves, but it was interesting to see the difference.

Vere: I don't think we have said much about other ways of prolonging drug action and have focused a great deal on the short-acting drugs. I thought it might be right to mention Dr Martin Wright's contribution at the Medical Research Council, who not only designed the peak flow meter, which made it possible for us to measure respiratory depression in some ways, but also designed the syringe driver pump, which has made such a difference to continuous pain control,[133] and one can certainly remember what a splendid

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[131] The Bandaranaike Memorial Home for the Aged, Indolamulla, Dompe, Sri Lanka. See www.acbc.lk/nat_soci_ser.htm (visited 23 February 2004).

[132] See, for example, Ida *et al*. (2002). See also www.aphn.org/content/Disarticle.asp?I=4 (visited 19 May 2004).

[133] Martin Wright's portable instrument for the continuous administration of analgesics, marketed by Pye Dynamics Ltd and covered by British patent No 9947/77, is described in Wright and Callan (1979). See also Dickson and Russell (1982).

thing it was to see patients at Northwick Park, for example, who had been out shopping that day, who had had a metastasised tumour for two years with severe pain, and had continuous diamorphine treatment for two years, with a syringe driver pump, going about their daily business.

The other thing is that the drug one would naturally have thought of early on was methadone, and it was Dr Twycross who made the first observations about what happened if you did give methadone to patients for this indication and showed that it in fact shortened their life in a measure.[134] Now that was not expected and I think it wasn't because we hadn't been appraised sufficiently of the three-step half life of methadone, which was shown by Inturrisi and Verebely quite a few years before,[135] though to be fair the third step in the half life was shown around the time when the clinical trials were being done.

Clark: Are you saying that was a candidate drug for the slow-release formulation?

Vere: Well, yes, and what was very amusing about it was that a well-known pharmaceutical company came to see us that very year to say that they were thinking of developing a sustained-release opiate preparation, and I remember saying to them – and I think Robert [Twycross] had the same conversation with them around the same time – 'What are you putting in it?' And they said methadone and I said, 'For goodness sake, don't do that' (because of Robert's work), and they said, 'Well, what should we put in?' I said, 'What about morphine? It's a sustained-release preparation, [and] this will make morphine available in a sustained-release way.' I think Robert advised them in exactly the same manner. They then produced MST.[136] It's interesting how these things happen.

Main: We have had a lot of discussion about cancer pain and of course it is of terrific and profound importance, but I do just want to redress the balance a little and talk about non-cancer pain. I think the way people have thought about how we should approach the treatment and management of non-cancer pain has changed quite a lot during the last century. In particular, how people have understood the relationship between pain and suffering and what our objectives of assessment and intervention should be. The Clinical Standards

[134] Hanks and Twycross (1981).

[135] Inturrisi and Verebely (1972).

[136] Oral slow-release morphine sulphate tablets (*MST Continus*, Napp).

Advisory Group (CSAG) report[137] emphasized that pain and disability needs to be understood from a societal as well as individual perspective and that there have been significant changes in public perception of what we ought to do about pain in the context of disability.

There is a significant group of patients who are extremely disabled, a proportion of them as a consequence of ill-advised clinical decisions, but I think in understanding pain from a societal perspective we have got to understand that individuals cope with pain in many different ways. And indeed if we look at the epidemiology we will see that there are a lot of patients in the community who do not consult their GPs with pain at all. Indeed, one of the best ways of managing non-cancer pain is to change what you do. The trouble is if what you decide to do is to lie down all the time and do nothing, the cost is too high. I should like, therefore, to broaden the discussion to include pain associated with suffering and disability, because I think in terms of a comprehensive way of looking at pain, we have to move beyond the symptom of the pain itself. It seems sometimes when we talk about pain we are talking about it as if it were a physical sign, but of course this is incorrect. Pain is a physical symptom that is multi-determined and I think we have focused too much on the 'sign' at the expense of the 'symptom' this afternoon.

Joranson: Two brief comments on the question of methodologies for achieving changes in public health policy that are necessary to implement the WHO guidelines. The first is that since the WHO guidelines recommended that opioids such as morphine be available in every country,[138] now there need to be guidelines about how to evaluate the national policies that govern opioids in every country. Such guidelines have been produced by WHO,[139] and are listed on the bibliography that I handed out.[140] They provide a book-end to the earlier 1986 WHO guidelines, where 14 years later in 2000, there are guidelines for evaluating any national narcotics control policy, to see if it is 'balanced', that is to say, does a national policy have the provisions necessary to ensure the availability of opioid analgesics for pain relief when needed. It's

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[137] CSAG (1994).

[138] WHO (1996).

[139] WHO (2000).

[140] The bibliography distributed at the meeting is included in the References on pages 85–102, and will be deposited along with other records from this meeting in Archives and Manuscripts, Wellcome Library, London.

a part of a treaty to which most countries are party. The second point is that in the evaluation and addressing of barriers to pain relief, whether it be for opioids or not, we have always found the model established by Everett Rogers, who has written a series of excellent communications and social policy studies from around the world that shed great light on how change occurs.[141]

Saunders: Just going back to the Japanese research described earlier. There's a Japanese man who wrote a book on dying in Japanese hospitals, translated into English, and which was a best seller,[142] and it's really quite a horrific thing. He was completely moved by reading Elisabeth Kübler-Ross's book[143] and has turned into a hospice doctor. He took me round his hospice in Tokyo and I don't know what drugs he was using, but what he describes at the end of his book, we are talking about beautiful surroundings and so on for dying, but what really matters is the relationships and there was no doubt at all that the relationships between that man and his patients were a major part of the pain relief that they were obviously experiencing.

Stjernswärd: May I just ask a question, with so much expertise around? What is the total size of the problem, estimated number of sufferers needing palliative care and how will we be able to cover the need? The hospices alone will certainly not be able to cover all, nor an institutionalized governmental approach. Giving figures for the need and pointing out that there are relatively simple and affordable solutions will be a strategy for achieving commitments to implement pain relief and palliative care, not only for cancer patients, but also the terminally ill in chronic diseases, AIDS and those with neurological diseases. For the chapter to the next edition of the *Oxford Textbook of Palliative Medicine*[144] that I am writing with David Clark, I have used as a rule of thumb: the global deaths and for estimating the need of different countries I have used their death rates, estimating that 60 per cent of those will need pain relief and palliative care. Considering that most cancer and AIDS patients will need it and data show that pain is one of the most common symptoms together with fatigue in the terminally ill, that 60 per cent may be an underestimate than overestimate. With 56 million deaths a year there will be 33 million needing pain relief and palliative care. Underestimating that at least two care-giving persons, usually family

[141] See, for example, Rogers (1962, 1966, 1997); Singhal and Rogers (2003).

[142] See Kashiwagi (1978).

[143] Kübler-Ross (1969).

[144] Stjernswärd and Clark (2004).

members, also will benefit, this gives a figure of 100 million people a year who could receive an improved 'quality of life and death' if palliative care could be offered. These figures also indicate it is a public health problem worthy of attack and the necessity for a public health approach. If anyone present today can give me another figure than the 60 per cent used it would be appreciated.

When advocating and getting commitments for establishing and planning national palliative care initiatives, the use of the death rates for estimating the need for palliative care has served the purpose well, such as in Uganda and Jordan.[145]

With the future age distribution, age pyramids, and the compressed ageing, we are healthy up to a late age, but then there is an explosive need for palliative care. The future looks grim, as from earlier figures there are four to 12 care-givers per care-taker, and these figures soon will be in a ratio of around two or fewer givers to one taker. This also will mean the number of taxpayers per recipient will be fewer. Will the working young be willing and able to cover palliative care as we see it when practised optimally in the hospices today for the elderly in the future?

