# THE MEDICALIZATION OF CANNABIS

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 24 March 2009

**Edited by S M Crowther, L A Reynolds and E M Tansey**

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# ILLUSTRATIONS AND CREDITS

# ABBREVIATIONS

| | |
|---|---|
| **ACMD** | Advisory Council on the Misuse of Drugs, Home Office |
| **ACT** | Alliance for Cannabis Therapeutics |
| **AIDS** | acquired immune deficiency syndrome or acquired immunodeficiency syndrome |
| **BMA** | British Medical Association |
| **CBD** | cannabidiol |
| **DDA** | Dangerous Drugs Act |
| **DEA** | Drug Enforcement Agency, US |
| **EMEA** | European Medicines Agency |
| **EEG** | electroencephalogram |
| **GSK** | GlaxoSmithKline |
| **HIV** | human immunodeficiency virus |
| **HODI** | Home Office Drugs Inspectorate |
| **IND** | Investigational New Drug |
| **MCA** | Medicines Control Agency |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **MRC** | Medical Research Council |
| **MRI** | magnetic resonance imaging |
| **MS** | multiple sclerosis |
| **NIH** | National Institutes of Health |
| **NIMH** | National Institute of Mental Health |
| **NSAID** | non-steroidal anti-inflammatory drug |
| **QUANGO** | quasi-autonomous non-governmental organization |
| **RCP** | Royal College of Physicians of London |

| | |
|---|---|
| **RPS** | Royal Pharmaceutical Society of Great Britain |
| **THC** | tetrahydrocannabinol |
| **THCV** | tetrahydrocannabivarin (tetrahydrocannabivarol) |

# WITNESS SEMINARS:
## MEETINGS AND PUBLICATIONS[1]

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

The Witness Seminar is a particularly specialized form of oral history, where several people associated with a particular set of circumstances or events are invited to come together to discuss, debate, and agree or disagree about their memories. To date, the History of Twentieth Century Medicine Group has held nearly 50 such meetings, most of which have been published, as listed on pages xiii–xvi.

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

Each meeting is fully recorded, the tapes are transcribed and the unedited transcript is immediately sent to every participant. Each is asked to check his or her own contributions and to provide brief biographical details. The editors turn the transcript

[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 UCL.

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

'The Medicalization of Cannabis' was suggested as a suitable topic for a witness seminar by Professor Virginia Berridge, who assisted us in planning the meeting. We are very grateful to her for her input and for her excellent chairing of the occasion. We are particularly grateful to Professor Leslie Iversen for writing the Introduction to these published proceedings. Our additional thanks go to Dr Paula Lincoln Smith, Dr Paddy Wiesenfeld and Ms Gloria Gridley for biographical articles about Dr Monique Braude. We thank Dr William Notcutt and Professor Roger Pertwee for help with illustrations.

As with all our meetings, we depend a great deal on colleagues at the Wellcome Trust to ensure their smooth running: especially the audiovisual, catering, reception and security departments and Wellcome Images. Mr Akio Morishima supervised the design and production of this volume; Ms Liza Furnival provided the index; and Mrs Sarah Beanland, Ms Fiona Plowman and Mr Simon Reynolds were our readers; Mrs Jaqui Carter transcribed the seminar and Mrs Wendy Kutner assisted us in running the meeting. Finally we thank the Wellcome Trust for supporting this programme.

*Tilli Tansey*

*Lois Reynolds*

*Stefania Crowther*

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

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# UNPUBLISHED WITNESS SEMINARS

1994 **The early history of renal transplantation**

1994 **Pneumoconiosis of coal workers**
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1995 **Oral contraceptives**

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2003 **Thrombolysis**
(partially published in volume 27, *Cholesterol, atherosclerosis and coronary disease in the UK, 1950–2000*)

2007 **DNA fingerprinting**

The transcripts and records of all Witness Seminars are held in archives and manuscripts, Wellcome Library, London, at GC/253.

# OTHER PUBLICATIONS

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

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

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

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

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*Haemophilia* **4**: 769–77.

**Witnessing the Witnesses: Pitfalls and potentials of the Witness Seminar in twentieth century medicine**
Tansey E M, in Doel R, Søderqvist T. (eds) (2006) *Writing Recent Science: The historiography of contemporary science, technology and medicine.* London: Routledge: 260–78.

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Tansey E M, in Cook H J, Bhattacharya S, Hardy A. (eds) (2008) *History of the Social Determinants of Health: Global Histories, Contemporary Debates.* London: Orient Longman: 279–95.

**Today's medicine, tomorrow's medical history**
Tansey E M, in Natvig J B, Swärd E T, Hem E. (eds) (2009) *Historier om helse* (*Histories about Health,* in Norwegian). Oslo: Journal of the Norwegian Medical Association: 166–73.

# INTRODUCTION

The medical use of cannabis has a very long history; it was used for thousands of years in Indian and other Asian medicine and was first introduced to the west in the mid-nineteenth century by a brilliant young doctor, W B O'Shaughnessy, returning to England after service in India. Cannabis was taken up enthusiastically by physicians in Europe and the US and was widely used for almost a hundred years until it fell out of favour as new and more easily standardized medicines became available and government regulations were imposed. Tincture of cannabis finally left the British Pharmacopoeia in the mid-1970s.

This Witness Seminar, however, was focused not on this early history but on the resurgence of interest in medical cannabis that has occurred in the past few decades. It brought together a group of people with diverse expertise who had witnessed at first hand the development of this field. Although the seminar did not deal at all with the recreational use of cannabis, it is impossible to consider the history of medical cannabis without considering the impact that the rapid growth of the illicit recreational use of the drug in the latter part of the twentieth century has had. The 'cannabis wars' have been fought between those who believe it to be harmless and medically useful, and those who see it as a danger to health and to society without any legitimate medical use. For many years the stigmatization of cannabis had a negative influence on the availability of research funding and promoted reluctance on the part of doctors and pharmaceutical companies to be involved in research on the medical uses of cannabis.

This changed, at least temporarily, with the elucidation in 1973 by Raphael Mechoulam of the structure of THC as the principal active ingredient of cannabis. A number of pharmaceutical companies began active research programmes aimed at designing THC-like synthetic compounds that would retain the medical benefits of THC without having the unwanted psychoactive effects. Such a separation was never achieved, although several very potent synthetic cannabinoids were synthesized and proved valuable later as research tools. Only one licensed drug, *Nabilone*®, emerged from all this effort (page 17). THC itself underwent successful clinical trials as an antiemetic and as a treatment for 'AIDS wasting syndrome' and was approved as a prescription medicine with the trade name *Marinol*®(page 5). Neither product made much impact, however, and interest in the medical uses of cannabis fell to a very low level for more than a decade.

The discovery of THC and the potent synthetic cannabinoids, together with the development of synthetic antagonists, such as rimonabant, sparked the modern revival of research interest in the field. Many of the key players in this were able to provide first-hand descriptions of the research discoveries that followed. New animal behaviour models were developed to investigate the psychomotor, analgesic and reward properties of cannabinoids. A major step forward was the discovery and cloning of the CB1 receptor in the brain and the demonstration that it mediated the principal psychoactive actions of cannabis (page 17). This was followed by the discovery of the CB2 receptor in the immune system in the periphery and further development of CB1 and CB2-selective ligands. As with the discovery of the opiate receptors 20 years earlier, this new knowledge prompted a search for possible endogenous ligands for the cannabinoid receptors, and this culminated in the discovery of a family of naturally occurring lipid signalling molecules, the endocannabinoids. Roger Pertwee, who with Raphael Mechoulam played a key role in this discovery, related how his work on the first endocannabinoid, anandamide, was performed in the same laboratory in Aberdeen used by John Hughes when he discovered the enkephalins 20 years earlier (page 16).

This avalanche of new scientific information was not accompanied at first by any revival of interest in the medical uses of cannabinoids. This happened partly as an unexpected by-product of the rapid growth in the recreational use of cannabis on both sides of the Atlantic during the 1980s and 1990s. As seminar speakers emphasized, the increasing number of self-reports of the beneficial actions of cannabis in treating the symptoms of a number of intractable disorders began to have a significant impact. Anonymous surveys such as that conducted by the Multiple Sclerosis (MS) Society revealed that a surprising number of MS patients were willing to use the illegal drug, and claimed medical benefits. The increasing level of interest in this possibility prompted a number of medical organizations to undertake reviews of the available evidence. The British Medical Association's report was followed by an enquiry by the House of Lords Select Committee on Science and Technology, published in 1998. This was my own introduction to the field of cannabis research as I was privileged to act as scientific adviser to this group. Although these reports seemed to have little immediate impact, they imparted a degree of respectability to the concept of the medicalization of cannabis. The initial reports were followed by an extensive review by the US Institute of Medicine and more recently by the Royal College of Physicians. All of these august bodies concluded that there was evidence for genuine medical applications of

cannabis, but that more research was needed, particularly to supplement the sparsity of properly controlled clinical trial data.

This led to the sponsoring by the Medical Research Council of the first large-scale clinical trial of cannabis in MS, which recruited more than 600 patients and lasted for up to 12 months. Although the results were mixed, there was evidence for a genuine, if modest, benefit on symptoms of pain and spasticity. The changing attitudes to medical cannabis also prompted Geoffrey Guy to form a company, GW Pharmaceuticals, to undertake the systematic development of a standardized herbal cannabis extract and a novel sublingual spray delivery system for the product called *Sativex*. Guy's background in developing conventional pharmaceuticals and herbal medicines gave him the necessary experience to undertake this difficult task. In the seminar, he provided important insights into the courageous decisions taken by the Home Office and by the Medicines Control Agency to provide GW Pharmaceuticals with licences to grow a standard crop of cannabis plants, and to undertake clinical trials with what remained a Schedule 1 drug (pages 30–4 and 36–8). Sufficient clinical data was amassed with *Sativex* to persuade the Canadian Government to approve it as a prescription medicine for treating pain in MS patients, and the product may ultimately be approved in many other countries, including the UK.

On the other side of the Atlantic, progress towards the medicalization of cannabis gathered pace towards the end of the twentieth century. The Canadian Government made a medicinal form of herbal cannabis available as a medicine, as the Dutch had done some years earlier (page 43). In the US, voters in several individual states approved the medicinal use of smoked cannabis, and 'cannabis pharmacies' were established, despite continuing resistance from the Federal Government in Washington (pages 42–3). The state of California in particular has led this movement, and provided state funds for controlled clinical trials.

Seminar participants speculated on possible future developments in the field. International pharmaceutical companies are focusing major research efforts to develop CB2 receptor selective ligands as potential anti-inflammatory/analgesic agents. The CB2 receptor is not associated with any psychoactive effects and is thus seen as 'safe'. Pharmaceutical companies had great hopes for CB1 antagonists for the treatment of obesity, but the first to be developed, rimonabant, ended in an expensive failure (pages 5 and 42). There may, nevertheless, still be other applications of cannabinoid antagonist

drugs. Meanwhile, research on the development of cannabis itself or novel compounds arising from endocannabinoid research remain largely the domain of smaller pharmaceutical or biotechnology companies or academic groups. Nevertheless, the future for the medicinal applications of our new understanding of cannabinoid mechanisms looks bright.

Leslie Iversen
University of Oxford

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# THE MEDICALIZATION OF CANNABIS

Participants

Professor David Baker
Professor Virginia Berridge (co-chair)
Dr Vincenzo Di Marzo
Professor Griffith Edwards
Professor John Galloway
Dr Edward Gill
Dr Geoffrey Guy
Dr Clare Hodges
Dr Anita Holdcroft
Ms Victoria Hutchins
Professor Raphael Mechoulam
Professor Anthony Moffat
Dr William Notcutt
Professor Roger Pertwee
Dr Philip Robson
Dr Ethan Russo
Professor Tilli Tansey (co-chair)
Ms Suzanne Taylor

**Among those attending the meeting:** Professor Paul Andrews, Dr Natalie du Sert, Ms Ruth Evans, Dr Martin Gorsky, Dr Vanessa Ho, Mr Andrew Hutchins, Dr Samuel Jackson, Professor Susanne MacGregor, Mrs Alice Mead, Dr James Mills, Ms Mel Porter, Miss Catriona Rooke, Ms Emily Sargent, Ms Sophia Sissay, Dr Gyorgy Szabadkai, Mr John Witton

**Apologies include:** Dr Jeffrey Aronson, Professor Heather Ashton, Dr Victoria Chapman, Dr John Clements, Dr Imogen Evans, Miss Mary George, Professor Allyn Howlett, Dr Ian Hudson, Professor Leslie Iversen, Dr Susan Kohlhaas, Dr Vivienne Nathanson, Professor Andrew Nunn, Dr Tony Peatfield, Mrs Jayne Spink, Professor Alan Thompson, Dr Ben Whalley, Dr Brian Whittle, Professor John Zajicek

**Professor Tilli Tansey:** Good afternoon ladies and gentlemen and welcome to this Witness Seminar on 'The Medicalization of Cannabis'. I'm the convenor of the History of Twentieth Century Medicine Group at the Wellcome Trust Centre for the History of Medicine at UCL. In 1990 the Wellcome Trust set up this group to create links between medical and scientific practitioners and historians of recent medicine and science. One of the techniques we devised is this format: the Witness Seminar, where we get together a group of people who've been involved in particular events, discoveries or debates, to discuss among themselves what really happened, the whys, hows and wherefores of what things went right and what things went wrong. We've now held over 50 meetings and have published more than 38 of them. All of our meetings are freely available as downloadable pdfs on the website of the Wellcome Trust Centre for History of Medicine at UCL, so do please feel free to have a look at them, and to use them if they are of interest.[1]

We never get everybody we want to these meetings. What we hear this afternoon will be the reminiscences and debates of those of you who are here. There are undoubtedly gaps and we are well aware that we are not going to be able to cover everything. Four years ago, the Royal College of Physicians working party reported on cannabis and cannabis-based medicines. If I can just quote from the first point in the executive summary:

> This report is concerned with the potential benefits and risks to health from the use of cannabis and cannabis-based drugs as medicines, rather than with the moral or legal status of cannabis.[2]

This focuses the way we want to structure our meeting this afternoon. We want to look at the benefits and possible risks to health from the use of cannabis as medicines, not any other aspect of cannabis. The topic was proposed by Professor Virginia Berridge, who has a postgraduate student working on a project in this field.[3] Virginia and I are going to chair this meeting between us; we are going to try to cover the early science and industrial and regulatory aspects, possibly devoting about 55 or 60 minutes to each subject. But before that, I'll hand over to Virginia who is going to say a little bit more about her project.

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[1] Available at www.ucl.ac.uk/histmed/publications/wellcome_witnesses_c20th_med, or by following the links to publications from www.ucl.ac.uk/histmed.

[2] Royal College of Physicians (2005): vii. Available at www.rcplondon.ac.uk/pubs/books/cannabis/cannabis_executive-summary.pdf (visited 12 January 2010).

[3] See Taylor (2008).

**Professor Virginia Berridge:** This derives from a three-year project, which was funded by the Wellcome Trust history of medicine panel, on the factors that have aided or been concerned with the medicalization of cannabis since the 1950s, but in particular since the 1970s and 1980s. I was the principal investigator on that grant and Suzanne Taylor was the research student and she is currently completing a PhD on this topic. So this Witness Seminar comes at a very opportune time for her. We're now going to hand over to Suzanne to give a brief historical introduction to this seminar.

**Ms Suzanne Taylor:** As Virginia said, I'm just going to give a very quick, potted history of the medical use of cannabis. Cannabis can be considered something of a curious boundary substance, capable of shifting between the categories of licit medicine and illicit drug, and back again, depending on the different scientific, cultural or political understandings of the day. Throughout its history, cannabis has been different things to different people, used as a medicine either through its extracts or as a leaf, it's been something of a pain for policy-makers, but also valued as a pain reliever for people suffering from intractable diseases. For some, it's been a harmless recreational drug, for others, a danger to mental health and, perhaps, society. As a medicine, cannabis was introduced to the UK from the colonies around the nineteenth century and it became something of a wonder drug, used for a variety of purposes, from alleviating vomiting caused by cholera and muscle spasm by rabies to use as a sedative or antibiotic.[4] But its usefulness was relatively short-lived. Cannabis's active principle had not at that time been isolated, unlike in the case of the opiates. Also, because of its properties, particularly not being water-soluble, it wasn't usable in new drug delivery systems with a hypodermic syringe, thus it slowly fell out of favour. There were also concerns about its link to insanity and crime.[5] So, research really fell by the wayside.

It was in the 1960s, when it re-emerged as a recreational drug in the counter-culture, that interest was renewed in the scientific community, perhaps through

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[4] See, for example, O'Shaughnessy (1839a); Mills (2003); Berridge (2003).

[5] Dr Edward Gill wrote: 'Cannabis was incorporated in the UK Dangerous Drugs Act (DDA) of 1925, on the same footing as opium. The DDA was the UK enactment of the League of Nations' International Opium Convention, 19 February 1925, which was debated at the Second Opium Conference in Geneva, November 1924–February 1925. This convention was really about the regulation of the traffic in opium, but at the last minute there was an impassioned appeal by the Egyptian delegate that cannabis was socially harmful and it was included in the convention, almost as an afterthought. There is an account of this as an appendix to the Wootton report.' E-mail to Mrs Lois Reynolds, 26 June 2009. See www.ukcia.org/research/wootton/apII.php (visited 22 February 2010); Berridge (1999); Mills (2007).

interest in drug dependence.[6] Also, importantly, the active principle, THC (tetrahydrocannabinol), was isolated and the pharmacology of cannabis could proceed apace.[7] With wider use in the general public, anecdotal reports of its usefulness in the treatment of disease began to emerge. But running parallel to this renewed interest in the science was increasingly prohibitive international legislation, for example, the 1961 UN Convention on Narcotic Drugs, and increasing regulation within the UK, and tincture of cannabis was banned by the mid-1970s.[8] With research on the pharmacology having taken off, but not much progress on the mode of action and other drugs beginning to take precedence in concern and increasing legislation, research interest began to contract again, though in the 1980s we saw the introduction of synthetic cannabis-based drugs for the treatment of nausea caused by cancer chemotherapy, for example *Marinol*® (dronabinol).[9] In the late 1980s and early 1990s there were important breakthroughs with the discovery of the cannabis receptor and the endogenous cannabinoids.[10] This opened up new avenues for research and stimulated interest in the field. Thus by the late 1990s, early 2000, we saw the re-emergence of pharmacological interest. A particular interest in the UK was the development of GW Pharmaceuticals, which was interested in the extracts of cannabis for the treatment of multiple sclerosis (MS) and pain.[11] We saw the start of clinical trials, developing an evidence base to support the anecdotal reports.