Twycross: I share Chris Main's concern about the bias in the afternoon's proceedings and I fear that the written version will be a very lop-sided view of innovations in pain management during the twentieth century. But I guess we couldn't hope to have been comprehensive.[146] So I am going to continue the bias. I think you know there are a lot of good things on the horizon. You know that 30 years ago, even 20 years ago, progress certainly in relation to drug therapy was largely serendipitous. We had morphine and aspirin, and a few related drugs, but with all the adjuvant analgesics, it was serendipity that got us on to their track, and research grew from serendipitous observations. But, now in pain management, the research is being driven by a much more profound understanding of the underlying mechanisms. It is truly remarkable what people like Tony Dickenson and other more basic pain researchers know. In ten years' time the whole drug therapy may well have changed. Certainly it will be dramatically broadened, widened and deepened. That's because in the last five to ten years research has increasingly been driven by basic scientific knowledge, and not serendipity.

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[145] See Stjernswärd (2002); WHO and Jordan Ministry of Health (2002).

[146] See Dr Tilli Tansey's comment on page 71. For other approaches to the management of pain, for example, see Finlay (1996); Addington-Hall and Higginson (2001); and the September 2001 issue of the *Journal of the Royal Society of Medicine* (vol. 94) devoted to palliative care and HIV/AIDS.

Bond: Could I do what Robert didn't and that is to support what Chris Main said and just say a little bit about the other side, because what Robert said is absolutely right. The work done by Pat Wall and Ron Melzack in 1965[147] was in fact well grounded on existing research. Willem Noordenbos had even suggested the existence of the gate mechanism, but he hadn't demonstrated it in the way that Pat and Ron did. And since their time in 1965, there has been an explosion of biological research. I entirely agree with Robert's comments. The picture in psychology is actually rather different, because up to the middle of the twentieth century the psychological approaches were based mostly on psychoanalytic theory and on psychosomatic theory, which were not very helpful for either the understanding of chronic pain or the management of chronic pain problems. It was of some help, but not as much as one might have imagined.

And then in the 1960–70 era a profound change occurred in that approach to pain management with the appearance, first of behaviour theory, and more recently of cognitive theory, so that we got the cognitive behavioural approach,[148] which has been amplified in various ways as we have come to understand through research more and more about the psychological side of pain and suffering. I think Descartes might have been proud of the way we have conducted ourselves today, because it seems as though there is still only one aspect of pain and that is the biological one. But everyone in the room of course, in reality I don't think they would, shares the view that we have to use a bio-psycho-social model, which is something that appeared just a few years ago to encompass totality and it also includes a spiritual dimension amongst others. So I think that if we are going to present ourselves as real pain experts we cannot leave out of this discussion the contributions made towards pain management, whether it be in pain due to cancer, and whether it be in pain in non-cancer conditions, but I think a substantial expansion in the knowledge of the psychological and social aspects of pain itself.

Professor John Walker-Smith: As a paediatrician, could I just say a few words about pain in neonates? It is astonishing that in the past neonates were not believed to suffer from pain in the way older children did. I remember, as a young doctor in Sydney [Australia] in the 1960s, performing routine circumcision of neonatal boys. At that time all Australian boys were routinely

[147] Melzack and Wall (1965). See Appendix 1, pages 73–82.

[148] See, for example, Williams *et al*. (1993).

circumcised unless there was a parental objection. The poor little fellows would scream in pain. It was assumed that babies didn't experience pain. In 1983 it was shown that physiological stress was reduced by local anaesthesia in children being circumcised, but it was not until neonatologists demonstrated hormonal and metabolic responses to surgery with or without narcotic analgesics, that proof was provided that neonates reacted adversely to painful stress.[149] This occurred quite recently. It is astonishing that we were so terribly ignorant in the past.

Dr Jeremy Johnson: Just a very brief comment. Quite rightly looking forward to pain relief, locally and globally, mention has been made of research, but there's also the delivery of the molecules to where it matters in terms of the need. And there's also been mention of inappropriate use, particularly of methadone and fentanyl. Is there a feeling that perhaps the pharmaceutical industry might in fact highjack some of the work of WHO?

Stjernswärd: The large multinational drug companies are already doing it, ruthlessly caring for their profits, single-eyed, introducing unaffordable but not better or needed new drugs through aggressive unethical marketing while refusing to provide affordable generic versions allowing a meaningful coverage. Together with bought-up or naive colleagues they do a lot of intellectually seducing masturbation on the WHO pain ladder.[150] This gives a false impression of credibility but facilitates the marketing of their products. As mentioned earlier, as soon as we, with lot of efforts, have paved the way for efficient pain relief, the industry comes in and takes the market with drugs not recommended, thus making the initiatives non-sustainable. In Syria, for example, one big multinational company that knew I was coming even sent beautiful representatives from a neighbouring country to see leading key clinicians with their information materials, free samples and even establishing 'research trials' with their fentanyl plasters[151] in the leading cancer centre two weeks before our Ministry of Health workshop. It was obvious that lot of misinformation on how bad IRM and SRM[152] were had been given to the local 'pain expert' in the centre, or he was simply stupid or opportunistic in his statements. One week after the workshop the company held a 'scientific

[149] Walker-Smith (2003). See Williamson and Williamson (1983); Anand *et al.* (1987).

[150] For WHO three-step pain ladder, see Figure 5, page 43.

[151] *Duragesic* patch (Fentanyl transdermal system, Janssen Pharmaceutica Products). See also Appendix 2, note 186.

[152] Immediate-release and slow-release morphine.

seminar' in the cancer centre. Even the USA has difficulty affording the new expensive drugs, where another company aggressively markets a new drug that earns it US$1.8 billion a year, while due to this marketing the drugs are being over-used by non-chronic pain patients and where addiction may become a problem.[153] In Malaysia, we had a national workshop in the early 1990s. I learnt there that they had non-generic expensive MST available, which they did not when we planned the workshop. Six months earlier the same company mentioned above had visited the leading cancer specialist who then approached the Chief Pharmacist and pledged the need for pain relief drugs according to WHO recommendations.

The tobacco industry had similar approaches when, as cancer chief of WHO, I addressed tobacco control and cancer prevention at big international conferences. Usually after my lectures a guy stood up claiming that pollution and other substances caused more lung cancers than tobacco, so why was I bothered? Asking the person to identify himself, the answer usually was 'I am a consultant' or 'a researcher'. When asked from where, it was clear that he was from the tobacco industry. Finito comedia!

Hunter: Has anybody in the audience had any experience of working with the City of London Migraine Clinic? Because the treatment of that particular kind of headache was very significantly improved by research done by its Director, Dr Marcia Wilkinson. She discovered that the nausea of migraine significantly slowed down and impaired the absorption of oral paracetamol and that this problem was eliminated by giving oral metoclopramide 15 minutes before the paracetamol.[154]

Clark: Seemingly not. Can we have a comment to finish on rather than a question?

Vere: I am aware of this clinic, I have worked with some of the people in it and, yes, what you say is true. There was a very bright observation made and some good research done about it. But again, I think migraine is an example of a pain syndrome and a situation where people have taken, particularly the industry, far too narrow a view. And it was the lateral thinking that went on at the Bart's clinic and there's a need for a lot more.

Clark: I would hate to be the cause of migraine among those assembled here. Dr Saunders pointed out to me earlier that alcohol is an excellent drug and hasn't been mentioned yet. We are coming bang up to our time. When we spend four

[153] Anonymous (2004).

[154] See Wilkinson (1982); Lewis (1993).

hours together discussing a subject and in the last 15 minutes strong words come forward about how imbalanced that discussion has been, that to me is the outcome of a good afternoon. And probably suggests that this was 'Innovations in Pain Management I', and that even now the sequel is being prepared.

I would like to thank Tilli Tansey and her colleagues for the organization, the Wellcome Trust for its funding support, Marcia Meldrum for her introduction, the American Pain Society for financial assistance with travel and most of all to thank all of you for contributing to what I believe has been a fascinating afternoon. Thank you very much indeed.

Dr Tilli Tansey: May I add my comments to those of the Chairman? Thanks to all of you who have travelled here to contribute to this afternoon. I would like to add, in view of Dr Twycross's concern, that this is not going to be *the* recent history of pain management, but *a* contribution towards that, and I thank you all very much for contributing to the proceedings of this afternoon.

So may I thank our Chairman, David Clark, for the excellent chairing of this meeting and I hope you will join me in thanking him. This meeting has been recorded, and we will be preparing a transcript for publication.

Appendix 1

Extract from an annotated Physiological Society interview with Professor Patrick Wall (1925–2001)

by Dr Martin Rosenberg and Professor Steve McMahon on 5 February 1999[155]

Professor Pat Wall: The first question that interested me was connectivity in the nervous system. I should say that in Oxford at that time Sir Charles Sherrington was still alive and the nervous system was really the only subject to work on and in fact the spinal cord was the only get-at-able bit. But the major issue of the time was connectivity and in terms of anatomy the question was, how did you find out if one place was connected to another?

Paul Glees[156] had invented a silver-staining method in which you could just about see degenerating terminal arborizations. You saw a series of dots in the area of terminal arborization. That was what I did as an undergraduate with Glees and that was why I got my first job at Yale with Fulton in 1948. Fulton was American but had been in Oxford, first as a Rhodes scholar and then with the Sherrington group in the 1920s. John Eccles had been his graduate student. Yale had gone through a revolution in the late 1920s, in which they decided to make themselves into a proper medical school and they had called in all sorts of people, including Fulton who was brought back from Oxford to set up physiology at Yale in 1929.

It was 1948, when I was 23. Thanks to the war, everything had been wonderfully speeded up so that one could get a label of a medical degree very quickly. Then because of my work with Glees, I was picked up by Fulton and went to physiology at Yale on to this frontal lobe project: very classical stimulation of cortex, looking to see changes, and lesions in cortex and looking for anatomical changes. What I did then was to look for autonomic changes as a result of cortical stimulation and first found that in fact autonomic responses were very widespread and that was because in monkeys the fifth nerve innervates the skin and you can get autonomic changes because you are

[155] The full transcript of this interview will be deposited in the Archives of the Physiological Society, SA/PHY, held in Archives and Manuscripts, Wellcome Library, London.

[156] Glees (1946); Marsland *et al*. (1954). This silver method was developed for the study of normal and degenerating synaptic boutons and demonstrates neurofibrils, but obscures axons and terminals.

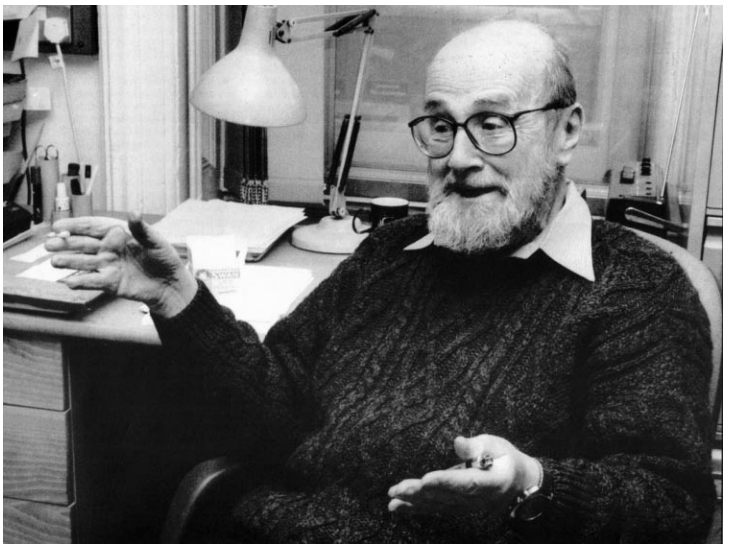

Figure 9: Professor Pat Wall.

stimulating the fifth nerve. But when you cut the fifth nerve you can then see the true cortical systems. So it was immediately apparent that the motor cortex produced autonomic changes…in blood pressure, heart rate, respiration changes and then we rapidly found that there was a strip of cortex which starts in the cingulate cortex, goes forwards and over the supra-orbital cortex and then continues extending laterally to the insula. So we described this as an autonomic response area for the first time,[157] although Papez[158] had described it before. I then set about finding out the anatomy.

I was at Yale for two years to 1950, by which time because of my attack on strychnine neuronography I had been picked up by Warren McCulloch, at that time in Chicago, at the University of Illinois, cooperating with two absolute geniuses, Walter Pitts, a mathematician, and Jerome Lettvin,[159] a neuropsychiatrist who had turned to physiology. McCulloch and Pitts had already started neuron modelling, so the Pitts–McCulloch neuron is still the basis of many of the neuron models.[160]

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[157] Howland *et al*. (1955).

[158] Papez (1929).

[159] See Lettvin talking about his scientific career in Anderson and Rosenfeld (eds) (1998): 1–21.

[160] McCulloch and Pitts (1943).

McCulloch organized for me to get the job of assistant professor at the University of Chicago in anatomy. Lettvin was a technical genius, and had really spotted the possibilities for electrophysiology, who had set up his own lab in a lunatic asylum, called Manteno State Hospital, a gigantic state hospital about 50 miles south of Chicago.

David Lloyd and John Eccles had defined circuitry within the cord: polysynaptic, monosynaptic reflexes and descending controls.[161] So we set about first doing very classical recordings, mass recordings. Pitts, who was very strongly in with Norbert Wiener at MIT, had become fascinated with the nervous system. Wiener's *Cybernetics* was actually written largely by Pitts. The next stage of the story is why we four migrated in 1953 to MIT at the invitation of Wiener. We were going to explain the nervous system in the ways that Wiener knew it worked.

There were some technical abilities that hadn't appeared at that time, that is to say to do with the electronics. At Chicago, Ralph Gerard had made the first microelectrode and in order to use the microelectrodes you had to know about grid currents.[162] All this became very, very simple as transistors appeared in the late-1950s, which had electronic valves. By the mid-1950s, people began not just to record mass potentials, which had obviously been done for a very long time, but to record single-unit potentials, and to make various types of metal microelectrodes. So it was an exciting time because the technical possibilities had suddenly hugely exploded.

We moved in 1953 to MIT which was fantastic in terms of technical support, because they'd been the major developers of radar. We were in the research lab of electronics. There were computers, of course, but they were very cumbersome things. MIT had a group of 'calculating women'. It was an astonishing sight, a room of at least 40 women, calculating collision tracks, and a lot of cosmic ray data on hand calculators. It was possible for us to make multi-channel recordings in the spinal cord of point variations and to give these ladies the numbers and they would hand calculate the interpolations and maps, field potentials and source–sink maps.[163]

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[161] Eccles (1961); Lloyd and McIntyre (1955).

[162] Graham and Gerard (1946); Ling and Gerard (1949). See also Gerard's biographical note on page 105.

[163] For the procedures used at the time in making these maps, see Howland *et al.* (1955). For a discussion of volume source and volume conductor, see http://butler.cc.tut.fi/~malmivuo/bem/bembook/07/07.htm (visited 29 June 2004).