Also important throughout this history has been the role of the patient perspective and the use of self-medication. Activism in the UK related more to MS and pain, where people have pressured for more research, clinical trials and, perhaps, in the meantime, access to cannabis itself. So, today we're interested in

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[6] See, for example, World Health Organization (1971); Home Office (1968).

[7] Mechoulam *et al.* (1970). See also Mechoulam and Hanuš (2000); Di Marzo (2006); Pertwee (2006).

[8] The United Nations Conference for the Adoption of a Single Convention on Narcotic Drugs met at UN Headquarters, New York, NY, 24 January–25 March 1961; see United Nations (1972).

[9] *Marinol* is an antiemetic produced by Unimed Pharmaceuticals, a subsidiary of Solvay Pharmaceuticals Inc., Marieta, GA, see www.solvaypharmaceuticals-us.com/products/marinolproductinformation/0,998,12413-2-0,00.htm (visited 13 January 2010). For results of clinical trials published in 2005 and 2006 see www.solvaypharmaceuticals.com/researchanddevelopment/clinicaltrialsdisclosure/ClinicalTrialResultsDatabase/Marinol/0,,63138-2-0,00.htm (visited 13 January 2010). See pages 18 and 42.

[10] Matsuda *et al.* (1990).

[11] GW Pharmaceuticals was founded in 1998 in Salisbury, Wiltshire by Dr Geoffrey Guy and Dr Brian Whittle. It was floated on the London Stock Exchange AIM market in 2001. See pages 34–8.

the process of the medicalization of cannabis, considering themes including the trajectory of research, the importance of the growing international regulation, the role of industry, the preparation for clinical trials and the importance of activism. Within these themes perhaps factors to consider would include the importance of technological change, the development of drug delivery systems, the debate over extracts versus synthetics and issues of funding and supply. I'll hand over to Tilli Tansey, who will be chairing the first section on the early science, THC and receptors.

**Tansey:** As we start looking at the process of medicalization and the trajectory of research about what really happened and how, I'm reminded of Peter Medawar's paper, 'Is the scientific paper a fraud?' suggesting that the way we write scientific papers is constrained by the actual format and one never really knows the fine detail of what went on, how and why.[12] So, we want to ask you to tell us what was going on in the 1950s, 1960s and 1970s in the labs conducting the early research on cannabis. We have a number of pioneers here, people who were there at the time. We have already asked one or two people to say a few words to begin with, but please comment and add your own reminiscences and debates. Perhaps I could ask Professor Mechoulam to make some comments to begin with?

**Professor Raphael Mechoulam:** Cannabis has been used as a medicine for thousands of years. I understand we're not going into that aspect, but there is quite a lot of literature on it, some of it published, some of it just mentioned.[13] I understand that we are not going into the historical use of cannabis over centuries or millennia.

**Tansey:** No, we would really like to hear people's personal witness experiences.

**Mechoulam:** Suzanne Taylor mentioned that as cannabis became a drug used by young people in the 1960s, it led to the investigation of cannabis as it had not been investigated before. Actually, a lot of work had been done on it previously, but, surprisingly, the active component or components of cannabis had not been identified.

Here I come to something personal – I understand that this is what is asked for: in the early 1960s I was back in Israel after my first postdoctoral visit to the US, where I was at the Rockefeller Institute, New York, NY, working on

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[12] Medawar (1963).

[13] See, for example, Russo (2005); Mathre (ed.) (1997).

natural products. I returned to the Weizmann Institute of Science, Rehovot, Israel, where, at that time – and it's still the procedure today – a young person who is appointed has to come up with a few projects and then goes on working on them alone, or if he gets money, with some help. After five or six years the academic board at the Weizmann Institute decides whether he has done significant work in the field he has chosen. Then they may, or may not, give him tenure. As I mentioned, I had just come back from the US and I was interested in the chemistry and biological effects of natural products, and chose a few topics, one of which was cannabis. I asked the National Institutes of Health (NIH) in 1961/2 to support Dr Yehiel Gaoni and me.[14] The head of pharmacology at the National Institute of Mental Health (NIMH), Dr Daniel Efron, told me that they hadn't awarded a single cannabis grant; they were not interested in cannabis; they thought that it was a drug used mostly in Mexico and South America: 'It's not an American problem; when you come up with something more significant and relevant, please call us.' Nevertheless, my colleague, Dr Yehiel Gaoni, who was more or less at the same stage as I was at the Weizmann Institute, and I went ahead. We joined hands and started working together on the topic. About a year later, I got a call from Dr Efron asking me whether I was still working on cannabis and when I said: 'Yes,' he asked, 'Can I come over?' So, he came over and I inquired: 'What's the rush?' He said: 'Well, a senator called us and asked whether cannabis will ruin his son's brain because he was caught smoking pot.' The senator asked the NIH whether they had any medical or physiological information on cannabis. They had none, because nobody was working on it; they hadn't given a single cannabis grant ever, I believe, maybe a decade previously, but anyway, at that time, they had no projects. By that time we had isolated THC and elucidated its structure. Dr Efron took with him the world's supply of THC, about ten grams. Quite a bit of the early pharmacological work in the US on THC was done with the material that Dr Efron got from us and NIH was happy.[15] We got a grant and then later had to reapply many times; the grant continued for nearly 40 years,

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[14] Professor Raphael Mechoulam wrote: 'Yehiel Gaoni gained a PhD at the Sorbonne, Paris. He joined the Weizmann Institute in the early 1960s. He worked with Professor F Sondheimer on the syntheses of annulenes, a very important group of compounds. We collaborated on the chemistry of cannabinoids for about five or six years until I moved to Jerusalem. He retired as a professor of chemistry at the Weizmann about 15 years ago.' E-mail to Ms Stefania Crowther, 9 March 2010. Dr Yehiel Gaoni discusses his research on THC in the film, *Waiting to Inhale* (dir. Jed Riffe, 2005).

[15] Professor Raphael Mechoulam wrote: 'Personal communication from the late Dr Monroe Wall, who worked on THC at the time, and from the late Dr Daniel Efron.' Note on draft transcript, 9 March 2010.

and this was my main source of support. This is how my work began. There was not a lot of interest in cannabis when we started working on it. We began research on cannabis because it seemed strange that an illicit drug, widely used, was not as well known as morphine and cocaine. It was 150 years behind its time. There were good technical reasons why it was not known.

Morphine and cocaine are alkaloids, so they produce salts, which are crystalline and can be purified easily. In contrast, THC is part of a huge group of cannabinoids present in the plant; all of them boil at more or less the same temperature so they were very difficult to separate with the techniques available in the nineteenth and early twentieth centuries, and therefore the active component had not been isolated. At that time, only the structure of cannabinol, one of the components, was known and had been investigated quite thoroughly. It had been isolated in the UK in Cambridge at the end of the nineteenth century.[16] The structure was more or less completed, again in the UK, in the mid-1930s, more or less – not fully. It was fully identified and elucidated by Alex Todd (Lord Todd of Trumpington from 1962) in the UK and Roger Adams in the US, in the late 1930s and early 1940s.[17] But that was the one compound that was really well known, and as it is a compound formed on oxidation of THC, it's probably not an actual natural product. Another compound that had been isolated was cannabidiol, but its structure was not fully known (see Appendix 1). So, it seemed that the best thing for us to do was to re-isolate cannabidiol, a crystalline compound, and elucidate its structure. This was our first paper on the cannabis constituents.[18] We then went on isolating and elucidating the structures of a lot of the compounds that are there – cannabigerol, cannabichromene, cannabicyclol and cannabinoid acids.[19]

The reason that we could do this was that techniques had improved. There were new chromatography techniques that were available. At that time, almost 50 years ago, they were considered well advanced. And there were also techniques for elucidating the structures that were not available in the 1920s or 1930s, like nuclear magnetic resonance and mass spectrometry. So, we had the techniques both for separation and for elucidating the structures, and that is what we did. We isolated delta-9-tetrahydrocannabinol (delta-9-THC) in 1963 and

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[16] Cannabinol was first isolated in Cambridge, published as Wood (1899), but was incorrectly assumed to be the active ingredient of cannabis. See also Mechoulam and Hanuš (2000).

[17] See Work *et al.* (1939); Todd (1946). See also Maddox (1997); Mechoulam (1997); Adams (1940, 1941).

[18] Mechoulam and Shivo (1963).

[19] See Mechoulam (ed.) (1973); Iversen (2000); Pertwee (ed.) (2005); Pertwee (2006).

published the identification in 1964; we called it at that time delta-1-THC. We elucidated the structure mostly by physical measurements. We showed that there is essentially only one psychoactive compound: previously, people didn't know whether there was one compound or a number of compounds that were active. And this compound thus became available. Pharmacologists don't like to work with mixtures, for obvious reasons, but did a lot of work with the compound that we had isolated and which we supplied to many researchers. We devised later (and there was another group at that time in Switzerland that did the same) a synthetic pathway to natural THC, which is a (-) enantiomer I mean it rotates light to the left.[20] By our method one can also synthesize the (+) enantiomer, and this, I think, is still the only synthesis which does both things, and both enantiomers were evaluated at that time.

Another point: how does the plant synthesize these compounds? These are not very complicated compounds from the point of view of a chemist, and yet there is only one plant that synthesizes cannabinoids; the *Cannabis sativa*. Very strange. The cannabinoids are simple compounds and there are lots of them in the plant; about 60 are known. We isolated most of the major ones and biosynthetic pathways emerged. It was quite obvious how these compounds go from one into the other in the plant. Alex Todd had done some work on that, but he didn't have the actual compounds – hence it was very difficult for him.

Surprisingly, Alex Todd left the field in the early 1940s and went into other things for which he got the Nobel prize; so his interest waned.[21] And, surprisingly again, there was essentially no competition at that point. There was almost no work on the chemistry of the cannabinoids in the early 1950s, no work in the late 1950s, there was a little bit of interest in the early 1960s, but essentially no work was done, which was very, very surprising.

Tansey: May I ask Dr Gill what was the impact of the discovery of THC?

Dr Edward Gill: Well, I can more easily answer that by saying how the Oxford group, of which I was one, got involved in it. I think the trigger as far as Oxford was concerned was that *c.* 1970-ish, a report had been commissioned and published, known as the Wootton report (the subcommittee was chaired by Baroness Wootton). It may have been concerned with other things as well, but it was essentially addressing the question of whether cannabis should be

[20] Petrzilka *et al.* (1969).

[21] See Brown and Kornberg (2000).

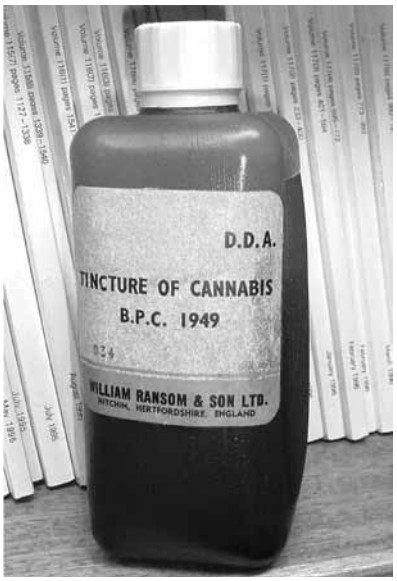


Figure 1: Tincture of cannabis, manufactured by William Ransom and Son Ltd.

decriminalized or not.[22] At that point, I think as far as Wootton was concerned, they were very much inclined to take the view that the inclusion of cannabis in the Dangerous Drugs Act (DDA) was causing more harm than good. They were therefore inclined to recommend that cannabis should be withdrawn from the DDA. That provoked a letter from Professor Sir William (Bill) Paton, who was then the head of the Oxford pharmacology department, to Baroness Wootton effectively agreeing with what Raphael Mechoulam has just said, which was that this was actually a very rash recommendation given that there was in fact very little known about cannabis; there was very little hard scientific evidence available in the literature to support a judgment one way or the other. Therefore, in a sense, it was considered to be more prudent to leave things as they were. That led to an obvious retort from Wootton back to Paton to the effect that: 'Well, if there isn't that much pharmacology, isn't it about time that you did some?' And that is how we started on it.

We needed a sample of THC, which was then recognized as the principal active constituent. There was no obvious source, so it was a question of doing it yourself. By trade I am a chemist, although I was based in the pharmacology

[22] Home Office, Advisory Committee on Drug Dependence (1968); the chairman was Sir Edward Wayne. The report includes the report on cannabis by the hallucinogens subcommittee chaired by Baroness Wootton of Abinger.

department and I came into it simply as an exercise in natural product chemistry. Most of my work up until then had been on straight synthetic chemistry so I really regarded it as an exercise in natural product isolation. Fortunately, a lot of the work had already been done by Raphael Mechoulam and others, so it was a relatively straightforward exercise to isolate pure THC. There was a firm called Ransom that had the country's entire stock of tincture of cannabis at that time (Figure 1).[23] So my job there was simply to isolate a sample of pure THC.

To carry the story on a bit, we used column chromatography to isolate a crude sample of THC and then, at the final stage, a method known as countercurrent distribution. I won't go into it, but it's essentially a multiple solvent extraction procedure, which has the advantage that it can be scaled up quite easily to handle gramme quantities.[24] I isolated a main fraction and identified it as THC from its mass spectrum, among other things. There was a second peak that emerged from the countercurrent machine, which I put aside at that stage. Having got the sample of THC I then thought: 'I wonder what this slow-running component is going to be?' I isolated it, took its infrared spectrum, which was at first glance identical with that of THC, which caused, I must say, an absolute panic on my part. I thought: 'Oh gosh, I've got the samples muddled up!' But we pursued it and found that this actually contained the propyl homologue of THC, with the terminal carbon chain shortened by two carbon atoms (see Appendix 1).[25] It turns out that other people had seen traces of the propyl homologue in mass spectra, but Ransom's sample had come from Pakistan and was very unusual, in that there were roughly equal amounts of the propyl homologue and THC itself.

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[23] Professor Roger Pertwee wrote: 'Tincture of cannabis was a commercial product that was prepared from *Cannabis sativa* grown in Pakistan and imported into the UK under licence. See Gill *et al.* (1970).' E-mail to Ms Stefania Crowther, 8 March 2010. William Ransom and Son was established in 1846 in Hitchin, Hertfordshire, and produced extracts of cannabis for pharmaceutical use until prohibited by law in 1973. Since 2005 the company's development team has been part of an EU-funded consortium researching the application of cannabis extracts to treat rheumatoid arthritis and migraine. See www.williamransom.com/about_us.asp?pid=4&nid=153; www.williamransom.com/research_and_development.asp?nid=198&pid=47cannabis; http://eprints.pharmacy.ac.uk/401/1/Heinrichcannabisforum.pdf (sites visited 18 January 2010).

[24] Dr Edward Gill wrote: 'Countercurrent distribution is a liquid–liquid partition system whereby a train of up to 100 interconnected glass tubes is mounted on a rack and mechanically agitated, and a substrate is repeatedly partitioned between two immiscible solvents moving in opposite directions… Countercurrent distribution is not widely used nowadays, being superseded by high performance liquid chromatography.' E-mail to Ms Stefania Crowther, 1 March 2010. See Ito and Bowman (1970); Korte and Sieper (1965).

[25] Gill *et al.* (1970); Gill (1971).

Roger Pertwee can say much more about the pharmacology that we were doing in the department at that time. As far as my own group was concerned, we were interested in whether the biological activity could be solely attributable to THC, or whether it was due to a metabolite. It was known that THC was hydroxylated in the seven position, and we, Roger particularly, did some work where we came to the conclusion that the metabolite, the 7-hydroxy, did make a contribution to the pharmacology of cannabis, but wasn't, as has been suggested, totally responsible for it; it was roughly half and half. I think at that point, as far as my group was concerned, we got to the point of saying: 'Well, there it is.' Roger and Bill Paton had worked out the catalepsy assay and had explored the basic pharmacology.[26] We came to the conclusion that cannabis probably could be classified as among the group of lipophilic general anaesthetics, very non-polar, as Raphael Mechoulam said, so totally different in its physical and chemical properties from the other centrally-acting alkaloids. We did some work with spin labeled phospholipids bilayers and showed that THC produced the same sort of perturbation (fluidization) of membrane lipid bilayers as other non-volatile anaesthetics, e.g. alphaxalone, did.[27]

At that point, my group withdrew from the field. I think the trigger, as far as the Oxford group was concerned, was very much the Wootton report and the fact that quite a lot of the hard work had already been done as far as the isolation was concerned. Raphael had completed the structure determination and there were several procedures available in the literature for its isolation, so it was simple to follow up this work, get hold of some pure THC and then start doing pharmacology.[28]

**Tansey:** Who was funding the research?

**Gill:** Most of it was funded out of departmental resources. The MRC did support it subsequently, but in those days departments could afford to do some research out of their own resources.

**Tansey:** Oh yes, golden, golden days!

**Gill:** Those were the days. As far as my group was concerned, it wasn't until much later on that we used grant money. We had MRC student support grants, but as far as the actual funding of the research is concerned, my impression is

[26] Paton and Pertwee (1972).

[27] See, for example, Lawrence and Gill (1975).

[28] See, for example, Korte and Sieper (1960).

that we really did it out of our own resources. In fact we were quite pleased as it made us, without being chauvinistic about it, independent of the NIH, which was then circulating samples of THC. I must confess, I hadn't realized that Raphael Mechoulam was so generous – I wondered actually where the NIH got their material from; I hadn't realized their THC came from your lab, Raphael.

**Tansey:** Can I ask Professor Pertwee to carry on the story about the pharmacology with Bill Paton.

**Professor Roger Pertwee:** I entered the cannabinoid field in the 1960s, which was, as we've already heard, a time when tincture of cannabis was actually still a medicine. My wife, Teresa, whom I first met around that time, told me that it was in fact still being used. She was a nurse and used to give it to hospital patients. So it was still being used as a medicine in the early 1960s. It was a time when we thought, quite rightly as it turned out, that THC was probably the main psychoactive constituent of cannabis, but we knew very little else about the pharmacology of cannabis. The structure of THC, thanks to Raphi Mechoulam, had just been elucidated, and indeed, it had also just been synthesized by him – a very important step, as it meant that we didn't have to rely solely on plant-derived cannabinoids. That said, it was very difficult initially, although possible eventually, to get hold of synthetic THC.

At that time, recreational cannabis use had become a major issue and certainly in the US, a lot of research was focusing on the harmful effects of cannabis and much less on its potential medicinal uses. In fact, in the early 1970s, tincture of cannabis was banned.[29] It was no longer a licenced medicine. The main interest then was in asking why cannabis is bad for you and why it is taken recreationally. A lot of the early pharmacology was descriptive, because so little was known and you could go in any direction you liked and there would be new stuff to learn about what THC and cannabis were doing. There was a lot of interest then in establishing whether THC is indeed the main psychoactive constituent of cannabis and hence in comparing the two pharmacologically. Tincture of cannabis remained very important to me because, before it was banned as a medicine, it was our main source of cannabinoids. Edward Gill

[29] Tincture of cannabis received a 'licence of right' under the 1968 Medicines Act that enabled doctors to prescribe it. However, this was not renewed when the 1971 Misuse of Drugs Act repealed the earlier Dangerous Drugs Act (1965). The regulations listed cannabis, cannabis resin, cannabinol and its derivatives in Schedule 4, which prohibited medical use altogether. See www.publications.parliament.uk/pa/ld199798/ldselect/ldsctech/151/15103.htm (visited 18 January 2010).

has already mentioned the countercurrent chromatography machine.[30] It was a vast machine, that would have stretched from about where I'm sitting now to that window [*c.* six metres], chuntering away in his lab. At one particular point, there would be the THC you could run off, and a bit further down, cannabidiol (CBD). Without it we couldn't have done any of our early cannabinoid research.[31]

I began my research on cannabinoids in 1968. I was completing my DPhil at the time at Oxford; this was on anaesthetics, which was probably one of the reasons I was asked to work on cannabinoids. Thus Bill Paton, and I think Edward Gill as well, believed very strongly that because cannabinoids are very lipid-soluble (lipophilic) molecules, they produce their effects by perturbing membrane lipids in the same way that some general anaesthetics are thought to do, they used the term 'partial anaesthetic' for cannabinoids because these compounds cannot produce complete anaesthesia, possibly because they are too water-insoluble, but that's another story. My own contribution was to develop a good bioassay for cannabis and THC and for this I decided to exploit their cataleptic effect. Cannabis and THC produce a very marked cataleptic effect in rodents. Treated animals wander around normally, or so it would seem, for part of the time, and then suddenly go off into a trance-like state, getting what looks like a total high. They then seem to recover before going off into another trance-like state.[32] Very strange. I'd read a paper by a chap called Sigmund Loewe, who in the 1940s produced a large tome on cannabinoids.[33] One of the things he mentioned was that if you place a mouse across the rim of a beaker, when you've given it some cannabis it goes off into a strange trance-like state for a short period of time and then recovers and so on. So I developed my assay by exchanging the rim of the beaker for a wire ring and called it the ring test, and we published a paper on this in 1972.[34] That test was included later by Billy Martin's group as one of a set of four tetrad assays.[35]

This takes us forward a bit, as it was a time when the receptors had just been discovered. It was a challenging time because there were no antagonists around

[30] See discussion on page 11.

[31] See note 24.

[32] For a demonstration of this effect see *Horizon: Cannabis: the evil weed?* (dir. Andrea Gillings, broadcast on BBC2 TV, 2 February 2009).

[33] Loewe (1944, 1946, 1950).

[34] Pertwee (1972).

[35] The tetrad assays measured tail-flick response, rectal temperature, catalepsy and motor activity in mice after administration of cannabinoid. See Smith *et al.* (1994).

and you needed to have some way of telling when you were looking for new compounds whether they were acting like cannabis or THC or not. Martin picked four assays, the idea being that if the compound was active in all four assays then it was probably a cannabinoid-like compound with a similar pharmacology to THC. At that time there seemed to be no other kinds of compound that behaved like THC in all four assays, though a few compounds that are active in the tetrad but do not have a THC-like mode of action have been discovered more recently. Another assay that forms part of the tetrad exploits the hypothermic effect of THC. We had studied the effects of THC and other molecules on body temperature, but I won't bore you with the details. Suffice to say that we obtained very good evidence that whereas fever up-regulates your set point, THC in mice seems to lower the set point, such that although they continue to thermoregulate they do this to maintain a subnormal temperature. This is something we might want to come back to in the future, because maybe endogenous cannabinoids have got something to do with hibernation.

As well as working with THC, we also did a bit of research with CBD and showed that it can target P450 enzymes. This research was done at a time before too much was known about these enzymes, but we were able to show that, for example, CBD had a very marked inhibitory effect on the metabolism of barbiturates in the liver.[36] It's really quite an effective inhibitor of P450 enzymes. Time and again, new techniques and ideas emerging in the general scientific field have influenced the direction that the cannabinoid field has taken. Research supposedly should be hypothesis-driven, but it is, in reality, technique-dependent. This happened in the early 1970s with P450 enzymes, at a time when nearly every other pharmacological paper seemed to be on these enzymes.

Another cannabinoid we looked at was the one that has already been mentioned by Edward Gill, the propyl analogue of THC, and that was, again, in the late 1960s. We found that it did in fact behave rather like THC, it was just a bit less potent; end of story at that time, because we were really focusing on THC.[37] But much more recently, in 2004, Geoffrey Guy nagged me into having another look at propyl THC, also known as tetrahydrocannabivarin (THCV), and we got some really interesting findings with it. These showed that although it does indeed behave the way we had found it to do back in the 1960s, at much lower concentrations it's actually an antagonist: it actually blocks cannabinoid

[36] Paton and Pertwee (1972).

[37] See Gill *et al.* (1970) and page 11.

receptors.[38] So, as I was saying to them earlier, I'm surprised that these two guys (Raphael Mechoulam and Edward Gill) are sitting next to each other and not quarrelling, because we have the discoverer of the agonist (THC) sitting next to the discoverer of the antagonist (THCV). Both THC and THCV are present in the same plant material and in the tincture, of course, in roughly equal amounts, so I'm not quite sure exactly what the tincture was doing, since it had both the agonist and the antagonist present. One thing I learned from meetings at the Royal Pharmaceutical Society, something I hadn't really appreciated before, is that cannabis does not itself contain much THC. It contains the acid of THC, I was told, though Raphi Mechoulam doesn't agree with this. I was told that it is when cannabis is heated that a lot of the acid gets converted to THC. There may be some THC there, but the amounts increase when you heat it or burn it. Moving on, all of the obvious research had been done with cannabinoids by the early 1980s and things went into the doldrums for a while, a situation that changed dramatically with the discovery that there are cannabinoid receptors.

**Tansey:** So you're now in Aberdeen? Just for the record.

**Pertwee:** I'm now in Aberdeen, yes, I moved there in 1974. I actually took over from a chap called John Hughes, who gave up his lectureship in order to work in Aberdeen on compounds that came to be called the enkephalins (endorphins). It was shortly afterwards, of course, that he and Hans Kosterlitz did indeed discover the enkephalins.[39] What is quite weird is that at that time when we got that fantastic compound sent to us by Raphi Mechoulam, which we subsequently called anandamide, I was based in the actual lab in which Kosterlitz and Hughes had worked on enkephalins, as they had by then moved into a different lab. This was down in Marischal College in Aberdeen. It signalled the end of the time when cannabinoid research was in the doldrums as indicated by the lack of funding for it available at that time. I had, by the way, been funded at Oxford by the MRC as I had a postdoctoral MRC position there.

People like Billy Martin in the US had, to some extent, moved into amphetamines, cocaine and that sort of thing, away from cannabinoids.[40] I think the whole thing was saved by big pharma in the form of Pfizer, who came up with this very interesting compound, CP55940 and its tritiated

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[38] Thomas *et al.* (2005).

[39] For discussion of Hughes and Kosterlitz's work on endogenous opiates, see Tansey and Christie (eds) (1997a).

[40] See, for example, Dewey *et al.* (1982). See also Klein *et al.* (2008).

version. One big challenge then had been to explore the possibility that there might be cannabinoid receptors by seeking out specific binding sites for THC, something that Billy Martin's group had tried to do. THC is too lipophilic and doesn't have a strong enough affinity for the cannabinoid receptors, so you get nearly all non-specific binding – very little specific binding, and so that approach was not successful. But CP55940 has much higher affinity for what turned out to be the CB1 receptor and also the CB2 receptor, and it was possible to actually do decent binding studies with tritiated CP55940. Allyn Howlett in the US was the first person to do that, along with a chap called Bill Devane, who was her PhD student at the time.[41] They were able to demonstrate these high-affinity binding sites and that led to the discovery of the receptors. They also carried out signalling studies, as this was a time when a huge amount of research on G protein-coupled receptors was going on. G protein research was a big thing in the 1980s and Allyn Howlett was an expert on that. She was able to show that THC and CP55940 were probably acting on something that relied on G protein-mediated signalling.

Another important technique developed around that time was receptor cloning, and that happened for the CB1 receptor in 1990, in Tom Bonner's lab at the National Institute of Mental Health (NIMH), Bethesda, MD. In his lab, Lisa Matsuda had been able to clone a new receptor, but had no idea what she'd cloned. I don't know the complete story, someone else here may know, but I think one day she or Tom Bonner saw where another NIMH scientist, Miles Herkenham, had found the CB1 receptor binding sites to be located in the brain. The cloned receptor was located in the same brain areas, so they put two and two together and came up with the idea that they must have cloned a CB1 receptor and went on to demonstrate that. Their paper was published in 1990 and after that, the field really exploded as far as the science was concerned.[42]

In parallel with all of this, of course, and we'll probably discuss it later, there were clinical trials happening that resulted in two cannabinoids becoming licenced medicines. One was a compound called *Nabilone*®, developed by Eli Lilly, which entered the clinic in 1981 as an antiemetic.[43] The other was THC itself; a lot of people don't know that synthetic THC was and still is a medicine

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[41] See, for example, Devane *et al.* (1986, 1988); Howlett *et al.* (1990).

[42] Matsuda *et al.* (1990, 1992).

[43] See, for example, Einhorn (1982).

called *Marinol* (dronabinol). It entered the clinic in 1985 as an antiemetic and again in 1991 as an appetite stimulant, particularly for AIDS patients.[44]

With the discovery of the CB1 receptor the field really exploded. Particularly important was the discovery of endogenous cannabinoids; Raphi Mechoulam asking the fantastic question: 'If there are receptors, are there also endogenous ligands for these receptors?' And anandamide was discovered and was followed two years later by 2-arachidonoyl glycerol.[45] The discovery of the CB1 receptor was of course followed by the discovery of the CB2 receptor.[46] The discovery of these two receptors led to the development of new synthetic ligands, by us and others, of compounds that targeted CB1 or CB2 receptors selectively as agonists and, very importantly, of antagonists, initially by Sanofi-Aventis, who came up with rimonabant (*Acomplia*®), which although it has now left the clinic – and that's something we'll come back to later maybe – it constituted a major advance as it made all the difference to us pharmacologists to have a selective antagonist around to work with.[47] Eventually, evidence emerged that the endocannabinoid system can be auto-protective in some instances and auto-impairing in others; that it has its own pathology, in other words. Very often it is actually protective and again this is clinical, and something we may come back to later when we move onto clinical issues. A search also began for additional cannabinoid receptors and there is in fact a heated debate currently going on about whether the orphan G protein-coupled receptor, GPR55, is another cannabinoid receptor. Also, we have discovered an allosteric site on the CB1 receptor, which means we can modulate that receptor allosterically, which could be very important, not only experimentally but also clinically.[48]

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[44] See note 9 and page 42.

[45] Devane *et al.* (1992); Mechoulam *et al.* (1995).

[46] Professor Roger Pertwee wrote: 'The CB2 receptor was first cloned by a British scientist, Sean Munro, in the UK. Munro *et al.* (1993).' Note on draft transcript, 3 March 2010.

[47] See page 42. Professor Roger Pertwee wrote: 'The discovery of the CB1 receptor also prompted us to develop in vitro bioassays for CB1 receptor ligands, for example, one that is performed with the mouse isolated vas deferens and played an important role in the discovery that anandamide is an endocannabinoid and that there are CB1 allosteric sites, a second bioassay that is performed with myenteric plexus-longitudinal muscle tissue obtained from guinea pig small intestine, and a third that is performed with mouse isolated bladder. See Pertwee *et al.* (1992); Pertwee and Fernando (1996).' Note on draft transcript, 3 March 2010.

[48] See, for example, Price *et al.* (2005).

I'd like to end by pointing out one or two factors that facilitated all of this. One of them was actually that in the 1990s large numbers of press reports were published claiming that a lot of people were self-medicating with cannabis. That, I think, acted as a spur to people to reconsider the clinical potential of cannabinoids. A very important person in all that was Clare Hodges, who is here today, and we'll come back to her contributions later, I'm sure.[49] I would just like to mention now that it was really thanks to her that we were able to carry out an anecdotal study in which we contacted patients who were self-medicating with cannabis to find out why, and what the claimed benefits were. These were MS patients. We wrote this study up as a paper.[50] It was largely due to Clare that we were able to do this because she put us in contact with those patients. The interest in cannabis and MS at that time led David Baker, who is an expert in MS, to come into the field and explore at the preclinical level how cannabinoids might affect MS and what the mechanisms for this might be. David is here as well and I'm sure will say something later.[51]

Another facilitatory factor was the emergence of more democratically organized scientific meetings. We'd had a lot of meetings run by one or two people who always seemed to invite the same speakers, and it was kind of undemocratic. But then, in a timely way, in 1990 the International Cannabinoid Research Society was formed (initially as the International Cannabis Research Society) and that made a great difference.[52] This was a time, remember, before e-mail, when it was very difficult to communicate with one another efficiently. Now it's so much easier, but there was a real need for a society like that, certainly before e-mail, and I think there still is.

UK organizations were also very important. The British Medical Association (BMA) got very interested and finished up by producing a book.[53] The Royal Pharmaceutical Society (RPS) was also very important, but more on the

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[49] See pages 20–1 and 61.

[50] Consroe *et al.* (1997). See pages 55–6, below.

[51] See pages 51–3.

[52] See http://cannabinoidsociety.org/ (visited 19 January 2010).

[53] British Medical Association (1997). Professor Roger Pertwee wrote: 'The production of the book was prompted by a report the BMA had commissioned me to write (Pertwee (1997)). In December 1997, I also represented the BMA at a meeting at Westminster of the All-Party Parliamentary Committee on Multiple Sclerosis that had been convened to answer questions about the BMA report, *Therapeutic Uses of Cannabis*.' E-mail to Ms Stefania Crowther, 8 March 2010.

clinical side.[54] The House of Lords, again, was very important from the clinical side.[55] And then funding: for my own lab, the MRC initially at Oxford and then the Wellcome Trust, that funding was very important for us. I got two very good re-entry research fellows from that and one of them (Ruth Ross) is now a professor in Aberdeen and it's great that she is still there.[56] The MRC funded a cannabinoid cooperative group in Aberdeen. That was good because it encouraged non-cannabinoid scientists in Aberdeen to begin working on cannabinoids. We also got UK funding from the Biotechnology and Biological Sciences Research Council and US funding from the NIH.

Finally, the involvement of pharmaceutical companies was very important. They provided very useful pharmacological tools: CP55940 and rimonabant I've mentioned, but there was also SR144528, which is a very important CB2 selective antagonist, again a Sanofi-Aventis compound. It was possible for some of us to become consultants for one or other of these companies and that meant we had access to interesting novel compounds and it was really as a result of getting compounds from Organon,[57] for whom I was a consultant a few years ago, that we discovered the CB1 allosteric site. When I got their compounds we didn't realize that they were allosteric modulators, but from the experiments we did, it became clear that they were, and that led us on to discover this allosteric site on the CB1 receptor, which I think could be really important therapeutically.

Tansey: You've raised a lot of questions there. Dr Hodges, do you want to come in at this point?

Dr Clare Hodges: This made me think about the great increase in interest, since the real social change, and realize how much difference it made to scientists that

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[54] Professor Roger Pertwee wrote: 'In April 1998, I was invited to the House of Commons to present scientific and clinical evidence about the therapeutic potential of cannabinoids to the Parliamentary and Scientific Committee. In May 1998, I was invited to the House of Lords to give evidence to its sub-committee on cannabis, a transcript of which was published as House of Lords, Select Committee on Science and Technology (1998): 64–83, 280. I also contributed to a written memorandum by the Royal Society and the Academy of Medical Sciences that is published in the same report (pages 293–8, 300–1).' E-mail to Ms Stefania Crowther, 8 March 2010. See page 35, below.

[55] See pages 38–9.

[56] Professor Roger Pertwee wrote: 'Ruth Ross is professor in the school of medical sciences, Institute of Medical Sciences, University of Aberdeen. See, for example, Ross (2009).' E-mail to Ms Stefania Crowther, 8 March 2010.

[57] Organon International became part of Schering-Plough Corporation, Kenilworth, NJ, (Merck & Co. Inc., Whitehouse Station, NJ, from 2009) in 2007.

so many patients used cannabis. As Dr Pertwee said, I helped him to interview by post all those people who were using it, and that changed everything.[58] Then politicians, doctors and everyone started taking it very seriously, because so many people were using it. They realized it was worth finding out what was going on and that was when research started happening.

**Tansey:** It was very important. We will come back to the question of patients and activism towards the end of the meeting.

**Mechoulam:** Let me go back a bit, as I didn't mention any pharmacology. The basic technique of identifying an active compound in a mixture is to have feedback from a biological test of some kind. When we started identifying the components in the cannabis mixture, we had to use feedback from monkeys. At that time a good friend and colleague, Dr Habib Edery, who was the head of pharmacology at the Biological Research Institute, not far away from the Weizmann Institute, had a colony of monkeys and we would give him extracts, chromatographic fractions or purified compounds and when we got the results back we could put aside the inactive fractions.[59] What was the activity? Edery found that half a milligram of THC given to a small rhesus monkey would sedate it.[60] This was the first pharmacological test that we used. Then we had to find out whether the other compounds were active; they were not. But we also had to find out whether the other compounds had some kind of synergistic activity when added to THC. So we got all the inactive compounds we had and put them together with THC and looked for any changes in activity. Habib Edery found that there was no change.[61] So we could say that THC is the only active compound. This was the pharmacology we used at that time; the less expensive tests in mice were not available and we didn't have dogs to test for dog ataxia, which was the standard technique for evaluating cannabinoids.