Claude Shannon was there, having started at Bell Telephones, simply looking at information theory, which again was really an anti-noise strategy.[164] These exceedingly practical engineers, physicists, electronic engineers, were fascinated with the brain. Somehow the brain was doing what they would like to do. They had set us up all in this electronics laboratory, mainly militarily supported, but no secrecy at all. There were secret projects going on, but they were completely divided and separated and funded separately.

We were regarded as the group who was going to lay golden eggs, but you could chivvy the goose. There was a sense – particularly by people like Wiener – of huge confidence that he knew now the methodology by which you could understand complex circuits. It was then our job to prove him right, or that was his idea. Wiener was a great, massive, self-obsessed, manic genius. This was a difficult time but impressive people like Jerry Wiesner,[165] who was the boss of the whole thing, an electronic engineer who had been involved with radar and an absolutely brilliant organizer, protected us from this crazy man.

The important thing that Pitt, Lettvin and I did was to do a source–sink analysis of the input to the spinal cord, to try and follow a volley through the spinal cord from dorsal root to ventral root. Then we manipulated it by inhibiting the reflex and remapping. The results were very startling, to show an inhibition precisely where it was happening and as far as we could see happening presynaptically. We came out with a new method that involved calculation, the understanding of the second differentials and you can imagine that that was enough for most physiologists and for most people. …We said that you could inhibit an impulse presynaptically, which everybody knew was absolute nonsense and impossible. However, we published these maps and these conclusions in the *Journal of Neurophysiology* in 1955.[166]

I went to the 1953 International Physiological Congress in Montreal and gave these results. I was summoned to what consisted of a star chamber of Wilder Penfield, who was the head of neurosurgery in Montreal, E D Adrian, John Eccles, and Herbert Jasper, the electrophysiologist with the Montreal Neurological Institute, who was on his home territory. They called me in, just the four of them, to Penfield's office and said, 'Would you explain to us what

[164] Shannon and Weaver (1949).

[165] Rosenblith (ed.) (2003).

[166] Howland *et al.* (1955).

you have been saying?' So I gave them a sort of five-minute summary and they then said right out in the open, 'Look here, Wall, you are obviously a smart guy, you have been to the right places, but you are in the wrong company. This is simply impossible. This is some sort of artefact you are wasting your time on. Goodbye'. That really was something as you can imagine. Eccles was the strong one in that meeting. I thought, 'My God, if those characters are going to tell you that this is nothing more than an artefact as a result of using electrical stimulae', and so on. So in fact we backed off.

There was a question, 'Is there some other way in which you could follow the passage of nerve impulses, other than mass recording?' There was also the problem at that time that nobody was successfully recording from small cells and certainly not from small axons. It was just on the edge of being possible. Lettvin went off looking at small axons and started on the optic nerve of the frog, and out of that came Lettvin and Maturana, 'What the frog's eye tells the frog's brain'.[167]

I thought of another method, because I was impressed by Katz and Schmidt who had shown that if you took one group of active nerve fibres, and looked very carefully at the threshold of its neighbours, as the volley went by in one group you could see there was this slight shift as a result of the field spread in the other fibres. I thought, 'Here's a way in which we could see whether impulses have passed in one group of nerve fibres. We'll test the threshold of another group of nerve fibres'. So that's what I thought I was going to do, but what happened, of course, was that I then saw huge threshold changes as a result of presynaptic depolarizations.

At that time it [pain] was all to do with Sherrington, Eccles, Lloyd and reflex circuits which were a physiological event, not anything to do with behaviour or sensation. Eccles having said that this was all an artefact, then took up my technique and it suddenly became the popular, accepted technique. At first Eccles needed a technique that he could use which was microelectrode stimulation in order to find the threshold shift of terminal arborizations. So he became extremely complimentary of me, never gave me any credit, but complimentary, and he proposed that I must come to Canberra, which I happily resisted.

So then here in the spinal cord, and I could see these threshold shifts all being done with relatively large metal microelectrodes, but the circuitry had improved and now I could use real microelectrodes and I shifted to glass

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[167] Lettvin *et al*. (1959); Maturana *et al*. (1960). See also 'bug detector' in Anderson and Rosenfeld (eds) (1998): 415. For the wider influence of this work, see interview with Peter Bishop in note 169.

potassium chloride-filled microelectrodes. Then I could easily see single units. And so then I started recording single units in the dorsal horn[168] and first of all classified what the cells did, and it was at that stage that the question of pain arose, because I went naturally on to a search for cells which would only respond to intense stimuli [natural stimuli and/or electrical stimuli] and I simply couldn't find them and I still haven't seen one really.

By that time E D Adrian, Ynge Zotterman, and Peter Bishop had decided that there were modality-specific peripheral nerve fibres and therefore it was extremely natural to expect modality-specific cells, relay cells, in the spinal cord.[169] They thought I was somehow missing the point. I could find cells that only responded to low-threshold afferents, that was clear, touch cells, but I simply couldn't find these nociceptive specific cells.

Don't forget that inhibition or mixtures of stimuli was also very classical. That …had been set up certainly by Lloyd and Eccles and it was exactly what they were doing as was Lundberg [defining the flexor reflex].

I found one inhibition which actually came from an accidental personal observation. When pushing a hand-pushed motor mower with a hellish vibration, I began to realize that after enough vibration, my hands were really remarkably numb, and I thought, 'Well, let's try that on a cat.' So Cronly-Dillon and I published on the fact that vibration outside the receptive field of a cell would inhibit it. That was the first trigger for the gate control.[170]

Ron Melzack happened to be in psychology at MIT at that time and psychology at MIT at that time was at a very low level. It was in fact in the business school. But Ron had worked with Livingston[171] who was interested in pain and had raised puppies in isolation and said they took some time to develop pain. Melzack had done work in Oregon, so he was interested in the physiology of pain and we just started talking together and put together everything we knew at that time. This was all talk, but it was partly his

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[168] Wall (1973).

[169] See, for example, Adrian (1928); Wolstenholme and O'Connor (eds) (1959); Bishop (1989). For Peter Bishop's work on how the brain sees objects, see www.science.org.au/scientists/pb.htm (visited 28 June 2004).

[170] See Figure 9 and page 37.

[171] Professor William K Livingston was head of the Department of Surgery at the University of Oregon at that time. For background details, see Livingston (1998).

experimental work and a lot was my experimental work. Melzack did mainly behavioural experiments, but some electrophysiological.[172]

It's interesting that we wrote two major articles, one published in *Brain*,[173] describing our views on gate control. It had no effect at all. 'Gate control' was used, I think, for the *Science* article, the one that is always quoted.[174] And we had in fact been swapping our names backwards and forwards, some were Wall and Melzack and some were Melzack and Wall, it happened to be his turn to be first.

I drew that goddamn diagram. We first thought of it as 'gate control' …because we were always using triode valves which had a gate. That was my meaning of the word 'gate'. We'd been struggling with gate currents and used a gate control all the time for varying amplification. In that diagram which is an absolute minimum diagram, I'd introduced the smallest number of possible components, and some pure guesswork, like the fact that the proposal that the *substantia gelatinosa* was the origin of the inhibitory control. We already knew, and this again goes way back, that there were descending controls. It really goes back to Sir Charles Sherrington, who knew that a decerebrate animal had conspicuous proprioceptive reflexes. If you spinalize the decerebrate animal, the cutaneous reflexes dominate. So we knew that cutting the spinal cord released the cutaneous reflexes so we could install in the gate control, a descending control, on to a local circuit, which was being affected by the type of impulses that came in and the activity of the local cells.

The original paper explained that the diagram was a cartoon [Figure 10]. …That diagram is run entirely by presynaptic control and we knew at the time there were also postsynaptic inhibitions – it said so in the paper – but it was always a squabbling.

The previous joint papers hadn't been related to pain, but to all sensory inputs, which I still think is the case, and we decided, 'OK, just let's talk about pain in the 1965 *Science* paper.' But there was antagonism from the physiologists, …Adrian and Zotterman and Perl.[175] So the dictum of the physiologists was

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[172] Melzack *et al*. (1958).

[173] Melzack and Wall (1962).

[174] Melzack and Wall (1965).

[175] For example, Zotterman (1969–71); Perl (1971).

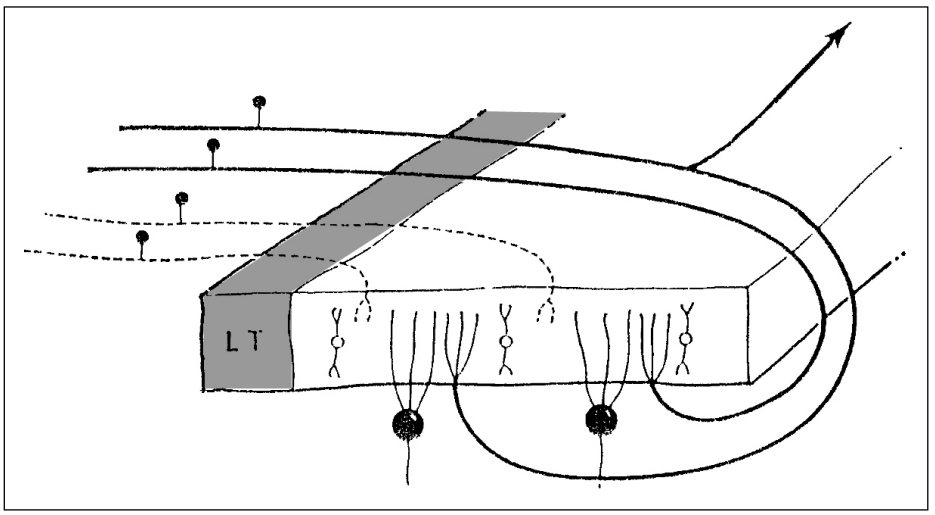

Figure 10: Cross-sectional representation of posterior dorsal horn of the spinal cord, showing the main components of the cutaneous afferent system in the upper dorsal horn. The large-diameter cutaneous peripheral fibres are represented by thick lines running from the dorsal root and terminating in the region of the *substantia gelatinosa*; one of these, as shown, sends a branch toward the brain in the dorsal column. The finer peripheral fibres are represented by dashes running directly into the *substantia gelatinosa*. The large cells, on which cutaneous afferent nerves terminate, are shown as large black spheres with their dendrites extending into the *substantia gelatinosa* and their axons projecting deeper into the dorsal horn. The open circles represent the cells of the *substantia gelatinosa*. The axons (not shown) of these cells connect them to one another and also run in the Lissauer tract (LT, shaded to distinguish it from the *substantia gelatinosa*) to distant parts of the *substantia gelatinosa*. From Wall (1964). Adapted from *Science*, 1965, **150**: 974.

very, very strong in favour of specific transmission and here was a challenge to them, which made them very, very annoyed.

Two things happened: one was that I could already see this powerful inhibition produced by low level inputs, so immediately we started trying it on ourselves, we made up simple stimulating gadgets to stimulate peripheral nerves, and then I went to W H Sweet, who was the head of neurosurgery at Massachusetts General Hospital at Harvard, and we tried on ourselves and then we tried on patients and came up with TENS [transcutaneous electrical nerve stimulation] and a paper called 'temporary abolition of pain in man'.[176] Now that of course

[176] Wall and Sweet (1967).

was then a very difficult challenge for a physiologist to dismiss, since it worked, and furthermore it recruited the clinicians. So the clinicians immediately leapt on this as an explanation for the various hyperpathic states and so on. The anaesthetists caught on very rapidly indeed. Willem Noordenbos was an important ally from the clinical world and it spread, but surprisingly slowly.[177] As a matter of fact, in the citation index it eventually became a *Citation Classic*, and they wrote an article on this, pointing out this was a highly unusual paper, that usually a paper comes out and is cited essentially immediately, the highest citation is within the first year and then it peters off. This one took something like five years before people were beginning to cite it and that was this whole recruitment, not of physiologists, but of the clinicians, pharmacologists, and so on.[178]

Zotterman, for example, had wondered what scratching was about and so he recognized 'why do you itch?' It's because itch fibres are excited, that's according to Zotterman, but how and why does scratching then work?[179] There must be an inhibitory process somewhere. Livingston and Noordenbos, as clinicians, had said, 'Look here, there must be central interactions to produce what we see in the patients'. I then had some very good students, Mendell for example,[180] and we …showed 'wind up',[181] so then we got into facilitation as well as inhibition.

I was really interested in the basic fundamental properties, almost on a cellular level, but it turned out that it was relevant to pain processes. That's a different story, which starts almost 25 years back, but really in 1973 or so. I realized that the reverberations of this were going through the pain field. I had a huge ally and that was John Bonica in Seattle, who was a great organizer, a great character, almost pure clinician, who invented the thought that pain was a special problem, a clinical problem, that it needed lots of experts focusing in [on it], even on an individual patient. First he set up his own clinic in this cooperative way in Seattle in 1947 and then wanted to expand it.

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[177] See, for example, Noordenbos (1960, 1962, 1964).

[178] Melzack and Wall (1982b), also available at: http://garfield.library.upenn.edu/classics1982/A1982NR10500001.pdf (visited 29 September 2004).

[179] Wolstenholme and O'Connor (eds) (1959).

[180] Mendell and Wall (1965).

[181] Wall and Woolf (1986).

There's a practical reason for pain clinics in hospitals and that is that the anaesthetists decided that people could not get their Fellowship of the Royal College of Anaesthetists (FRCA) until they had done *x* months in a pain clinic, so no training hospital can be a training hospital, unless it's got a pain clinic. Now it is true that that idea came certainly from Bonica, with me encouraging, obviously. I think it remains in doubt whether this is the right approach and whether what actually happens in a pain clinic is what is supposed to happen. You know 60 per cent of the pain clinics here have only a single consultant in one subject, well, that's instantly against the ideal.

I was always affected by C Judson Herrick, who said if you want to succeed in science, you must do three things: first, find something nobody else is working on, and he found the brain of the tiger salamander; second, write a book about it, so he wrote a book called *The Brain of the Tiger Salamander*, which is a very important book, the beginning of detailed comparative neuroanatomy;[182] and third, start a journal and he started the *Journal of Comparative Neurology*. So I followed his advice. Nobody was working on pain, because it was simply completely understood and there was no point in working on it. Melzack and I had written a Penguin, so the book was there.[183] We then decided to write *The Textbook of Pain*. Publishers told us that pain was not a subject. They had their boards of advisers who said, 'It's ridiculous, it's just not a subject'. Eventually Churchill Livingstone agreed to publish it and, to their absolute astonishment, it was a huge success.[184] While Bonica was setting up the International Association for the Study of Pain, the IASP, I said, 'Right, here is a chance to start a journal', because I still thought that this is an orphan journal, nobody is going to buy it, we need a society whose members will automatically buy it. So Bonica and I were in agreement and …this year [1999] is the 25th anniversary of that journal, *Pain*.

[182] Herrick (1948). C Judson Herrick was Professor of Neurology at University of Chicago, and published *An Introduction to Neurology* in 1916.

[183] Melzack and Wall (1982a).

[184] Wall and Melzack (eds) (1984) [4th edn, 1999].