**Tansey:** Could you put a date on that for us, please?

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[58] See pages 55–6.

[59] Professor Raphael Mechoulam wrote: 'Dr Habib Edery was born in Argentina, I believe, and came to Israel in the 1950s. He was head of the pharmacology department in the Biological Institute, Nes Ziona, Israel. In the late 1980s he had a stroke. Feeling that he was losing his memory, he became depressed and committed suicide.' E-mail to Ms Stefania Crowther, 9 March 2010.

[60] Edery *et al.* (1971).

[61] Mechoulam *et al.* (1970).

**Mechoulam:** We started collaborating with Habib Edery in the early 1960s – 1963 or 1964. We later published a paper in *Science* showing that the other cannabis components were not psychoactive and did not synergize the psychoactivity of THC and therefore, from that viewpoint, they were not interesting.[62] They had, however, many other pharmacological activities, which were published later on.

A few words on the metabolism of THC: strangely enough, there were four papers, including ours, published essentially simultaneously, saying more or less the same thing: in the initial step a hydroxyl group goes to the seven position (today it's called the 11 position).[63] Thus, THC first forms an active component, which has a lot to do with the activity in the body, and then it is converted into an acid, a cannabinoid acid, which we discovered together with a Swedish group, which is not active, and stays in the lipids in the body for many weeks.[64] Therefore, today, if you want to find out whether somebody is using cannabis, you can analyse the urine and find the cannabinoid acid, THC acid, almost six or eight weeks after their last use of cannabis. All this goes back to the 1960s and early 1970s. Would you like me to say something about anandamide at this point?

**Tansey:** Yes, please do.

**Mechoulam:** As was mentioned earlier, Allyn Howlett identified an active site, a receptor, in the 1980s. The reason why a receptor was found only about 20 years after THC was discovered was that there was a mix-up in the literature, partly because the Oxford group had thought, and rightly so, that it may act as a partial anaesthetic. Let me explain. When there is a compound that exists in two mirror images, enantiomers, normally only one will be active in the body, because the active sites, the receptors, DNA or enzymes, are all asymmetric. Therefore, only one enantiomer should be active. If both are active then probably the activity is not due to a receptor or an enzyme or DNA or other body constituents, but is 'unspecific'. It was shown that with synthetic THC, both the (-) form and the (+) form were active. Therefore, THC was probably not acting on a receptor. Well, it turned out that people were synthesizing THC, the (+) form, from commercial starting material, which is not very pure and

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[62] See note 61.

[63] Burstein *et al.* (1970); Wall *et al.* (1970); Nilsson *et al.* (1970); Foltz *et al.* (1970).

[64] Professor Raphael Mechoulam wrote: 'Led by Stig Agurell.' Note on draft transcript, 9 March 2010. See Nilsson *et al.* (1970).

contained some of the (-) form. Therefore, at the end, rather than having pure (+) THC, they had (+) THC with some (-) THC and therefore some activity was noted. Due to that, well I wouldn't say mistake, but just an unfortunate situation, the existence of receptors was not investigated. When we and others published that there is actually a complete separation of activity between the two enantiomeric forms, it became almost certain that THC acts on some body molecule, enzyme, receptor or DNA. Allyn Howlett took up the challenge, went ahead and found the main CB1 receptor.[65] Later, a second group, in the UK, found the CB2 receptor.[66]

Obviously, receptors are not around to be activated by plants; that is not the way nature works. So we went ahead looking for something in the mammalian body that would act on the receptor. There were several groups looking for compounds of this type, and most of the groups that were looking for them and actually published something on such compounds were looking at proteins, because most of the active compounds that stimulate receptors are proteins or peptides, small peptides. But in this case we went the other way; as THC is lipid-soluble, we thought that the active compound in the body would also be a lipid-soluble compound. The main lipid-soluble compounds, the main lipids, are fatty-acid derivatives. So, we went ahead looking for lipid-soluble materials and indeed the first compound we identified, which we called anandamide, was a fatty-acid derivative. The isolation and identification involved quite a lot of work. Bill Devane, who had been a student of Allyn Howlett, joined my group in 1991 to study chemistry. As he knew the techniques with cannabis receptors, I thought it would be a nice project for him to look for the endogenous cannabinoid. We looked at pig brains because, strangely enough, pig biochemistry is close to human biochemistry and we were, of course, interested in human biochemistry.[67] We soon found that there was a problem because the endogenous cannabinoid was not very stable. We had to do a lot of chromatography, and while the purification went ahead, the activity (namely the binding to the receptor) went down, because the compound was deteriorating. We now know that it was being oxidized, as there are lots of labile double bonds in the molecule. It took us about two years to obtain an almost pure compound, which, with then modern techniques – now about 18

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[65] Devane *et al.* (1988). See also note 41.

[66] Munro *et al.* (1993).

[67] Professor Raphael Mechoulam wrote: 'At that time Lumir Hanuš from Czechoslovakia joined us.' Note on draft transcript, 9 March 2010.

years ago – we could identify its structure with very, very small amounts which we isolated from the pig brains. This is the way arachidonoyl ethanolamide, anandamide, was identified. Two or three years later, we identified a closely related active compound, arachidonoyl glycerol, 2-AG, an ester.[68] A few months after we published the identification of 2-AG, a Japanese group published the same compound.[69] They had been working on the same topic; we didn't know that they were working on it, but they came to the same conclusion that we had already published. Since then, quite a few other components have been identified but anandamide and 2-AG still seem to be the main endogenous cannabinoids. There are also a lot of synthetic compounds with the same activities. There is also a huge family of endogenous compounds which belong to the same chemical group of fatty acid derivatives with either amino acids, ethanolamine or glycerol, known as endocannabinoid-like compounds. Most of them do not bind to the cannabinoid receptors but it seems that they are doing a lot of interesting things in the body. As a matter of fact, one can see some of these compounds involved in almost all physiological systems, and I assume that work on them will be a major thing in the future.

Gill: I thought it might be interesting, before we move into the rather later clinical phase, to go back to a point that Roger Pertwee made about the flurry of activity that took place in the late 1960s to the mid-1970s, which you might call the first wave of proper scientific work. I think it worth emphasizing that a lot of the interest over that period was in trying to establish whether cannabis was harmful. And, although, as mentioned, there were references to clinical use dotted around in the literature, I think the main thrust of the work that was being done then was trying to establish whether there was a clear-cut case for de-criminalizing cannabis. It's clearly difficult to prove a negative, i.e. to demonstrate that THC was not harmful, and therefore one rather got the feeling that a lot of the work that was being financed was really simply to establish whether you could clearly demonstrate a harmful effect. If that was the case then that would really take care of the legislative problem; there's no question of getting involved in all the other side issues; the stuff was dangerous so it ought to be controlled. There was a lot of work that went on, I think, in the early 1970s, of people trying to detect all sorts of mutagenic effects. There were arguments about whether or not you should use solutions of pure THC; the fact that it was smoked and inhaled meant that there were people puffing smoke

[68] Mechoulam *et al.* (1995).

[69] Sugiura *et al.* (1995).

at Petri dishes full of bacteria and whatever.[70] It was interesting; I don't think the NIH was in itself particularly biased one way or the other about THC toxicity. There was a lovely woman, Monique Braude, who was, I think, then the main coordinator from the NIH for THC research and she was the main source of samples of pure THC. She was touring around Europe trying to identify groups that were working on THC.[71]

As Roger has reminded me, there was a sort of asymmetry of judgement, and there was a character called Gabriel Nahas who was totally persuaded that cannabis was very harmful; he was a great one for organizing conferences of like-minded workers, to reinforce the message.[72] In evaluating all that quasi-toxicological work that was being done in the 1970s, there was a sort of asymmetry of judgement. A lot of people came at it with the preconceived view that it was dangerous and so you would find reviews that were written that very much emphasized the negative findings. You would then find another review that assembled an equal number of papers to show that the alleged harmful effects couldn't be reproduced. It was a very tangled field. One rather got the impression, or rather I got the impression, that by the time we got into the middle of the 1970s, the effects were at best marginal, second-order; there was no overwhelming case that could be made against cannabis on the grounds of toxicity. It was at that point that the subject lost momentum. If it hadn't been for the discovery of the receptor in the second wave, I think it would have gone like alcohol as a research topic, it would have simply have died; there would be odd little clusters of workers around the world pottering around, and nothing would have happened to it. But, looking at the reviews and the comments that were being made at that time, it all struck me that there was, as I say, this asymmetry in the judgement of a lot of it. I have

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[70] See, for example, Nahas (1973, 1976); Paton and Pertwee (1973).

[71] Dr Monique Braude (1925–2010) received a diploma from the Institute of Pharmacy, University of Paris and a doctorate in pharmacology from Ohio State University in 1955. She worked at the National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD until 1987, where she became head of preclinical research in 1974 and directed a programme to determine the preclinical biological effects of marijuana and other drugs of abuse. See, for example, Rosenkrantz *et al.* (1972). Dr Edward Gill wrote: 'Because we (the Oxford group) were self-funded and had our own source of THC, we did not have very close contacts with Monique Braude and the NIH. She came to visit us a couple of times and we talked at conferences, but our relationship was quite informal.... As far as her tours round Europe were concerned, I think they were mainly to find out what was being done (there was an active group in Holland, for instance) and, possibly, to provide support.' E-mail to Ms Stefania Crowther, 1 March 2010.

[72] Professor Gabriel Nahas is emeritus professor of anaesthesiology and medicine at Columbia University, New York, NY. See, for example, Nahas (1973, 1976).

to say that I think Bill Paton himself was slightly asymmetric in his view of the literature. He applied all his very considerable critical skills to a lot of what you might call the positive evidence (i.e. that it was not harmful) and was much more tolerant about the negative evidence.[73]

Dr Vincenzo Di Marzo: I would like, if I may, to go back to the importance of the discovery of the endocannabinoids, because some people view this issue as possibly separate from the medicalization of cannabis. In fact, we got, and were getting, many hints from knowing how the endocannabinoids are made and how they are regulated and how to use the plant cannabinoids. The discovery of the endocannabinoids, which we owe, again, to Professor Mechoulam, in fact, in addition to what Roger Pertwee just mentioned, I think, opened new avenues of research. One with which we were particularly involved was to try to understand, through the physiology of mammals and eventually of human beings, how the levels of these compounds could be regulated during physiological and pathological conditions. By developing some analytical techniques to isolate, measure and quantify the endocannabinoids in physiological and pathological conditions, in our lab and in many others, we and others could understand how these endogenous compounds, which we named endocannabinoids, could behave as prohomeostatic protective endogenous mediators and therefore tell us where to use THC to activate CB1 and CB2 receptors and in what pathological conditions. On the other hand, it also allowed us to understand that this system can be regulated, so it can alleviate some symptoms of disorders, while exacerbating others. The typical examples of that are obesity, hyperphagia and metabolic disorders; that is, conditions in which we should use antagonists of cannabinoid receptors like rimonabant, of which THCV is the plant counterpart.

More recently, the third way in which the endocannabinoids can help us in using plant cannabinoids therapeutically is by understanding how the endocannabinoids are made, to identify the enzymes that make and degrade the endocannabinoids, some of which can be targeted by phytocannabinoids, plant cannabinoids and, I think, mostly of cannabidiol, for which there are many, many potential targets. Very interesting therapeutically; a potentially interesting plant cannabinoid for which there is still no single molecular target receptor. One discovery is that endocannabinoids, anandamide in particular, are quite promiscuous – they bind to other receptors, not just to the so-called cannabinoid receptors, but to other proteins, completely different from CB1 and CB2, for example – and

[73] See Paton and Pertwee (1973). Sir William Paton's papers are held in archives and manuscripts, Wellcome Library, London, at PP/WDP.

the serendipitous finding that some plant cannabinoids do the same – they also interact with these other, non-canonical cannabinoid receptors. So, I think there are at least three other ways through which the discovery of the endocannabinoids can help us decide when and for what pathologies we can use plant cannabinoids.

**Professor John Galloway:** Could someone clarify whether the endogenous opioids were already established by the time you started looking for the endogenous cannabinoids?

**Pertwee:** Yes, the enkephalins were discovered in the 1970s and the first paper on anandamide was published in 1992.[74]

**Galloway:** In that case, I wanted to make a comment, because Hans Kosterlitz told me that he gave the credit for the idea of the endogenous opioids to Thomas Mann in *The Magic Mountain*.[75] I wonder whether anyone else had ever come across that suggestion? There is a quote in *The Magic Mountain*: 'A sort of poisoning, an auto-infection of the organisms, so Dr Krokowski said; it was caused by the disintegration of a substance, of the nature of which we were still ignorant, but which was present everywhere in the body; and the products of this disintegration operated like an intoxicant upon the nerve-centres of the spinal cord, with an effect similar to that of certain poisons, such as morphia, or cocaine, when introduced in the usual way from outside', which he reckoned was a clear indication that there were endogenous opioids. I once wrote a short article for the *New Scientist* in which I pointed that out.[76] I thought people might be interested to know that.

**Tansey:** That's really moving us into the realm of medical humanities.

**Pertwee:** One race we did win was to clone a receptor: the CB1 receptor was cloned in 1990, a year or two before any of the opioid receptors.[77]

**Tansey:** Thank you very much for all of your very helpful and interesting comments about the basic science that underpins the medicalization of cannabis. I'm now going to hand over to Virginia Berridge, who is going to chair the session on industry and regulation, which leads on very nicely from what Dr Di Marzo has just been saying about therapeutic implications.

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[74] Devane *et al.* (1992). See also Tansey and Christie (eds) (1997a).

[75] Mann (1960): 188.

[76] Galloway (1986).

[77] See page 17; Evans *et al.* (1992).

**Berridge:** I wonder, talking about the debates that went on in the 1970s, which Dr Gill referred to,[78] whether Griffith Edwards has any comment to make from his involvement with expert committees in that period.

**Professor Griffith Edwards:** I feel like a child among my elders listening to such fascinating and distinguished accounts of laboratory science, so please know that I am aware I have no standing there. I am a witness to history in that I knew Bill Paton very well, a man I was very fond of and who assisted me in various ways. From the early 1970s, I was involved with a British body called the Home Office's Advisory Council on the Misuse of Drugs (ACMD), which is a statutory organization; its existence is embedded in the Misuse of Drugs Act of 1971, so even when Mrs Thatcher was trying to get rid of QUANGOs (quasi-autonomous non-governmental organizations), she couldn't touch it. Its powerful technical advisor over many years was the pharmacologist Jamie Graham.[79] And if you talk about asymmetry, Jamie Graham was asymmetry personified: he believed that cannabis should be legalized. Incidentally, I don't think you can get that out of Barbara Wootton: I think she was more cautious; she was a liberal-minded person, but I don't think she recommended outright legalization. The ACMD was not a cutting-edge organization for its efficiency and it could take six years for any working party to report. It got bogged down with cannabis and I actually made the suggestion that we needed a working group specially to look at the damage questions. I persuaded the council to ask Bill Paton to join us because, for some extraordinary reason, he was never a member of that council. We produced a report, which I believe was objective, on the possible harms with many open questions.[80] My understanding of the temper of the times was that we felt that we needed to know more about damages and dangers and that open-mindedness should be the order of the day. The medical profession had made an absolute hash of it by underestimating the dangers of barbiturates; we got it wrong with amphetamines; later, we were going to get it wrong with benzodiazepines and there was therefore a case for caution. We also felt that the epidemiological science on danger was pretty primitive because one likes to look at a dose–response relationship, as one can so easily do with tobacco, but you never knew the strength of the cannabis

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[78] See discussion on page 24.

[79] Dr James Graham was professor of pharmacology at the University of Wales, Cardiff from 1950 to 1989. See www.nedprod.com/cannabis/essays/wraltnet.txt (visited 11 June 2009).

[80] Home Office, Advisory Council on the Misuse of Drugs (1982) includes a section by Sir William Paton on 'Cannabis and the cardiovascular system', page 9.

being smoked and you never knew how many people shared a reefer; you were floundering around in the dark. I don't think there was ever any feeling in the official mind that one was out to diabolize cannabis, or grubbing around to find damaging implications, but one did need to know more, and one didn't know nearly enough. The debate did, at times, become very clouded. One couldn't live in the world of pure reason that one would like to inhabit, when there were people signing a petition in *The Times* in 1967 demanding legalization.[81] That was a tremendous act of very clever publicity, but it did rather cloud and popularize the background to the debate. Later on, when the *Independent on Sunday*, quite scandalously, had marches with people suffering from MS at the front of the parade, science and passion were much confused.[82] So, I think, the official mind-set would have been – who dares speak for the official mind? It's a very personal reading of it – that one should be very willing to determine the therapeutic value of THC, even if it were dangerous, because we knew we needed better drugs for pain relief. The pain specialists really made us feel a bit ashamed if we had thought that morphine and heroin were enough; they weren't. We needed better drugs. If there were drugs that were effective, but still carried some dependence risk, or some toxicological danger in high doses, one should determine that by controlled trial. I always naively hoped to inhabit the world of pure reason and pure science, but the world, of course, isn't like that. With drugs we live within a context, often of passion, muddle, overstatement and betrayal of logic. I'm sure it's always going to be like that.

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[81] Soma Research Association, led by Steve Abrams, placed an advertisement in *The Times* on 24 July 1967 that stated: 'The law against marijuana is immoral in principle and unworkable in practice', signed by 65 prominent people, including Paul McCartney (later Sir Paul) and Brian Epstein, who Adams credits with having provided the finance. See Abrams (1997); Grunberg and Harris (2005): 97–8. Bipartisan legislation to decriminalize cannabis was reintroduced by Reginald Maudling MP and became law as the Misuse of Drugs Act 1971, with the maximum penalty for possession of cannabis on summary conviction halved to six months, and received the Royal Assent in 1973.