Appendix 2

Morphine: Optimal potential for benefit with a minimum risk of adverse events and burden

Professor Jan Stjernswärd wrote: [12 April 2004]:

Morphine has been scientifically proven to be the single most effective opioid to achieve both immediate and long-term control of pain, and to manage breakthrough and procedural pain in either oral or parenteral formats. It has a very low incidence of adverse effects and less than 0.1 per cent of patients who use morphine to control pain ever go on to misuse it.

Oral morphine has been shown to control more than 90 per cent of patients' chronic pain. Injections or infusions of parenteral morphine are only needed to control 3–5 per cent of patients with difficult-to-control chronic pain syndromes.

In contrast, more expensive preparations of other opioids, such as transdermal fentanyl:

- do not add any increased potential for benefit;
- may have a much greater risk of misuse on the black market (they are both chewed, and the gel dissolved and injected);
- may be more difficult to use effectively in a hairy population in a hot climate where people who are prone to perspire tend to lose their patches (and receive ineffective dosing).

While pethidine has been used as though it were a step-three opioid [see Figure 5, page 43], it is only a step-two analgesic with weak efficacy. In addition, due to the accumulation of its toxic metabolite, it is associated with a high risk of serious adverse effects and is not appropriate for chronic pain management.

Cost effective

Both immediate and slow-release morphine preparations can be produced generically at a cost similar to acetylsalicylic acid tablets (ASA/aspirin).[185] In contrast, more elaborate preparations, such as transdermal fentanyl[186] may be much more expensive for the same morphine-equivalent dose. In our experience at WHO the relative cost of opioid preparations has been:

Drug	**Morphine**			**Fentanyl**
preparation name	oral immediate-release (tablets and liquids)	oral slow-release tablets	parenteral	transdermal
relative cost	1 ×	3 ×	5	20 or more

To control severe, chronic pain, use oral immediate and slow-release morphine preparations that have optimal efficacy, minimal risk of adverse effects and optimal cost-effectiveness. Parenteral morphine and other opioid formulations [should] only [be used] when oral morphine preparations cannot be ingested or in the few cases where they produce unacceptable adverse effects.

Oral immediate-release morphine	**Oral slow-release morphine**	**Parenteral morphine**	**Other opioid preparations**
30%	60%	5%	5%

WHO experience suggests that the following proportions are likely to be needed to control chronic pain on a national scale:

Oral immediate-release morphine	10 and 20 mg tablets 5 and 20 mg/ml liquid
Oral slow-release morphine	30, 60 and 100 mg tablets
Parenteral morphine	2, 10 and 50 mg/ml injectable solution (preferably preservative-free)

[185] Aspirin, generic tablets 300mg, cost 8p for 20 in March 1989. See *BNF* No. 17, p. 171.

[186] N-Phenyl-N-(1-2-phenylethyl-4-piperidyl) propanamide (*Duragesic* patch, fentanyl transdermal system, Janssen Pharmaceutica Products) was first synthesized in Belgium in the late 1950s and marketed for injection as *Sublimaze*.

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Biographical notes*

Professor Henry Knowles Beecher (1904–76), anaesthestist at Harvard University, observed during his wartime service that soldiers with serious wounds complained of pain less often than his post-operative patients at Massachusetts General Hospital, Boston. See www.library.ucla.edu/biomed/his/painexhibit/panel5.htm (visited 16 March 2004).

Professor Sir Michael Bond Kt FRSE FRCS(Ed) FRCP(Glas) FRCPsych DPM FRSA (b. 1936) qualified from Sheffield University in 1961 and was a lecturer in the Department of Psychiatry there from 1964 to 1967, and in the department of neurosurgery at the University of Glasgow from 1971 to 1973. He was appointed Professor of Psychological Medicine and Honorary Consultant Psychiatrist, University of Glasgow, from 1973 until 1998, later Emeritus. He was President of the International Association for the Study of Pain in 2002–03. He established the first psychologically/-psychiatrically-based clinic and in-patient Rehabilitation Unit for Chronic Pain Patients in Glasgow in 1982. With Issy Pilowsky, he developed the Analogue Scale for Pain Measurement in 1964. See Bond and Pilowsky (1966).

Professor John Bonica (1917–94), anaesthestist, developed the use of the epidural in childbirth. He became chief of anaesthesiology at the Madigan Army Hospital [WA] in 1944, later founded the Multidisciplinary Pain Centre at Tacoma General Hospital [WA] in 1947, later at the University of Washington in Seattle from 1960, where he was head for 18 years. Arising from his work with regional blocks to control pain, and his wife's complications from ether anaesthesia, he devised a system of continuous epidural analgesia that permitted the control of labour pain without the patient losing consciousness. His two-volume work, *The Management of Pain* [Bonica (1953)], remains the standard text on the subject. The International Association for the Study of Pain was founded under Bonica's leadership in 1973 and he was its first President.

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Professor David Clark

PhD (b. 1953) was educated at the Universities of Newcastle-upon-Tyne and Aberdeen. He was appointed Professor of Sociology at Sheffield Hallam University in 1993 and in 1995 became Professor of Medical Sociology at the University of Sheffield. He has been Professor of Medical Sociology and Director of the International Observatory on End of Life Care at Lancaster University since September 2003.

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Professor Hans Eysenck

PhD DSc (1916–97), a psychologist, was raised by his grandmother in Berlin, moving to London at 18. A student of Sir Cyril Burt, he received his PhD in psychology from the University of London in 1940. In 1946 he founded the Psychology Department at the Institute of Psychiatry, University of London, where he was head of department from 1950 and Professor of Psychology from 1955, until his retirement in 1983, later Emeritus. See www.pbarrett.net/hans_eysenck.htm (visited 16 March 2004).

Professor Sigmund Freud

MD (1856–1939), psychoanalyst, was born in Moravia, later settled in Vienna, where he studied medicine. His research into the

clinical uses of cocaine was conducted from 1884–87. He first used the term 'psychoanalysis' in 1896. Among his many honours was as a corresponding Fellow of the Royal Society of London in 1936. After the Nazi invasion of Austria in 1938, Freud and his family moved to London where he died the following year. See www.freudfile.org/coca.html and www.freud.org.uk/.(visited 16 March 2004).

Professor Ralph Gerard

(1900–74), American physiologist, had worked with A V Hill in London and Otto Meyerhof in Kiel on a National Research Council Fellowship in 1926–27, returning to the University of Chicago Physiology Department in 1928, where he remained until appointed Professor of Neurophysiology and Physiology in the College of Medicine, University of Illinois, in 1952. With Ling and Graham in 1949 he introduced the intracellular recording capillary microelectrode. See also Libet (1974); Libet and Reynolds (1974).

Sir George Godber

GBE FRCP HonFRCS HonFRCGP HonFRCPsych HonFRCOG (b. 1908) joined the Ministry of Health in 1939, became Deputy to Sir John Charles, the Chief Medical Officer, and succeeded him in 1960. He retired in 1973.

Dr Peter Hunter

MRCP (b. 1938) qualified from Middlesex Hospital, London, in 1963 and was Consultant Physician at the Royal Shrewsbury Hospital, from 1974 to 1993. From 1994 to 1997 he read pharmacology at King's College London, as preparation for full-time research on the history of discovery of drugs and medicines in the modern era.

Dr Jeremy Johnson

(b. 1950) developed an interest in symptom control in patients with advanced cancer, while training in clinical oncology. A career change to palliative medicine led him to Shrewsbury where he has been Medical Director of the Shropshire and Mid Wales Hospice since 1989.

Mr David Joranson

(b. 1941) graduated from the University of Wisconsin in 1970. He planned and administered a comprehensive drug abuse treatment programme at Madison, Wisconsin, in 1972, designed and administered a regulatory agency programme to address diversion of controlled substances in 1975; and was co-founder of the Wisconsin Cancer Pain Initiative and National

Association of State Cancer Pain Initiatives in 1986. He was appointed Senior Scientist at the University of Wisconsin and established and has directed the Pain and Policy Studies Group/WHO Collaborating Center since 1996.

Dr Leon Kaufman

FFARCS MAE (b. 1927) was Consultant Anaesthetist at University College Hospital, London, from 1969 to 1989, Honorary Senior Lecturer at University College Hospital Medical School, London, from 1969 to 2002, and at St Mark's Hospital, London, from 1965 to 1991.

Dr Elisabeth Kübler-Ross

(1926–2004), American psychiatrist and physician, born in Zurich, trained in medicine after being a hospital volunteer during the Second World War. She moved to the US shortly after marrying E R Ross in 1958, specialized in psychiatry and became assistant professor at the University of Chicago Medical School in 1965. Her bestseller, *Death and Dying* (1969), described five stages of dying: denial, anger, bargaining, depression and acceptance, although not everyone experiences all of them. See also Reed (2004).

Dr Suresh Kumar

(b. 1961), born in Kerala (India) and qualified in anaesthesiology, sociology and palliative medicine, has been a Consultant in Palliative Medicine at the WHO Demonstration Project in Kerala since 1997 and Director of the Institute of Palliative Medicine, Kerala, since 2002. He was part of the team that initiated Neighbourhood Network in Palliative Care (NNPC), the community programme in Kerala with massive grass roots-level participation.

Professor Louis Lasagna

(1923–2003) received his MD from Columbia University in 1947. He started the first academic group in clinical pharmacology at Johns Hopkins University. He was Chairman and Professor of Pharmacology and Toxicology and of Medicine at the University of Rochester School of Medicine and Dentistry from 1970–80, and Dean of the Sackler School of Graduate Biomedical Sciences at Tufts University, Boston, MA.

Professor Henry McQuay

FRCA has been Professor of Pain Relief at the University of Oxford and Honorary Consultant, Pain Relief Unit, Churchill Hospital, Oxford. See McQuay and Moore (1998).

Professor Chris Main

(b. 1947) was a clinical psychologist with Salford Health Authority from 1982 to 2002 and in 1983 set up the first pain management programme for low back pain. He is co-author of *Pain management: An interdisciplinary approach* (Main and Spanswick, 2000). He has been Professor of Clinical and Occupational Rehabilitation at the University of Manchester since 2004 and Visiting Professor in Primary Care Sciences at Keele University since 2004.

Dr Marcia Meldrum

(b. 1949) received a Master's degree in Healthcare Management from Boston University and worked for ten years as a medical administrator before beginning graduate study in the history of science and medicine, earning her PhD from SUNY Stony Brook in 1994. She is currently Co-Director of the John C Liebeskind History of Pain Collection at UCLA, where she also lectures in the history department. Her research interests include the history of pain management, of neuroscience, and of randomized clinical trials.

Professor Ronald Melzack

FRSC (b. 1929) received his PhD from McGill University, Montreal, Canada, in 1954, was appointed to Massachusetts Institute of Technology, Boston, MA, USA, where he met Patrick Wall, with whom he proposed the gate control theory for understanding the mechanisms of pain. He returned to McGill in 1963, and was E P Taylor Professor of Psychiatry from 1986 until his retirement in 1999. He developed the McGill Pain Questionnaire, (MPQ), the most widely used measuring tool for research on pain in human subjects, and served as President of the International Association for the Study of Pain from 1984 to 1987. See Melzack and Wall (1965); Melzack (1975). See also www.science.ca/scientists/scientistprofile.php?pID=199 (visited 22 June 2004).

Professor Harold Merskey

FRCP FRCPsych FRCPC (b. 1929) completed his DM thesis (Oxford) in 1964 on pain in psychological illness, while at the University of Sheffield under Erwin Stengel, and was a Physician in Psychological Medicine at the National Hospital for Nervous Diseases, Queen Square, London, from 1967 to 1976. He was appointed Director of Research at the London Psychiatric Hospital in London, Ontario, Canada, from 1976 to 1994 and was Professor of Psychiatry at the

University of Western Ontario, London, Canada, from 1977 to 1994, later Emeritus.

Professor Balfour Mount

OC OQ FRCSC (b. 1939) trained as an Urologist at McGill University and as a Surgical Oncologist at Memorial Sloan-Kettering Cancer Center, New York. His training in end-of-life care was at St Christopher's Hospice, London, in 1973–74. The following year he was appointed Founding Director of the Royal Victoria Hospital Palliative Care Service, part of the McGill University Health Centre, the Founding Director of the Palliative Care Division of the Department of Oncology at McGill in 1991, and the first holder of the Eric M Flanders Chair in Palliative Medicine at McGill in 1994.

Dr Peter Nathan

FRCP (1914–2002) qualified at Middlesex Hospital in 1939. He served as an army medical officer and in 1941 was sent to Sir Hugh Cairn's head injuries unit in Oxford, where the clinical aspects of the work led to his interest in understanding the neurological aspects of pain, and the investigation of new methods of pain relief. He became a registrar at the National Hospital for Nervous Diseases (later the National Hospital for Neurology and Neurosurgery) at Queen Square, London, in 1946, later Honorary Physician, and joined the Medical Research Council Neurological Research Unit there in 1948, where he became involved in research on the functioning of the brain and spinal cord. He and Pat Wall carried out the first UK trial of transcutaneous electrical nerve stimulation (TENS) for pain relief and tested the efficacy of acupuncture for pain relief and introduced its use into the NHS. He was a founder member and the first President of the British and Irish chapter of the International Association for the Study of Pain in 1979. His grandfather and father started the company in New Zealand that gave rise to the Glaxo drug company. See Schott (2003).

Dr Alexander Nicholson

MBBS MRCGP (b. 1970) qualified at the University of Newcastle-upon-Tyne Medical School in 1993 and has been training as a Specialist Registrar in Palliative Medicine in the West Midlands since 2001.

Dr Colin Murray Parkes

OBE FRCPsych (b. 1928) was a member of the research staff at the Tavistock Institute of Human Relations from 1962 to 1975. He

worked closely with Dame Cicely Saunders as Consultant Psychiatrist to St Christopher's Hospice, Sydenham, from its inception in 1967. Here he set up the first hospice-based bereavement service and carried out some of the earliest systematic evaluations of hospice care. He was a member of research staff at Harvard Medical College from 1965 to 1969 and Senior Lecturer in Psychiatry at the Royal London Hospital Medical College from 1975 to 1996. See Parkes (1975).

Professor Issy Pilowsky

FRCPsych, was Professor and Head of the Department of Psychiatry at the University of Adelaide and Head of Psychiatric Sciences and Consultant to pain clinics at the Royal Adelaide Hospital, Adelaide, Australia, until his retirement in 1998. He was a founder member of the Australian Society for Psychiatric Research and has been a Past Councillor of the International Association for the Study of Pain.

Mrs Jennifer Raiman

(b. 1936) joined the Department of Pharmacology and Therapeutics at the Royal London Hospital and Medical College in 1978 as a Research Fellow undertaking a study of protracted pain in patients in the hospital and local community. She developed the London Hospital Pain Chart and was seconded to Macmillan Cancer Relief as Education Advisor in 1983, becoming Head of Medical Services in 1986. She initiated and developed Macmillan's Medical Services Programme in cancer and palliative care.