[82] Verity Lesson, a 20-year-old MS patient, was placed in her wheelchair smoking cannabis at the front of a march to Hyde Park, London, on 18 March 1998, led by Labour MP Paul Flynn and reportedly attended by 16 000 people aiming to pressurize the government to downgrade cannabis from class B to C. See Ball (1998); http://news.bbc.co.uk/1/hi/uk/70856.stm (visited 15 February 2010). The march was part of the legalization campaign initiated by Rosie Boycott, editor of the *Independent on Sunday* in September 1997. On 11 December 1997 the newspaper held a conference on cannabis: Cannabis: Should it be decriminalised? *Independent On Sunday* debate, Queen Elizabeth Conference Centre, Westminster, London; see Wynne-Jones (1997); www.ukcia.org/library/11dec97debate.php (visited 15 February 2010). Boycott's campaign lasted for ten years before the *Independent* printed a retraction and an apology to the public. See Anon (2007); Owen (2007).

**Berridge:** I think we'll move now onto the industry interest, and we've already heard about Pfizer and Eli Lilly, but latterly it's been GW Pharmaceuticals, which has taken cannabis up as a medicine, so I think Geoffrey Guy is going to start the ball rolling for us on this.

**Dr Geoffrey Guy:** To understand why we set off with cannabis extracts, I think one has to understand a little bit about the regulation of medicines. Since the Second World War, and certainly since the 1960s, the Dunlop report and afterwards, medicines regulation pertained to single chemical entities.[83] Nearly all the regulations in the last 25 years relate to those and, therefore, the methods of preparation, manufacture, testing, quality control, consistency, in all the regulations, relates to single chemicals. So, the prospect of developing a medicine that contains something like 420 chemicals, in the regulatory environment of the late 1980s and mid-1990s was considered to be pretty nigh impossible. There are a number of European pharmaceutical companies that have prospered greatly with their lead products being whole plant extracts, but have never been able to achieve regulatory approvals on the basis of quality, safety and efficacy – mainly to do with quality (which is consistency in the Anglo-Saxon axis of regulation).

Why did we decide to buck the trend and try to be the first plant extract to be approved as a medicine in modern times: a whole extract? I think we have to go back to the early 1980s. I first started in the pharmaceutical industry in 1980. My responsibility was taking new chemical entities into man; I did about a dozen of those and that was interesting. The other part of the company I worked for made all of its money out of plant medicines and, in talking to the pharmacologists, it was very clear that when they looked for pharmacological activity using biological assays for plant medicines – these are a range of medicines that would be used in oncology, but also in other areas, as antidepressants, for prostatic hypertrophy, for example – they used laboratory models with which they then fractionated the extract looking for the active ingredient. This is something I've heard today: nearly everyone, except for Raphi Mechoulam, has used the phrase 'the active ingredient'. What we found was that, to find the active ingredient, we would look for the fraction that had activity and we'd throw the other fraction away. We would keep fractionating down until we did our last fractionation and neither of them had activity. We put them back together again and they had activity. Then we took one of the fractions we'd thrown away earlier on and added it back to one of the ones that

[83] See, for example, Dunlop (1970). See also Tansey and Reynolds (eds) (1997b).

didn't work, and we had activity again. It was absolutely clear that in a lot of biological processes, not just at a single molecular basis, you had clear synergy within these plants. Then, of course, some of the fractions of the plant, when you added them back in, took away the activity of a fraction that you knew had activity. So, the notion that there could be agonists and antagonists in the same plant was well understood. This was at the Laboratoires Pierre Fabre, Castres, France, I hasten to add, back in the early 1980s. Being a young physician at that time I told the boss that all medicines should be made out of chemicals and that plants should be left behind; a few decades in church told me otherwise.

So, moving forward, I think about another ten years, from the mid-1980s to 1990s, I was asked to develop a medicine for atopic eczema, which was derived from a Chinese medicine with ten components. We carried out clinical trials with very, very nice results, but we had to present the consistency of these materials to the regulators. After they'd picked themselves up off the floor and stopped giggling about all of this, we tried to engage in a sensible discussion as to how, under the modern regulations, you could obtain approval for something that was not a single chemical entity. I have to say that the regulators were absolutely marvellous in this country, even to the extent that I think a couple of them took a trip to China. But trying to crack this nut with ten extracts of ten plants, none of which we were able to see where they were grown, was nearly impossible. The issue about developing a medicine from a plant is that you must have control of your starting material. Anybody who has worked with plant medicines knows that if they are dried in the open, they will be covered in bird droppings; if they are dried in kilns they will be full of heavy metals; if they were cut down late in the afternoon and left overnight then they will have fungal growth on them; and then they could be put on a dock and left in 90° F temperatures for six weeks and put on a ship for another eight weeks. When we opened boxes shipped from overseas, out would come mice, rats and spiders, and that was just the macroscopic stuff!

The regulators were absolutely clear that they understood this: the materials were just like a biology project. What we decided to do was to build the quality into the extract – in my mind I wanted to have an extract because, you know, this medicine wasn't broken so I wasn't about to mend it – and it came very much from the mid-to-late 1990s, when the Government was very concerned about the MS patients being pushed up Whitehall as part of a campaign to have cannabis legalized.[84] When we looked at whether cannabis was a medicine in

[84] See note 82.

itself or contained elements that were therapeutic, I was quite convinced that we would need to have a material that was reflective of the material for which the data had been produced. Now, modern-day literature on the use of cannabis in medicine probably stems from 1839 with Sir William O'Shaughnessy, but Raphi Mechoulam would probably claim that it stems from the Assyrian tablets from about 2600 years ago, and Ethan Russo from the Chinese back in 2600 BC as well.[85] Here was the problem: most of the understanding of cannabis and its pharmacology in the 1980s and 1990s was, as you've heard, the pharmacology of THC. Now THC is the psychoactive product and for 50–100 years beforehand, people were growing cannabis for its psychoactive effects and there was a very simple biological assay for it: the cannabis that gave them a high, they kept and bred from, the ones that didn't, they threw away. If you assay US marijuana you will find almost the entire cannabinoid composition is represented by THC. You can hardly measure any others: CBD is a fraction; THCV is just a little bit. By the way, I think the highest composition of THCV, the propyl derivative, you'll find anywhere is about 20 per cent in Malaysian or south-east Asian or south-west African cannabis. So, we had a body of science describing the pharmacology of a plant that had been effectively grown for recreational use and it wasn't surprising that all of the measures and the laboratory measures of its effect were for its recreational use. If you go back to the 1850s and if you go back 100, 200, 300 years, or even as recently as the 1920s or so, a high THC plant would not have been used in medicine. The entire body of literature that related to the use of cannabis in medicine was not related to the materials that were being grown in the 1980s and 1990s in North America. In the early to late 1990s, most street cannabis in the UK that had, say, come from north Africa would have about a 50:50 ratio of CBD and THC. In nature, in wild types, CBD is the dominant cannabinoid, and Roger Pertwee is quite right: they're in their acid form.[86] You find very, very little neutral THC or CBD in the plant. So, when we look at the medical literature, we're looking at the literature of a plant that predominantly delivered CBD with some THC. The more recent science was science that related to THC. The very first e-mail that I sent to Raphi in 1997, I think, said, 'Tell me about cannabinoid ratios', because we understood from the work back in the 1980s that the ratios of the different

[85] O'Shaughnessy (1839a). See also Gorman (1984). The earliest known reference to cannabis is in Assyrian tablets of the seventh century BC. The Chinese emperor Shen Neng included cannabis tea in his pharmacopoeia of 2737 BC as a treatment for gout, malaria, beriberi, rheumatism and poor memory. See Jones (2006); Fankhauser (2002).

[86] See page 16.

constituents of the plant would determine its pharmacology. The ratios were determined by the genetics of the plant, how you grew it, how you harvested it and how you prepared it. And the Chinese know that: they've known that very, very well indeed. What we did was to go back in a detective role, to try to understand what the literature from the nineteenth century was referring to.[87] It isn't modern-day, high-THC, recreational cannabis.

That's why I was determined in the very early studies, which we did with William (Willy) Notcutt – when was it Willy? 1998? 1999? All of the early studies initially looked at ratios with THC, CBD and the combination together, and this is coming up to the clinical side so I'll step back a bit. So, when we determined that the medicine we wanted to develop and take to the regulators was one that had more than one cannabinoid in it, THC and CBD, and in fact we specified for at least seven minor cannabinoids, we then had to create a whole new set of tests, because the test that the regulators would normally recognize to standardize material simply didn't count. We had to go back and decide how we would assay and how we would measure them.[88] As Raphi said, when you make these cannabinoids you get enantiomers of them, but, of course, nature is stereospecific: you'll only ever find one enantiomer of a material in a plant. For example, one version of limonene makes the lemon taste like lemon, and the other version makes the orange taste like orange; it's the same chemical, but they're very, very different and the body would see those as very different.[89]

What we did was to set about growing very, very specific varieties of the plant, defined by their chemical components. We had one of the world's top geneticists to help us do that: we do no splicing; it's all breeding; it's all Mendelian (and unlike Mendel, we don't cheat).[90] We are able to virtually dial into the plant now,

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[87] O'Shaughnessy (1839b).

[88] Dr Geoffrey Guy wrote: 'New methods of sample preparation, extraction and separation were devised. We produced our own range of ultra-pure internal standards with which to calibrate laboratory equipment. We developed a complete suite of analytical methods more appropriate to measuring multiple plant constituents. Work undertaken to characterize each extract has now allowed us to identify and quantify approximately 90 per cent of the molecules present. Quality control and batch release specifications all had to be developed from scratch.' Note on draft transcript, 23 March 2010.

[89] Limonene is a chiral molecule, (R)-(+) limonene smells of oranges while its enantiomer (S)-(-) limonene smells of lemons because the nasal receptors consist of chiral molecules that interact with the enantiomers differently.

[90] Sir Ronald Fisher suggested that Mendel's results were 'too good to be true' in Fisher (1936). See also Mendel (1866); Pilpel (2007).

to select what cannabinoid component we want. Once we had the cannabinoid composition in the plant, everything else in the manufacturing and pharmaceutical process to arrive at consistency stems from that. The plants are grown indoors, away from bird droppings, away from heavy metals; no chemicals are put on them whatsoever; we used biological methods for pest control. We are able to get quite remarkable consistency. The consistency of THC, for example, from a THC breeding variety when we make a primary extract, is of a higher purity than the standard the FDA would accept for synthetic THC. So we are able to produce extremely consistent extracts with known quantities of the primary cannabinoids and known quantities of at least nine other cannabinoids. We've characterized about 90 per cent of the plant entirely: so this plant is now the most highly characterized medicinal plant anywhere in the world. The plants are all identical because they are grown from clones. By doing that, then we were able to develop a consistent product and a series of tests which we had to agree with the regulators what these tests were doing; we had to validate the tests all the way through.[91] We produced all our own internal controls and Raphi Mechoulam, Roger Pertwee and Vincenzo Di Marzo have helped us to standardize internal controls so that we know what we're measuring. By doing that we were able to produce a material that was consistent enough to meet international regulatory requirements in Europe and Canada, where the product is already approved, and in the US, where we're in Phase IIb trials. That was the challenge, the major challenge, to make a medicine from cannabis. It wasn't the cannabis aspect; it wasn't the clinical aspect or the safety aspect: the challenge was whether you could actually make a modern-day pharmaceutical from a plant.

**Berridge:** Could you go back in history a little bit and tell us a bit about how GW Pharmaceuticals was set up and where the idea came from?

**Guy:** [Laughs] Oh, yes, we're in the Wellcome Institute here (Wellcome Centre for the History of Medicine at UCL since 2000), aren't we? After working in France with plant medicines and new chemical entities, I then worked for Napp with opiates and did most of the early clinical development on morphine sulphate, the slow-release morphine, and then a number of other opiates and drug delivery.[92] In the early 1990s we (Ethical Pharmaceuticals) had approached the Home Office and said: 'We'd be interested in looking at cannabis,' because, as you know, we'd dealt with the opium plant with opiates, we knew about

[91] See note 88.

[92] For details of morphine sulphate in pain, see Reynolds and Tansey (eds) (2004). See also biographical note on page 91.

capsaicin and vanilloids – we'd actually been responsible for registration of the capsaicin product here in the UK.[93] We got a bit of a flea in our ear in the early 1990s, when the Home Office said: 'No, you're going to stick with your opiates.' And, like any other pharmaceutical company or chairman, I thought that we had other fish to fry, and so we did. I was reminded later on that my interest in cannabinoids had gone back to 1982, but I had entirely forgotten that, as Roger Pertwee had forgotten that he wrote the first paper on THCV after he'd done two more with our materials.[94]

What happened is that in the middle of 1997, having forgotten that I had an interest in the cannabinoids, and not because I understood any of the science going on, only because I understood that there was a human interaction with the material with which those humans had co-evolved, I went to a conference in London held by the Royal Pharmaceutical Society and the MS Society.[95] Was it a half-day conference, Tony Moffat? The whole day! – I managed half of the day, I think. [Laughs] Clare Hodges was there talking about the medicinal uses

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[93] Approvals PL 10670/0003, dated 20 August 1992, to Euroderma Limited for Axsain Cream 0-075%, active ingredient capsaicin HSE 0-075%, see www.london-gazette.co.uk/issues/53120/supplements/20087 and PL 16804/0020, dated 19 February 2003, to Elan Pharma International Limited, for Axsain Cream, active ingredient capsaicin, see www.mhra.gov.uk/home/groups/l-reg/documents/licensing/con026456.pdf (both visited 15 June 2009).

[94] Professor Roger Pertwee wrote: 'The first paper to present evidence that THCV is a cannabinoid CB1 receptor antagonist was Thomas *et al.* (2005). This was, in fact, my second paper on THCV – the first was Burstein *et al.* (1970). However, this first paper, published at a time well before the discovery of cannabinoid receptors, only alluded to the ability of THCV to behave like THC *in vivo,* at doses well above those we subsequently found THCV to behave as a cannabinoid CB1 receptor antagonist; see Thomas *et al.* (2005).' E-mail to Ms Stefania Crowther, 8 March 2010.

[95] The Royal Pharmaceutical Society of Great Britain and the School of Pharmacy, University of London, organized a public meeting on the medicinal use of cannabinoids at the School of Pharmacy in March 1996. In July 1997, the society held a symposium on the history, pharmacology and clinical uses of cannabis and the cannabinoids, published in a special issue of *Pharmaceutical Sciences* in November of that year. The society set up a working party in late 1997 whose objectives were: 'To produce guidelines for pilot clinical trials for cannabinoids as proof of principle of their effectiveness and assist those who wish to conduct such trials to successfully complete them and publish the results.' Royal Pharmaceutical Society of Great Britain press release: 'Society welcomes cannabis research findings', 11 November 1999, available at www.rpsgb.org.uk/pdfs/pr031111.pdf (visited 15 June 2009). These clinical trials were for muscle spasticity in patients with MS (Dr John Zajicek, Derriford Hospital, Plymouth) and acute pain following tonsillectomy or abdominal surgery (Dr Anita Holdcroft, Hammersmith Hospital, London). In June 1998, the society gave evidence to the House of Lords select committee on science and technology. The protocols for the 'proof of principle' clinical trials were launched at a meeting at the society's headquarters in January 1999.

of cannabis. I thought: 'Ho hum, this is interesting. I thought it was all very, very taboo.' I went to the conference and there was the MCA (Medicines Control Agency as they were called in those days, MHRA after 2003), the Home Office, some very eminent scientists – I remember Professor Patrick Wall was there as well[96] – there were some patients and patient groups, and a little smattering of pharmaceutical people I recognized, keeping their heads way, way down, because they didn't want to be seen at a cannabis conference. The question arose: if research is to be done on cannabis, how do you standardize it? How can you make a material, addressing the question that you can never tell how much is in a pull from a joint, or how strong or weak the material is? How can you standardize the material and how could you then do clinical trials? Because there's no point in doing clinical trials unless you have something you can make time and time again, fit for purpose. I stood up and spoke from the floor for about 15 minutes, and said that it could be done as long as you got the agreement from the Home Office and from the MCA, to be able to move ahead.

Following that meeting in 1997, I was invited to say the same sorts of things to a Parliamentary delegation, which was led by Austin Mitchell, on the 11 December 1997. The same array of eminent scientists and physicians were there: the minister was Paul Boateng. He started the meeting that was trying to get herbal cannabis reclassified so that research could be done. And there was great hope to do this because I think this was the second such parliamentary delegation. I hadn't been on the first one. Paul Boateng opened the meeting and said, 'Her Majesty's Government has no will to reschedule cannabis', at which point everybody's eyes went to the ceiling. 'However,' he said, 'we'd like the research to be done.' At which point most people thought: 'Well, this is bizarre – absolutely bizarre.' But he did suggest that if one wanted to do the research, one should approach the Home Office Drugs Inspectorate (HODI). Having worked in one of the most highly regulated environments for the previous 20 years with opiates and with a range of materials like that, when a Minister said 'Go and see my officials', that's what we did.[97]

A week later, I was sitting in front of the chief inspector of the HODI, Mr Alan MacFarlane, and said: 'Well, you know we'll have to grow tons of this.' You can't

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[96] For an extract from an annotated Physiological Society interview with Patrick Wall (1925–2001) by Martin Rosenberg and Steve McMahon (5 February 1999), see Reynolds and Tansey (eds) (2004): 73–82.

[97] See House of Lords (1998), especially Chapter 7: Changing the law on medical use and research: review of the evidence, available at www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/151/15109.htm (visited 20 January 2010).

just get a licence for six plants. If you want to standardize material you have to grow 20, 30, 40 tons of the material. You have to process it and standardize it. I thought that would put a stop to all of it, because they had handed out licences in the previous years, but for probably, you know, literally half a dozen plants in a professor's laboratory. They said: 'Of course you would.' I put a number of other things to them that they'd have to agree, that would have to be done, and they said, 'Yes'. I said it would have to be done on a commercial basis as well, because no one else is going to do this. They said: 'Well, we'd prefer to have GlaxoWellcome here', but I replied: 'I'm all you're going to get' because there was no one else who was interested in making, or thought it was remotely possible to make, a medicine out of cannabis, except that I'd had 20 years in narcotic analgesics, drug delivery, plant medicines and had retired two days earlier with my wife and young baby and had the time to think about it.

They invited us to write a proposal, which was easy for us because we'd had a trial run with the MCA many years earlier on Chinese medicines. We presented that to the Home Office in January 1998, and I nearly forgot about it again, because I thought it would be buried in there for two or three years. About four weeks later I received a phone call from the chief inspector of the Home Office Drugs Inspectorate, who individually is probably more responsible than anybody else in this room for the progress of our programme, and that's Mr Alan MacFarlane. He rang me up and said: 'We'll do this, but we don't know how we're going to do it: could you put a proposal in?' So I put together all of the knowledge I had on processing opiates, cytotoxics, antibiotics, all of the rules to do with difficult, expensive, controlled substances from pharmaceuticals and put together a 22-point plan, and said: 'I think this is how we would develop a medicine; how we would control it; how we would regulate it and how we would run it under the international Single Convention, which is the treaty under which they had to abide.[98] We spent some time with the Home Office legal officers to hammer this out, and in the beginning of June, only three or four months later, they were ready to issue the licence. I was in Guernsey at the time; we'd started a company called Guernsey Pharmaceuticals, and they suddenly realized that although the Home Office legislated on behalf of Her Majesty's Government for Guernsey, they had no jurisdiction over Guernsey under the 1970 Misuse of Drugs Act. So I had ten seconds to say what the name

[98] The United Nations' 'Single Convention' on narcotic drugs of 1961 is an international treaty prohibiting production and supply of specific drugs, which unifies and consolidates previous legislation, embracing nine multilateral treaties negotiated between 1912 and 1953. The UK signed the convention following the Dangerous Drugs Act 1964. See www.incb.org/incb/convention_1961.html (visited 15 February 2010).

of the company would be on the licence, and my initials were GW and my founding partner was Dr Brian Whittle, so one way or the other, Guy–Whittle or Geoffrey William, I said, 'We'll call it GW Pharmaceuticals'. And that's how GW Pharmaceuticals was created.

If I may take two more minutes of your time, because this is for the Wellcome Trust, about a week later we announced these licences to the world; we were still doing live interviews about six or eight weeks later to world press and television. I received a letter from GlaxoWellcome, a rather snotty letter actually – sorry, you can edit that out – saying: 'How dare you use the epithet GW? Don't you understand that we're GlaxoWellcome?' and sent me lots of press cuttings with GW in, because the journalists had abbreviated their name. I did a quick search and rang the chap back, because I was invited to ring him before they jumped on us, and said: 'It seems to me that you don't have any trademarks, nor have you registered the name GW, but I will show you my birth certificate.' There was a great hush at the other end of the telephone. I said: 'Well, I tell you what, we've only been going for a couple of weeks, you can buy the name from me. You can buy the name for X or you can buy the whole company.' The chap took me very seriously, went away for three weeks, came back and said: 'We don't want to buy the company, but we'll buy the name.' It took four-and-a-half months to come up with a four-page contract that even meant I couldn't use the initials GW, but by which time we'd created press throughout the entire world, which would have cost millions for Glaxo to produce and when I pointed that out to them, they called it off. That's why we were GW and that's why we are still GW. And then GlaxoWellcome became GSK.

**Berridge:** [Laughter] That's another history. It's fascinating that the government seemed to have changed its position very quickly. Why do think that was? Why do you think approval came so quickly?

**Guy:** No, I don't think they had changed their position. If you go back to the year before, I think it was Lord Williams of Mostyn, the Leader of the House of Lords and Attorney General in 2000, who said in the House of Lords and put forward the government's position: if a product could be approved by the MCA as an approved medicine then the government would move to reschedule that product – not cannabis, not the plant, not the raw material, but the finished product – to an appropriate schedule so that it could be used as a medicine.[99]

[99] See House of Lords, Select Committee on Science and Technology (1998); (2001): sections 11–12. Available at www.publications.parliament.uk/pa/ld200001/ldselect/ldsctech/50/5002.htm#note1 (visited 20 January 2010).

Therefore it was the government's position before I even got involved with them, because their concern was that if there is a medicine here, it must be separated from the advocacy debate. That was done, in a very, very straightforward way and very quickly then. For example, in the US, it is very difficult to separate that debate. The UK government was entirely consistent all the way through and we got an enormous amount of support from the Home Office, even directly from the Cabinet Office in the early days, to ensure that this programme would go ahead smoothly.

Berridge: I wondered whether Philip Robson, who has been involved in GW, would like to come in at this point?

Dr Philip Robson: Yes, I suppose I should just say that cannabis has dogged my career from early years of hospital medicine through clinical pharmacology and then psychiatry. I first became aware that it had a medicinal application as a young hospital doctor in London when I became aware of a patient with MS smoking the substance on the Victorian balcony. I spoke to the ward sister, a formidable woman who was very much of the old school, and asked: 'Are you happy with this?' She said: 'Well, yes. It does seem to help him.' I thought: 'Gosh, if it convinces her, there really must be something in it.' I spent a lot of time talking to this young guy and it was from him that I became aware of one of the most important things from the clinical point of view, as far as I'm concerned, about cannabis, which is that it has a very broad range of effects for people with multiple symptomatology. It isn't just a pain reliever or a stiffness reliever or something that improves your sleep; it does an awful lot of things for people who have a whole range of symptoms; that became a difficult issue later when approaching scientifically robust clinical trials. There was a period of clinical pharmacology and then I became a psychiatrist and combined clinical pharmacology with psychiatry to establish a drug dependency unit. In this context I treated a number of people who had HIV/AIDS, who, again, were smoking cannabis to relieve a wide range of symptoms. I worked a little bit with *Nabilone* as a potential substitute to try to achieve in a pharmacologically more reliable and dependable way the effects that they were attaining from illegal smoked cannabis.

At the request of the UK Department of Health, I carried out a critical review of the potential that cannabis might have as a medicine.[100] I think that it was

[100] Robson (1998). Submitted as evidence to House of Lords Inquiry: *Cannabis: The scientific and medical evidence*, which published its findings in November 1998 as House of Lords, Select Committee on Science and Technology (1998). An abridged version was published as Robson (2001).

at the House of Lords inquiry that I met Willy Notcutt and Geoffrey Guy, and Geoffrey persuaded me, as is his wont, to change my career by splitting my time between a research fellowship at Oxford University and joining GW Pharmaceuticals as medical director. I think he simply needed a clinician who had a belief in the potential of cannabis as a medicine and someone who was prepared to devote time to setting up clinical trials. We created a small research unit in Oxford, with my colleague Derek Wade, and conducted a number of early trials. One of the things that we tried to do very early on – unsuccessfully, I have to say – was to capture this breadth of effect in a scientific way. We are, I think, dealing in many ways with the rather intangible experiences that patients have, or at least experiences that are very difficult to measure objectively. If you experience spasticity, there are so-called objective measures, for example the Ashworth scale, which many people have called objective, but in reality are imperfect, both in terms of their validity and reliability, and often don't reflect the patient's experience in an accurate way.[101] The struggle has been to find ways of measuring a symptom like spasticity in a way that has more reference to the patient's experience, but at the same time is plausible and robust from the scientific criteria of reliability and validity. We think we have that in the shape of numerical rating scales or visual analogue scales. What we tried to do in the very early trials was to capture the breadth of experience by representing a number of symptoms, such as pain, spasticity, bladder-related problems and sleep disturbance with individual visual analogue scales, and then collapsing those into a composite measure to reflect this broad effect. That, sadly, was not a successful undertaking from a scientific point of view. I think that this is one of the great difficulties in working with cannabis-based medicines that have this breadth of effect, which patients value, while in a clinical trial context the focus has to be on a single symptom in a way that reflects the profile of other drugs – synthetic drugs – in that particular area. The unique benefit when the drug is used naturalistically is because of a whole range of effects, but the intensity of a single effect on spasticity for an individual patient may not be incredibly great. That has been one problem with clinical trials of a plant material.

I think another problem has been that the 'pariah status' of cannabis convinced ethics committees and, I suppose, regulators that only if a patient had tried and failed every existing medicine that was available, could they go on to try the

[101] The Ashworth scale is a five-point rating of spasticity: 0: normal muscle tone; 1: slight increase in muscle tone, 'catch' when limb moved; 2: more marked increase in muscle tone, but limb easily flexed; 3: considerable increase in muscle tone; and 4: limb rigid in flexion or extension. Modification to a six-point scale was suggested in Bohannon and Smith (1987). See also Fleuren *et al.* (2010).

cannabis-based medicine, which is an unfortunate thing because, of course, the risks involved in standard medicines are often very great and may even be life-threatening. The risks involved with cannabis-based medicines may relate to intoxication and there may be long-term psychiatric risks that we will no doubt talk about later,[102] but, nevertheless, the actual tissue toxicity of cannabis and cannabis-based medicines is incredibly low and from that point of view they are very safe in terms of acute toxicity. Nevertheless, the necessity was, in those early days and still, today, to select patients for clinical trials who had already failed to respond to existing medicines. Inevitably there will be a number of these people who will not react to any medicine, which, of course, raises the threshold and difficulty in producing a statistically significant result. In the early trials that was a major problem.

**Mechoulam:** Two points: one is that the discussion we are having can actually go back a couple of thousand years. The Romans didn't use cannabis as a psychoactive agent; if they did, their literature would have said something about it; they didn't. But they used it as an anti-inflammatory agent, because, apparently, they used cannabis that contains very low percentages of THC and very high percentages of cannabidiol and cannabidiolic acid. It is in the literature.[103] The differences between different types of cannabis that we see and that Geoffrey Guy has emphasized are in the literature; we should have known it. This is one point that I want to make. The second is that many of the major pharmaceutical companies in the 1960s, 1970s, 1980s and even today, had small groups working on cannabis. But as soon as it went up the ladder, the bureaucratic ladder in the companies, all of them, without exception, decided not to go with cannabis because of the publicity they thought they would get, the bad publicity: 'This company makes money from marijuana.' They didn't want it; they were afraid of it and therefore cannabis, as was mentioned earlier, remained a pariah drug although it obviously has effects that are helpful and therapeutic. It was a pariah drug for nearly 35 or 40 years.[104]

**Pertwee:** If I can add to that, in fact what happened, of course, is that many pharmaceutical companies turned to the antagonists. That was considered OK,

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[102] See pages 69–70.

[103] Russo (2004b).

[104] Similarly, in the late 1960s, clinical research into the benzodioxane derivative, alprostadil (prostaglandin E1; *Prostin VR*®; Pharmacia and Upjohn) and sildenafil (*Viagra*®: Pfizer), which had been shown to increase mounting in male rats, was halted due to the company's concerns about its impropriety. See Tansey *et al.* (eds) (1998): 179.

because you were doing something that was going to block all those effects and so we had Sanofi-Aventis with rimonabant, etc. A lot of the other very big companies also had programmes for developing antagonists. Now there is much less interest in antagonists because of the withdrawal of rimonabant from the clinic for various reasons.[105]

Professor Anthony Moffat: I'd like to talk about some products and the law, the regulations surrounding it. The regulations around the world come very much from the World Health Organization and its scheduling of drugs. Schedule I for drugs says: 'This has no proven therapeutic value, and therefore we ban its use across the world for any kind of therapy.'[106] That manifested itself in this country in the 1971 Misuse of Drugs Act, and therefore cannabis was identified by that act, and you could not from 1971 use any medicinal product with cannabis in this country. The day before you could, the day after you couldn't. Now dronabinol, or what we would call THC in the US, is the product *Marinol*, made by Unimed, which went into clinical trials and the FDA approved it, not for pain control, but for the relief of nausea from anti-cancer drugs and also, later on, for improvement of appetite in AIDS patients.[107] It went through the whole gamut and the FDA gave it a licence, and then the US government had to change the law within the US, which is unique across the world, to allow a cannabis-based medicine using THC. It was a synthetic THC, but derived from cannabis. Therefore they had to alter their laws. I just want to come onto that because it was interesting that in 1996 the state of California decided that they would allow the use and growing of cannabis within what they called 'ill patients'. So if I was ill, and I wanted to grow it for my own use, I could do that. Subsequently, eight other individual states changed their state laws to allow it as well, at which point the Supreme

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[105] Professor Roger Pertwee wrote: 'It seemed to be inducing severe depression or even suicidality in some patients.' Note on draft transcript, 3 March 2010. The European Medicines Agency (EMEA) withdrew marketing authorization for rimonabant (*Acomplia*) on 16 January 2009, after Sanofi-Aventis discontinued its clinical development programme of the drug for treatment of obese and overweight patients following reported adverse reactions, including severe depression. See Wathion for the EMEA (2009), available at www.ema.europa.eu/humandocs/PDFs/EPAR/acomplia/3945709en.pdf (visited 20 January 2010).

[106] For Schedules I and II of the 1961 single convention, see note 98. For further details, see http://apps.who.int/gb/ebwha/pdf_files/EB115/B115_12-en.pdf (visited 15 June 2009).

[107] The US Drug Enforcement Agency (DEA) reclassified *Marinol* from a Schedule II to a Schedule III medication under the Controlled Substances Act in 1999. Not all US states have reclassified the drug. See www.solvaypharmaceuticals-us.com/newsroom/pressreleases/0,,14591-2-0,00.htm (visited 15 June 2009). See also note 9.

Court of the land, the federal court, of course, said: 'You bad states: you must not do this. You must change your laws back to where they were before because no state laws can supersede a federal law, which bans its use because cannabis and medical products derived from it have no proven value.' Now that was quite interesting; that was in 2000.[108]

The following year, in Canada, a chap by the name of Terrance Parker, who was growing cannabis for treating his epilepsy, went to the Ontario Supreme Court and they said that he could do that.[109] The federal law, which banned the use of it like the rest of the world and the US, said it had no constitutional value at all. Completely the reverse situation: state versus federal law in Canada and the US. The Prime Minister of Canada at the time, who was a very clever individual, said: 'OK, if that is so, we will not change the law. However, what the government will do is to grow cannabis and convert it into a medical product that can then be prescribed by practitioners, so they can have something to write down.'[110] There was an old mineshaft in the province of Manitoba and they grew cannabis there for years. Every year when I go across to see my colleagues in Canada, I ask: 'Have they manufactured it into a medical product yet?' And they say, 'No, not yet, Tony, but we grow a lot of cannabis'. So, they haven't actually moved to that situation.

In 2005, in the Netherlands, they actually said, 'OK, we know perfectly well that people are using this material' and from 2005, again, they have not changed

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[108] Fourteen states currently allow access to cannabis for medicinal purposes: Alaska, Oregon, Washington (since 1998), Maine (since 1999), Colorado, Hawaii, Nevada (since 2000), Vermont, Montana (since 2004), Rhode Island (since 2006), New Mexico (since 2007), Michigan (since 2008) and New Jersey (since 2010). Additionally, Arizona state law allows physicians to prescribe cannabis (since 1996). See Seamon (2006); http://medicalmarijuana.procon.org/viewresource.asp?resourceID=000881 (visited 15 February 2010).

[109] Mr Terrance Parker was granted a constitutional exemption to use marijuana for combating the seizures he suffered as a result of his epilepsy on 10 December 1997. Parker was challenged in court on 31 July 2000 and as a direct response the Canadian government issued the Medical Marihuana Access Regulations on 30 July 2001, which created a process that enabled certain categories of ill people to obtain an authorization to cultivate and possess marijuana for therapeutic purposes; see Department of Justice, Canada (2001), available at http://lois.justice.gc.ca/eng/SOR-2001-227/index.html; www.johnconroy.com/library/parker.pdf; www.johnconroy.com/library/parker2.pdf (sites visited 3 February 2010).

[110] Prairie Plant Systems Inc, a biotechnology company established in 1988, was awarded a five-year, $5.5 million contract for 'The development of comprehensive operations for the cultivation and fabrication of medicinal marihuana' in a biosecure underground growth chamber in Flin Flon, Manitoba, MB, by Health Canada in December 2000. See www.prairieplant.com (visited 16 February 2010).

their law, but in Groningen, in one place, they grow cannabis, manufacture it into a product and it is sold through pharmacies in the Netherlands. Sorry, when I say 'sold', it's dispensed against prescriptions. But I must say that the patients say it is lousy and they can grow better stuff themselves.

Di Marzo: Very briefly, I want to go back to the stigma of cannabis and cannabinoid research. It's true that the major companies have always worked on cannabinoids: small groups getting bigger from time to time, and even getting to Phase I clinical trials sometimes. But there has always been a preconceived idea that those working on cannabinoids were doing something wrong, to the point that, as Raphi Mechoulam mentioned, in 1993, when the CB2 receptor – originally called peripheral cannabinoid receptor for THC – was discovered, companies saw this as a great opportunity to use THC and cannabis, or at least synthetic analogues of THC, to selectively target this receptor, since this strategy would be, in principle, devoid of any effect on the brain.[111] From this simple fact you can get an impression of how the stigma still operates. It's almost 15 years since the discovery of the CB2 receptor and several selective agonists for this receptor have been developed that are totally devoid of any psychoactivity, so they could easily bypass all the problems of the psychotropic activity of cannabis, but still there has been very little clinical development, if any, despite the fact that such compounds might have therapeutic applications in the fields of pain, inflammation and cancer, where there is a growing demand for novel treatments.

Tansey: To follow on from the end of the previous section, we're coming onto the issue of the impact of clinical trials and the setting up of clinical trials. I was wondering if I could ask Tony Moffat to say something about the Royal Pharmaceutical Society's role in this?

Moffat: The Royal Pharmaceutical Society held a meeting about cannabis as a medicine in 1996 and it was a lively meeting. I can remember Clare Hodges being there. Afterwards, Anita Holdcroft and I were there together with the dean of the School of Pharmacy, and she said: 'Why doesn't somebody do some clinical trials?' She wanted to treat people like Clare and others, who had MS, but she felt that she was inhibited because no clinical trials had been done. I thought: 'Well, she's absolutely right. The clinical trials that had been carried out were either too small – 20–30 patients – or had no real objective endpoints.' So, together with Vivienne (Viv) Nathanson, the chief of policy at the British

[111] See Munro *et al.* (1993).