Professor Emery Rovenstine

(1895–1960) was a general practitioner and a self-trained anaesthetist in Indiana before becoming an assistant to Dr Ralph Waters in the Department of Anaesthesia at the University of Wisconsin. He was Professor and head of the Department of Anaesthesia at New York University and Bellevue Hospital, New York, in 1935, he formalized a science-based approach to anaesthesia. See Bacon (2002).

Dame Cicely Saunders

OBE DBE OM FRCP FRCS (b. 1918) founder and Medical Director of St Christopher's Hospice, Sydenham, London, from 1967 to 1985 and Chairman from 1985 to 2000, first trained in nursing, qualified, but back pain barred practising. She returned to St Anne's, Oxford, gaining her diploma in Public and Social Administration and a war degree, becoming a Lady Almoner at St Thomas' Hospital in 1947. She

also was a volunteer sister at St Luke's, Bayswater, London, where she learned to use analgesics at regular intervals. She read medicine, and trained at St Thomas's, qualifying in 1957. She started as Halley Stewart Research Fellow under Professor Harold Stewart, St Mary's Hospital Medical School, London, working at St Joseph's Hospice, Hackney, in 1958 on pain in the terminally ill. Her 'scheme' of 1959 was a proposal for a 100-bed home for those dying of cancer and other diseases where pain could be controlled and symptoms alleviated, estimated to cost £200 000. St Christopher's was established as a charity in 1961 with a council of management. Funds accumulated, and the site in Sydenham was blessed in 1963, the foundation stone laid in 1965 and St Christopher's received its first patients in 1967. She has also been a member of the Medical Research Council from 1976 to 1979 and Honorary Consultant at St Thomas' Hospital since 1985. See du Boulay (1984).

Friedrich Wilhelm Sertürner (1783–1841) first isolated morphine from opium in 1805. He called it 'morphium' after Morpheus, the Greek god of dreams. See Huxtable and Schwarz (2001).

Professor Erwin Stengel (1902–73), Austrian–British psychiatrist and psychologist, was Professor of Psychiatry at the University of Sheffield from 1957 to 1967. See www.whoname dit.com/doctor.cfm/1492.html (visited 19 January 2004).

Professor Harold Stewart CBE DL FRCP FRSE (1906–2001) qualified at Cambridge and was in general practice in Barnet, Hertfordshire. Following his wartime activities, he became a consultant in pharmacology at St Mary's Hospital Medical School, London, in 1946 where he remained, as Reader in 1949, Head of the Pharmacology Department in 1950, Professor in the University of London in 1965 until his retirement in 1974, later Emeritus. His research was mainly on human fat absorption and transport and on problems of pain and analgesia. See Wood-Smith and Stewart (1962).

Professor Jan Stjernswärd PhD FRCP(Edin) (b. 1936) joined the World Health Organization in 1980. He pioneered the global development of pain relief and palliative care through a rational public health approach. As Chief of Cancer at WHO from 1980 to 1996 he initiated the 'WHO

Three-Step Pain Ladder' developed by a small team of specialists (WHO (1986)), produced manuals, policy guidelines for palliative care and cancer control, for National Cancer Control Programme and Palliative Care Programme and reoriented the WHO Global Cancer Control to an action programme for implementing the accumulated knowledge in cancer control.

Dr Mark Swerdlow

FFARCS DA (1918–2003) developed his interest in the problems of pain control as a Consultant Anaesthetist in Salford Royal Hospital from 1951 to 1980. He established one of the first pain relief clinics in Britain, the North West Regional Pain Relief Centre, in 1959; founded the Intractable Pain Society of Great Britain (later the Pain Society) in 1967, was elected Chairman in 1971 and later became an Honorary Member. Following his retirement he launched a new cancer pain relief programme for WHO, where he and a small group of specialists developed the WHO analgesic ladder method for treatment of cancer pain, first published in 1986. See Swerdlow (1974–89).

Dr Robert Twycross

FRCP (b. 1941) graduated from Oxford University Medical School in 1965 and was appointed Research Fellow in Therapeutics at St Christopher's Hospice, London, in 1971. He returned to Oxford in 1976 as Medical Director of Sir Michael Sobell House, a palliative care unit at the Churchill Hospital. He was Macmillan Clinical Reader in Palliative Medicine, Oxford University, from 1988 until his retirement in 2001. He has been Emeritus Clinical Reader in Palliative Medicine since 2001 and Academic Director of the Oxford International Centre for Palliative Care and Head of the WHO Collaborating Centre for Palliative Care.

Professor Duncan Vere

FRCP (b. 1929) was Consultant Physician at the Royal London Hospital from 1965 to 1995 and Professor of Therapeutics in London University at the London Hospital Medical College, later Emeritus. He was also chair of the Research Committee at St Christopher's Hospice, London.

Professor Gordon Waddell

FRCS has been Professor of Orthopaedic Surgery at the University of Glasgow, Consultant at the Glasgow Nuffield Hospital, visiting Professor at the rheumatology department of the

University of Manchester, and Associate Professor of Clinical Research at the British School of Osteopathy, London, since 1996.

Professor John Walker-Smith

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

Professor Patrick Wall

DM FRS (1925–2001) qualified in medicine at the University of Oxford during the Second World War, chose research as a career and worked at physiology laboratories at Yale, Chicago, Harvard and MIT until appointed Professor of Anatomy and Director of the MRC Cerebral Functions Group at University College London in 1967, where he remained until his retirement in 1992. He developed the gate control theory of pain with the Canadian psychologist Ron Melzack, which moved the focus of theories of pain to the spinal cord. With Sweet he also developed the transcutaneous electrical nerve stimulator (TENS) for pain. He was a founding member of the Brain Research Association (later British Neuroscience Association), the International Association for the Study of Pain and founding editor of the journal *Pain*, as well as joint editor with Melzack of the successful *Textbook of Pain*. See Melzack and Wall (1965); Wall and Melzack (1999); Wall and Sweet (1967) and appreciations of his career in the British Neuroscience Association *Newsletter* 40 (2001): 1–3.

Dr Martin Wright

FRCP (1912–2001), the inventor of the continuous infusion pump now universally used in terminal and postoperative care, was a bioengineer who joined the Medical Research Council Pneumoconiosis Research Unit at Llandough Hospital, Penarth, South Glamorgan, in 1949. He moved to the National Institute for Medical Research, Mill Hill, London, in 1957 to work solely on instrument development, then to

the MRC's Clinical Research Centre at Northwick Park Hospital, Harrow, in 1969 until his retirement. Among other equipment, he developed the Wright respirometer, an infant apnoea monitor and the standard breath alcohol detector. The MRC holds the patents on all his inventions. See Wright (2001); Davenport (1998).

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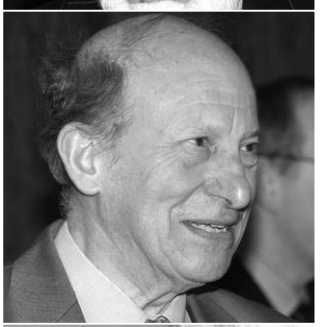

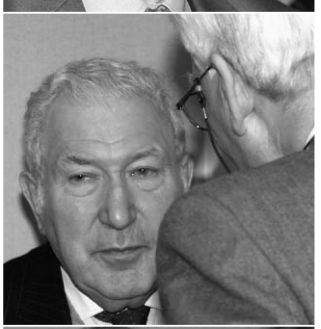

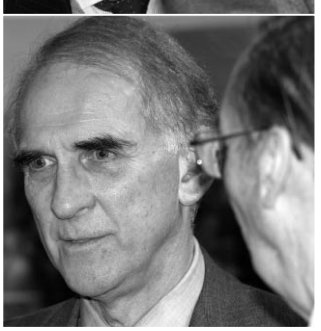

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