Medical Association (who was invited here today, but was unable to attend), I went to see the Chief Medical Officer and said: 'What do you think? Is it time to do this? What would the government view be?' He said: 'Go for it: let's do it.' I phoned up Alan MacFarlane, the chief inspector of the Home Office Drugs Inspectorate, to whom Geoffrey Guy has already alluded – I used to work for the Home Office so I knew all about that – and he said: 'Nothing against it, Tony, but you need a good proposition.' So, we thought: 'OK, how do we move forward?' And Viv suggested that I ask Sir William (Bill) Asscher, then head of the medical school at St George's Hospital, London, to chair a meeting and get all those people who might be concerned in running clinical trials and actually do it. So we thought: 'Right. That's exactly what we'll do.' So, the remit, which Bill put down quite clearly, was: 'We're going to have three meetings. At the end of that we want at least clinical trial protocols which will be proof of principle.'

The kind of people we got were Roger Pertwee from Aberdeen and one of his colleagues, Dr Derrick Bennett, who also came as a statistician, the number cruncher who told us how many patients we wanted. We didn't really want to listen to him, because every time we talked to him the numbers went up. We had Anita Holdcroft, who was going to conduct the trial afterwards. We had Peter Cardy and his representatives from the MS Society.[112] We had an MRC representative and somebody from the Wellcome Trust to the first one, after which the MRC said: 'Look, if this is going to be funded, we'll take it on. That doesn't mean to say we will, but we will help you put the bid together and make sure that it doesn't fall into a pit.' The Wellcome Trust therefore backed out. We had a huge meeting where we launched – I should say the Royal Pharmaceutical Society launched – two protocols for two clinical trials.[113] One was John Zajicek from Plymouth, who can't be here today, a multiple sclerosis trial, and the other was Anita Holdcroft as the principal investigator on pain.

Part of the problem was, of course, getting Home Office approval. They said: 'No problem at all. We can do that.' I was already working with the MCA, who said: 'We can get you an exemption for a clinical trial certificate.' No barriers there at all, but we had to have something to give to people. The MS Society was quite keen that their patients would take part in this and they said: 'Recruitment of patients would not be a problem through the hospitals,

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[112] Peter Cardy was chief executive of the Motor Neurone Disease Association, chief executive officer of the MS Society of Great Britain and Northern Ireland, and chief executive of Macmillan Cancer Relief (2001–07). See Brown (2002).

[113] See note 95.

we could promise you it was OK.' Anita and her colleagues in pain control and anaesthesiology in hospitals didn't think recruitment would be a problem either. But it came down to the question of what we were going to give to the patients. I contacted the CEO of Unimed, who made *Marinol,* and they were very keen: 'We'll supply you with all the *Marinol* you like. We make it in 2.5 mg, 5 mg and 10 mg capsules. What do you want?' They gave us the equivalent upfront of something like £500 000-worth of capsules for the trial. I should explain that the clinical trials were going to be in three different arms: in the first, patients would receive cannabis; the second one was a placebo; and the third was THC on its own – the *Marinol* from Unimed. The concept was that comparing the cannabis and the placebo together would answer the question: 'Is there any clinical effectiveness of the cannabis above a placebo?' And by comparing the cannabis to THC we hoped it would answer the further question: 'Is it just due to the THC?' So we got the THC part. There were two people I wanted to ask if we could use their materials: one was Geoffrey Guy, who kindly said yes, we could have the supply of his material, but since he was just organizing his new company, although he could provide the material that we could use, we would have to pay for it. The other was the European Oncology Institute in Berlin (the Institut für klinische Forschung) and they said we could have their product and it would be free. So I said: 'Sorry, Geoffrey.' Looking back on it, that might have been a mistake, but that was the way it was then. In terms of what we grew, we asked the people in this country what varieties of cannabis they used. For various political and legal reasons we produced one huge batch that was grown in Switzerland under state authority. It was then imported into Germany where it was manufactured into capsules and then imported into this country, and the Home Office was very, very helpful in doing that. I think it was true internationalism. It was only 'proof of principles', but nevertheless I think honours are due to the people who provided us with the materials, the government agencies who did it, but most importantly to those two principal investigators, John Zajicek and Anita Holdcroft, for going forward with it for the benefit of the patients. What we were trying to do, the whole essence of what the Royal Pharmaceutical Society of GB was trying to do, was to make life better for MS sufferers and pain control afterwards, because there weren't too many good drugs around. That was our driving force.

Tansey: Anita, could I ask you to take up the story, please, on your involvement in the pain clinical trials?

**Dr Anita Holdcroft:** I'll just reverse back a little into 1994 because I was running a pain clinic then at the Hammersmith Hospital, London, at the Royal Postgraduate Medical School. A patient came in one day and filled in my pro forma and he said that he used cannabis to help his pain. It was in the context of the scientific findings: we knew that there were cannabinoid receptors in the body. I turned round to him in his first visit to the clinic and said: 'Right, well, you've got to do a randomized placebo controlled trial.' And he said: 'Oh yes, if that's what you want me to do, I will.' I didn't know where I would get any supply from, but he had a condition that really made me think it would be amenable to cannabis, because he not only had pain, but inflammation as well, and I was aware from the scientific literature that cannabis might well help inflammation. He had an inflammatory condition of his gut called familial Mediterranean fever. Well, I guess none of you have heard of it.[114] But it was when the Home Office came along and said: 'Anita, you must do more of these,' and I couldn't, because there really wasn't any other patient with that diagnosis in my pain clinic. He was a smoker of cannabis; he took oral morphine to manage his pain and had difficulties with the side-effects from oral morphine and said that taking the cannabis helped him keep the dose of morphine down. He also described his experience in hospital: he'd been hospitalized on a number of occasions and, of course, if you smoke cannabis you've got to go outside the hospital, because it sets the fire alarms off otherwise. Anyway, that came out subsequently.

Also, in the scientific literature there was a paper by Fred Evans, who was a professor of pharmacognosy at the School of Pharmacy.[115] He'd written about pain and inflammation in 1991 and I realized that in previous studies the subjects had not been naive to cannabis, so he was a particularly useful patient to have in front of me in the clinic. I went along to see Fred at the School of Pharmacy and he carried a licence to grow cannabis, so over some coffee and a little bit more discussion, we decided that we would consider whether or not we could supply this patient with appropriate medication. Professor Evans took this proposal back to his colleagues and it was the School of Pharmacy, particularly Professor Michael Newton, who made the capsules for me by hand

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[114] Familial Mediterranean fever is an autosomal recessive disease characterized by recurrent episodes of fever accompanied by peritonitis, pleuritis, arthritis or erysipelas-like erythema. See Ben-Chetrit and Touitou (2009).

[115] Evans (1991).

for this particular study.[116] They were fragile; the patient had to keep them in the fridge. I was also up against barriers such as the capsules being an unlicenced preparation; the cannabis had to be standardized. When it was standardized, and the combination of CBD and THC was publicized (at an open public meeting at the School of Pharmacy held during Science Week in 1996), people looked at me and said: 'Oh, that's an ancient preparation of cannabis you've got there,' because it had quite a high content of CBD in it. It was important to get the hospital pharmacy on board with me, because it was an unlicenced preparation and I realized that if I was going to prescribe it, which I would have to do, I would need the various regulatory tick boxes to be agreed. It had to go through the ethics committee and one of my colleagues in anaesthesia was a member. He said that they'd really had a good discussion over this because it was so enterprising and they considered that it was the right sort of study for the Royal Postgraduate Medical School to be doing: it was a first, it was innovative and, yes, I should proceed. That was one problem solved.

Because we had the School of Pharmacy working with us, we'd found out what cannabinoids were in the capsules and the MHRA agreed that we could have their exemption. Then the Home Office came into the story; actually they invited themselves. Home Office regulations required that the cannabis was kept under lock and key, so we had to see the real locks and keys in the pharmacy. They also sat me down, one of them was Alan MacFarlane, but it must have been in his younger days because this was the early 1990s, and said that they wanted us to study more patients; he also put me under surveillance, and later my husband said: 'Please don't do this study, because our phones are being tapped.' It was very interesting, because MacFarlane came again in the year 2000 when we were setting up the MRC study and said: 'Oh Anita, we've lost all the paperwork on you. We've got to start again, but it won't be surveillance this time, don't worry.' [Laughs] I think they themselves were under different regulations in those times.

In that first Home Office meeting, one thing that MacFarlane stressed was: 'You must never trust patients who take cannabis.' Well, I took that with a pinch of salt, because, you know, if patients are taking cannabis as a medicine, they have some ideas they can share with us, about how to use it as a medicine, in contrast with recreational use. He put me in touch with Brian Smith at the Maudsley Hospital, London, who was a biochemist, and we agreed that we would make sure that the patient was compliant and would take his medication

[116] See, for example, Jover *et al.* (1996).

as he should, using urinary analysis for monitoring. Brian was our expert in cannabis biochemistry. First, we took a urine sample, which we never published while the patient was taking his own cannabis as a medicine; enough said about that. We wanted the cannabis washed out, so we did this before we started a dose-finding study. The patient then took different doses over about 10–12 days and from that we determined the dose that we were going to give him as pain medication. It was 10 mg, based on the THC content. The difficulty with these preparations is that you have the plant extracts but you've got to have a dose to write on your prescription form, so the dose was based on the THC content in the capsules. The study ran for six weeks, three weeks with placebo, three weeks with the active preparation and the patient was compliant. You can read the details in our paper.[117] His cannabinoid levels came down during placebo weeks but they didn't come down to zero because cannabinoids are fat-soluble and stay on board in the body, but they were not at levels that have any clinical activity. The patient found that after a couple of days, he knew whether he was on the active capsules or not, which, again, is a confounding factor in a clinical trial, yet something that was helpful to know. In his placebo weeks, because he knew down the street was the place where he could get something that would relieve his pain, it was quite difficult to counsel him over the phone. Again, I think this is something that matters in clinical trials when a patient can access the preferred drug outside the medical consultation. You need somebody there for your patients to talk to so they will maintain their compliance. We had to talk him through that difficulty. And then in the last two weeks, one active and one placebo week, he wasn't sure himself what he was taking, whether it was the active preparation or not. This is why we wrote: 'Is there a withdrawal phenomenon; is there tolerance to the drug?'[118] Those were questions that were raised from this study. I then experienced an author's dilemma, because one general publisher in this country, an editor, phoned me up and said: 'We will publish this case report if you say he was a habitual user.' Now this raised ethical problems, because it was not legal to use cannabis and the study was an *n* of 1 so it would be relatively easy to identify the patient. Needless to say, it was published in another journal without a caveat.[119]

At the same time, I was making an application for a study to investigate the efficacy of cannabinoids on MS with a randomized controlled trial at the

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[117] Holdcroft *et al.* (1997a).

[118] Holdcroft *et al.* (1997b).

[119] See note 117.

Central Middlesex Hospital. The application went to the MS Society but was turned down. I think that was before all the lobbying started by the BMA and the House of Lords, then culminating in the Royal Pharmaceutical Society workshops that Bill Asscher set up, that we've heard about from Tony Moffat.[120] These workshops on the use of cannabinoids in pain management and multiple sclerosis set us off on the right track and then the MRC set up their own workshops, so we had experts come in to say how we should run the trials. In postoperative pain, you need to recognize that in addition to wound pain, patients often feel nauseated, there is also an inflammatory element and often muscle spasm around the area where the surgery has taken place. Having a pain medicine that acts on all these would be quite useful to patients. How the pain study was set up was interesting. Again, we didn't know the dose so we designed an open label dose-finding study, and that was the study that was published.[121] But in that dose-finding study we were limited to a single dose. We had to have patients with moderate pain agree to be studied for six hours with only cannabis as their pain medication. That was not easy postoperatively. Yet again, we found doses of cannabis that were effective; the efficacy of the cannabis was similar to that of paracetamol, which is a moderate analgesic. This study has shown that as the dose of cannabis increases, postoperative pain relief also increases. We published the results in 2006, so almost ten years after we first set up the workshops to develop the clinical trials.[122]

**Tansey:** So your first trial, Anita, was an *n* of 1. When did you publish that?

**Holdcroft:** That was published in 1997. It was completed in 1995, after having gone through all the regulatory procedures over the previous year.

**Tansey:** And then when you were doing the MRC trial, how about patient recruitment? How did you recruit patients to that?

**Holdcroft:** It was interesting, because the people who'd helped set it up, had set it up to use a score for pain relief after surgery. Patients could only enter into the study if they'd had morphine after surgery. Also, the patient selection was very rigid. In the end, it was only possible to get a handful of patients recruited so we had to expand the protocol – increase the ages of the patients and the types of patients who could go on the study – to be able to recruit enough patients.

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[120] See pages 44–5.

[121] Holdcroft *et al.* (2006).

[122] See note 121.

In the end, it probably took us two years longer than we anticipated to do the dose-finding study and then the MRC stopped us continuing on the main randomized placebo-controlled study.

**Tansey:** What happened when the MRC pulled the plug?

**Holdcroft:** We redesigned the study using the remaining grant money, but they said that we could no longer proceed.

**Tansey:** When this trial was going on, was it simultaneous with the MS trial?

**Holdcroft:** Yes, with John Zajicek's study on MS.[123]

**Tansey:** Unfortunately, John Zajicek can't be here. The observation that cannabinoids might be useful for MS, was made first, I think, by Professor Baker.

**Professor David Baker:** I guess my interest in cannabis really stems from around 1998. The MS Society, who'd supported me for much of my career, had obviously started to listen to people who said: 'Well, maybe cannabis works.' I was invited to a symposium on MS at the University of Edinburgh (sponsored by the Scottish MS Society) in January 1998. I met Roger Pertwee there, and Lorna Layward, from the MS Society, who said: 'Well, you know, you do experimental work on MS, why can't you just do something and see if it works or not.' So, I thought: 'Well, I'm game for those types of things.' My background was immunology and at the time it was thought that MS was just a problem of the immune system, and I said to Roger: 'What drugs can we get and what can we try?' It was difficult initially for us to get cannabis, because we'd have to get a Home Office licence, so he said: 'Well, try a synthetic compound. It's very potent at the receptors and very cheap. It will stimulate both CB1 and CB2 receptors and we will see what happens.' We did the experiment and we have a model where animals get paralysed and get better and get paralysed as happens in MS; and we gave the drug and nothing happened. It just didn't work. We published that ten years later in 2008.[124]

However, at the time of doing that work, because we were actually interested in treatments for MS; we'd got our new wonder cure, as every scientist has, you know, the thing they are working on at the moment. We'd been doing some very long-term experiments on animals and we actually noticed a mouse that

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[123] Zajicek *et al.* (2003).

[124] Baker and Pryce (2008).

had a really bad tremor. I thought: 'People with MS aren't really using it to stop their relapsing attacks, they're using it for symptoms.' So, we thought maybe we could have a go. Once we got permission to do that, we gave the drug, and lo and behold, the tremor went away. We thought: 'Great!' We'd filmed this and we rushed over, I think, to give it to Lorna Layward, who was going to the House of Lords, probably with Tony Moffat, to talk about doing the trials.[125] So she had the data and she could see it with her own eyes. She asked: 'Well, what about spasticity?' I said, 'Well, I don't know if it happens.' We went back and we looked at the animals and, sure enough, we could see some animals that had very stiff limbs. That was because we'd been doing these very long-term experiments that normally people don't do. We gave the drugs and we could see that the muscles started to relax and we thought: 'Brilliant!' We could see it happening before our eyes, but that was not going to convince anybody, so we had to measure it. We contacted our friends in the clinic and asked: 'How do we measure it?' It took us about six to seven months to devise some equipment that allowed us to measure it, and, sure enough, we could give cannabinoid receptor agonists that would alleviate the symptoms.

The important thing, which really clinched it for us, was when we started to block the cannabinoid receptor system and things got much, much worse. That told us that there was something important here. It's not the fact that you stimulate a receptor and it gets better; well, that could be just because they're high as kites or whatever. It was really when we blocked the system and found that things got worse that told us that there was something that was regulating it internally. Then Vincenzo Di Marzo was very kind and looked at the endogenous system and we started to get the information that this endogenous system was trying to regulate these symptoms. That started us thinking: 'Maybe this is why it is controlling the symptoms; maybe what's happening is that these natural cannabinoids, endocannabinoids, are acting as brakes to limit excessive nerve signalling which may occur in MS.' Essentially, two years later, it transpired that the cannabinoid system was shown to be a regulator of the way nerves transmit information across synapses. Diseases, neurological diseases, are all a problem of altered neuron transmission. Once you start to see that the cannabinoid system can regulate synaptic neuron transmission, it then starts to fit into place, why cannabinoids can be beneficial in treating a number of symptoms: pain, spasticity, etc. You can also understand why cannabis can have adverse effects, such as psychosis: it is because the body is using that

[125] See page 45.

system to regulate nerve transmission whose outcome depends on which area of the brain it stimulates. That's where we got the excitement. I think at the time we were doing this, it was very fortuitous that we were doing the basic science at the same time that Tony Moffat and John Zajicek were doing the trials with the MRC and Geoffrey Guy was initiating his company. It started to put biology behind the patient perspective, so I think what it did was to give an indication that there is biology that these drugs are working on. We don't really understand the biology, but nevertheless there is biology, and the more we understand about it, the more we'll understand what these different drugs and the components in cannabis do. I guess at the time, it told us that maybe cannabis does have some usefulness medicinally.

Tansey: Could I ask the clinicians what impact, if any, that work had? Did people immediately pick it up? Did it seem to have some clinical relevance?

Dr William Notcutt: Yes, we picked that up. I was coming to this as a clinician having dabbled in some research into *Nabilone* in the mid-1990s and done much more research since, particularly in this area. These sorts of things were gradually becoming general knowledge. From my own point of view, as a pain clinician in the early 1990s, the scenario then was that we had opioids, non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, anti-convulsants, all with their own problems. All were potentially lethal in overdose and had side-effects. We were still seeing a lot of patients for whom we had no pharmacological answers to their chronic pain. This led me to start using *Nabilone*, a synthetic cannabinoid, as an agent and gathering up a group of patients and observing them. I found out that one-third of them said: 'Yes, it works'; one-third said: 'Well, it probably works, but I don't like the side-effects'; and the rest said: 'Thank you very much, but it doesn't work.' All of them said – and this was one consistent thing that came across from all of those who had previously used cannabis as an alternative – that cannabis was better. Was it because of the delivery method, was it something intrinsic in the material used, or what? At that time, we didn't know.

From that point of view, I linked up then with Clare Hodges, with Geoffrey Guy and others, and the process started moving forward. Clearly what we wanted to do, rather than to use *Nabilone*, a synthetic compound and a chemical, was to start to explore the uses of cannabis. Again, I was hearing the stories from patients, a few of whom actually put cannabis on my desk in my consulting room saying: 'What do I do with this, doc?' [Laughs] I've had that several times. The excitement for me was when we eventually had a preparation that one could

Figure 2: Two of the earliest group of patients being dosed with *Sativex* under supervision at the James Paget University Hospital, Great Yarmouth, mid-2000.
Left to right: patient, Geoffrey Guy, patient, William Notcutt, Sue Simmons, nurse.

Figure 3: Study team at the James Paget University Hospital, Great Yarmouth in 2000.
Left to right: Cathy Sansom, nurse; Mario Price, pharmacist; Sue Simmons, nurse;
William Notcutt, anaesthetist; Sam Podmore, research assistant.

give to patients that was purified and looked like a medicine, was consistent and did what it said on the tin, to copy the advert.[126] Then we could start to do serious clinical trials but initially we had no knowledge of what was going to happen. So on 1 May 2000 the first clinical trials started on GW products (Figures 2 and 3). We were sitting in an old, disused ward at the James Paget Hospital, Great Yarmouth, and we started out with *n* of 1 studies.[127]

Soon afterwards, Phil Robson and Derek Wade in Oxford also started these sorts of studies to see what happened when we gave real patients this new material. As we've said before, all were end-of-the-line in terms of treatment; probably the worst patients to study, because they are generally very complex, sometimes very frail and difficult to study. That provided us with a body of information that could then lead on to the more definitive studies, the tighter studies, the randomized controlled trials that have emerged from the GW stable over the last seven or eight years.

Over that time, we also gathered a large clinical experience using cannabinoids and one of the things that's been striking to me as a clinician using a range of other drugs is how safe these drugs are and how the side-effects are less unpleasant than those from morphine and tricyclic antidepressants. Even now, we've been starting to use a drug called ketamine as an analgesic, which has hallucinogenic effects.[128] So, in terms of all the other drugs we use in pain medicine and how we've got used to using them, my colleagues and I have become very comfortable with the use of cannabinoids.

**Guy:** I think the question was 'by how much' did the primary science influence the clinical use. Our programme was born out of straightforward medical empiricism. A large number of patients have reported, in the vernacular, that use of street cannabis in smoked, cooked or other forms, was giving them marked benefit. My temptation was to believe them. Why other people didn't, I'm not sure. What was interesting when we started the programme was that as soon as we announced it, people started writing to us. We had a secret address and still do, but they wrote to the newspapers that covered the stories; they wrote to the BBC; they wrote to the Home Office. We used to receive a mailbag from the Home Office once a

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[126] The phrase: 'Does exactly what it says on the tin' was coined in a UK television advertisement for Ronseal Quick Drying Wood Stain, which first aired in 1994.

[127] Notcutt *et al.* (2004).

[128] Ketamine is a short-acting but potent anaesthetic with hallucinogenic effects. See Hardman and Limbird (2001): 346–7.

week. Over time, we had about 4500 patients who wrote to us and about 30 per cent of them had experience with cannabis. We then drew up, I think, a 70-point questionnaire and wrote back to them all. We wanted to know everything about what they did: where they found their cannabis; what type it was; whether they felt some was better than others; what caused them to take more; what caused them to take less – supply was the problem that caused patients to take less, not side-effects – and what other medicines they'd been on. We began to form a very, very clear picture and we published that data about five years ago.[129] We found a very clear picture of what the material could do and what we had to do then was to try to maintain that. Information from David Baker's research, and a lot of research throughout the world, was beginning to add biological and scientific credibility to a quality of data, which sadly in this day and age, physicians don't heed very well. I think it is at their risk that they don't heed and don't seem to listen to the patients. I know that David's study was absolutely heralded as 'the actual proof', in that six mice got better; so that was fine. The fact that we had 4500 patients, 1000 of whom had got better, was irrelevant, because it was a different quality of data. I think what you have to do is to work out the difference between what impacts on developers like us who have to start from scratch to see where we're going to take a programme, as opposed to what impacts on those people who edit journals and who want the objective, scientific 'truth', given in a very nicely wrapped-up way.

**Tansey:** What happened to all the letters? Do you still have them?

**Guy:** My wife and I used to read them on a Saturday morning because they were addressed to me initially. If ever you'd had a bad week, you'd read some of these letters. But you would distinguish between those people with pain from MS, who wrote about a very different type of paradigm from those with arthritis. It was as if 20 of them had sat around a table and said: 'What should we write to Dr Guy?' The corroboration in what they said was stunning. It was a stunning piece of evidence, and we still have them all on file, and the survey as well.

**Tansey:** They are a fascinating resource for medical historians.

**Guy:** I think they would be, but they would have to go back and get permission, but I think nearly all our patients would be happy. Also, the letters we used to get often used to come with: 'And this is what I smoke, doctor.' Fortunately, the licences were given to me personally so it was legal for me to have them, but we'd have piles of all sorts of stuff, cookies made for us and all sorts of things. [Laughs]

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[129] Between 1998 and 2002, 3663 questionnaires were distributed, with 2969 returned, an 81 per cent response rate. Ware *et al.* (2005).

**Hodges:** I have lots of letters that were sent to me with the same sort of thing, and I don't know what to do with them.

**Tansey:** We're happy to talk to you afterwards about depositing them.[130]

**Robson:** I wanted to add that in these very early days, we did spend an unusually large amount of time actually talking to patients. That becomes less and less possible when you get into big clinical trials. In these early studies, a very striking thing was the variability of response. One of the great difficulties in using these medicines is the procrustean temptation to fit the prescribing routine to the convenience of the physician, or as a regulator would prefer it, when, in fact, because of the immense variability in both response of symptom relief and unwanted effects, the need for each patient to be able to determine their own dosing paradigm is important for this group of medicines. Obviously, when you're smoking cannabis to relieve symptoms you have the ability to titrate exactly as you wish it. But we have found it is very important when using cannabis-based medicines, to retain that self-titration element, as the individual patient is the one who best knows how he or she is reacting. I think that's a very important thing that we've learned and incorporated now into the big randomized studies that have at last been showing a positive effect very convincingly.

**Tansey:** As part of that issue of self-titration, does drug delivery play a part in this?

**Robson:** It does. I think that our particular system, which involves a mouth spray as opposed to a capsule or a tablet, does lend itself to that tremendous flexibility, because the patient can very conveniently carry this around in a handbag or a pocket (Figures 4 and 5). It's very easy to dose at any time, you know, someone could dose right now at this meeting without water or anything of that sort, and therefore the medicine can be taken through the day exactly as the individual needs it. Also, the advantage of an oral mucosa spray is that at least part of the preparation is absorbed through the buccal mucous membrane, not the gut.[131]

**Notcutt:** I was going to briefly add that I think that during the 1990s we also got used to the concept of patient-controlled analgesia with opiates after

[130] Staff from the archives and manuscripts department of the Wellcome Library, London, have been in touch with Dr Clare Hodges and it is hoped that it will be possible to arrange for deposit of the letters there (March 2010).

[131] Dr Philip Robson wrote: 'The buccal membrane offers a potentially useful route for systemic drug delivery. See Shojaei (1998).' Note on draft transcript, 10 March 2010.



Figure 4: The first canisters of the cannabis spray that was to become *Sativex,* 2000.
Figure 5: *Sativex* oromucosal spray, 2009.

surgery. Prior to that, we had also had Cicely Saunders, the founder of the modern hospice movement, recognizing that self-dosing of opiates by patients with cancer, for example, was critically important, and that while the physician didn't know what the dose should be, the patient did.[132] The patient knew when they were dosed to both optimal effect and minimal side-effect. They will go to the point where they say: 'That's enough, thank you very much.' We have seen exactly the same in the use of *Sativex* as well – both effect and side-effect. So, I think this has been built on our experience with opioids, both in chronic pain and postoperative pain.

**Tansey:** It also emphasizes listening to the patient?

**Notcutt:** Listening to the patients, yes.

**Holdcroft:** I think it's important to recognize that patients in hospital don't have access to smoking facilities, yet that is fairly common for cannabis medication. We found smoking to be frequent in our studies of HIV patients and patients with sickle-cell disease.[133] I have corroborative letters too, but I think the hospital experience with people who are taking cannabis as a medicine unlawfully is that

[132] Saunders (1964); Clark (1998). See also Reynolds and Tansey (eds) (2004).

[133] Howard *et al.* (2005); Woolridge *et al.* (2005).

it is very difficult to get a handle on what pain they may suffer. For even though I know how and what they are going to use at home, I think hospital-based patients have to have a cannabis preparation that is going to work in hospital because it may not be possible to self-medicate. Even today, patients may still be denied access to cannabinoids on prescription by healthcare staff.

Mechoulam: We did several clinical trials; I'll tell you about two of them. One had to do with children with cancer. Unfortunately, young children – babies even – get cancer, it's an extremely difficult time for them and for their families. We decided to go ahead; we had these young children from the age of several months to the age of 13; we gave them THC under the tongue.[134] It's difficult, obviously, to have them smoke and it is unpleasant for them to have another injection. We gave them THC under the tongue and initially the experiment was supposed to be blinded, i.e. giving the placebo to one group and THC to the other. Then the physician who did the work, Professor Aya Abrahamov, decided that, ethically, she could not do it, because all the children who got the THC stopped vomiting and didn't have nausea, and she could not go ahead giving children placebo when she knew that she had a compound that helps. So, ultimately she gave it 400 times: we didn't get a single case of nausea or a single case of vomiting: it completely blocked their nausea and vomiting; it had nothing to do with the cancer itself. We had problems publishing the results because we didn't have parallel placebo work.[135]

The other trial was done with collaborators in Brazil. At that time it was almost impossible to do clinical trials elsewhere and in Brazil they had good relations with their Ministry of Health. This was, I think, the first clinical trial with cannabidiol used in patients, a small number of patients that had intractable epilepsy of a certain type – I won't go into details here – and they found that high doses of cannabidiol, 300 mg per day or 200 mg per day for months, lowered the number of epileptic attacks that these patients had. We had to supply the Brazilian group with huge amounts of cannabidiol, almost half a kilo after a certain amount of time. We had special chromatography columns built for this purpose. Fortunately, the Brazilian colleagues didn't use all of it and they went on for another 15 years using cannabidiol with various types of patients and found that it reduced anxiety and has effects in certain neurological diseases.[136]

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[134] Professor Raphael Mechoulam wrote: 'In a solution of olive oil.' Note on draft transcript, 9 March 2010.

[135] Abrahamov *et al.* (1995).

[136] Guimarães *et al.* (1994).

**Tansey:** We held a Witness Seminar in 2006 on platinum compounds in chemotherapy, with paediatricians and oncologists there talking about using cannabis, exactly as you've described, particularly for children, although that, of course, has been superseded by a lot of more modern drugs, but we had these accounts in that seminar as well.[137] Would anyone like to make any further comments about clinical trials or clinical work before I hand over to Virginia Berridge, who will lead the discussion of patient experience and activism?

**Dr Ethan Russo:** We've heard about therapeutic applications in clinical trials, but I would like to mention a situation that comes from a different point of view. It was in patients using cannabis already. This is a story from across the pond in the US. Despite their political stance, there has been a programme in place since 1976 called the Compassionate Investigational New Drug program (Compassionate IND) by which, before 1992, patients who proved their clinical need for cannabis could get it supplied by the US government (National Institute on Drug Abuse), using cannabis that's grown at the University of Mississippi. At the turn of the millennium, I was having trouble getting clinical trials started in the US and I decided that I had better look at a group of patients who had cannabis legally, under this programme.[138] There were seven surviving patients at that time (2001). We looked at four of them. Three could be brought to the clinic and one was studied at home in the state of Iowa. These were patients who were smoking up to 10 g of cannabis a day for a variety of conditions: two had rare inflammatory conditions with pain – multiple cartilaginous exostoses (hereditary exostosis); one with nail-patella syndrome; one had glaucoma; and one had MS with a variety of problems, including spasticity and difficulty speaking. They were subjected to a battery of tests; we tested everything that had been reported as a sequela of cannabis use, including magnetic resonance imaging (MRIs), electroencephalograms (EEGs) and neuropsychological tests. To make a long story short, the only significant findings you might imagine were pulmonary sequelae; there were some minor changes in pulmonary function in these patients. Unlike in most tests, because they were smoking at the time of the testing, they did have minor changes in higher executive functions, but they all functioned well. I should mention that one of these people was a full-time stockbroker and very successful. He had been using cannabis at this very high rate for some 20 years. But immunologically, electroencephalographically, MRI imaging, all of these tests were otherwise quite benign, thus demonstrating that

[137] Christie and Tansey (eds) (2007): 47.

[138] Russo *et al.* (2002).

even with high levels of daily usage this seemed to be a very safe drug. The only problems seemed to be attached to smoking, as you might imagine. This was an important finding. At the time no one had studied these patients, but through an inability to do clinical trials of my own design, I had to resort to this. I think we're finding subsequently, as very much larger clinical trials with non-smoked cannabis have become available, that very much the same thing has been evident, that the adverse event profile is very, very low and, as mentioned previously, standardized cannabis materials compare extremely favourably to existing drugs so there is reason for optimism from this point forward that these agents will be available to treat a myriad of difficult clinical conditions in a few years.[139]

**Berridge:** Our last theme is the role of patients in pressing for changes and we've already heard something about that so far, but we'd like to devote the last part of this seminar to that, and wondered if Clare Hodges would like to open this session by talking about her experiences?

**Hodges:** My personal experience, which is how I first came across cannabis was that I started smoking it in 1992, after I'd had MS for ten years. I found this helpful in all sorts of ways: relieving pain, stopping spasticity, helping me to sleep, helping me to eat. I wanted to find out if it did the same for other people as well. I brought this about via doctors, newspapers and TV, to find out if there was anyone else with this experience, and there was. Then I wanted some scientific evaluation of what happened, because before then it was just anecdotal evidence: people said it helped them with this or that, but I wanted some kind of scientific evaluation and some trials, to find out if this was recognized by anyone. I wanted to get some trials done somewhere, which is where the idea for most of these trials that everyone has talked about came from. There were some trials, say with Roger Pertwee, when he found out about anandamide; but if individuals could be helped in the ways they say they are, could this be proven or shown rather than, as it was, just their accounts of what had happened to them? We wanted to have some official recognition that this happened, to flesh out the people's accounts of their experiences of how cannabis had helped them. I asked all these people to tell their doctor what had happened to them and to tell their local politician, to put it about to people that cannabis helped them. With requests or pestering by patients, eventually people tried to do trials to see if this could be authenticated in any way, whereas before it was just anecdotal evidence.

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[139] Russo (2006).

**Berridge:** And you set up the Alliance for Cannabis Therapeutics (ACT)?[140]

**Hodges:** Yes, I started that with a couple of other patients who found that cannabis was helpful.[141] I found them through the neurologist I see. I said: 'I've found this very helpful. Do you know of any other patients with MS who also use it?' And he did. So with those two, we decided to find more people who also used it. That's what the alliance was set up for.

**Berridge:** How did you operate? How do you operate?

**Hodges:** How do we operate? By bringing it to everyone's awareness, maybe through newspapers or television, just telling people at the time that I found this helpful, and other people did as well; that many people have found it relieved their pain. And so we asked: 'Can someone do some trials on this to show if there is anything to it?' Otherwise, it is only our personal experiences of cannabis. Is there any other way we could take it? So, that's really why the alliance was set up: we wanted to draw people's attention to the fact that cannabis helped us, and find out if anyone could authenticate this in any way.

**Berridge:** I think what's come across in talking this afternoon has been the importance of patients and I wonder whether perhaps Victoria Hutchins would also like to say something?

**Ms Victoria Hutchins:** I was diagnosed with MS in 1997, when I was 19, so I've had it for about 12 years. The pain really started to come in about 2001 and then got worse and worse. I was prescribed tablet after tablet: baclofen, gabapentin, tizanidine. I found that I couldn't tolerate the side-effects for the amount of tablets I'd have to take. Then, a couple of years ago, I got referred to the pain clinic with Dr Notcutt, and he tried me on *Nabilone*, which was great. I wanted to increase the dose, but I found that I couldn't think straight, I was slurring and I couldn't have a proper conversation. It wasn't working for me, so we tried *Sativex*; oh, it's just changed my life. It's changed my life, it really has. I can eat and sleep and the pain is less. It's just changed my life. Yes and I went on a withdrawal study: you could have been given the placebo or *Sativex*, and I knew within about 12 hours that I had the placebo. The first day wasn't too bad, but the second day it was like having boiling water poured down my legs, so I came off the study.

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[140] Dr Clare Hodges established the British branch of the US Alliance for Cannabis Therapeutics in 1993. See http://marijuana-as-medicine.org/alliance.htm (visited 25 January 2010).

[141] The other two patients were Bill Thorton-Smith and Elizabeth Mcrory.

**Notcutt:** Two things really: I wanted to pick up on something that Clare Hodges said because I got involved with Clare and the ACT, I think, in about 1993 or 1994 because of a letter in the *Guardian*.[142] But I think one of the things that came across as I realized, starting to talk about this publicly, and starting to speak out, I found myself sort of putting my head above the parapet, and actually became the BMA's unofficial spokesperson on this issue within about a year. They directed journalists to me and to Clare; we were forever getting journalists. I think it was one important factor that we, both of us, agreed that the first thing we would ever say to journalists, wherever, was: 'There are two issues here, there is the recreational use of cannabis and there is the medicinal use.' We kept on hammering this message home and I still do to this day, when they bother to come, so that we focused on the issue of cannabis as a medicine. If you want to look at it, you could compare it with opiates; street opiates and the medicinal use of opiates.

To pick up on Victoria's issue here: she very quickly found out that all of her symptoms came back when she went into trial and withdrew after she'd been on *Sativex* for about a year. After about 12 to 18 hours her symptoms came back with a vengeance. I mean the boiling water going down your legs; it feels like boiling water down your legs; if you've ever had that happen to you, it is singularly unpleasant and several of her other symptoms worsened at the same time. We saw this with a number of patients who had been on this particular withdrawal study; when they went onto placebo their symptoms came back, often within 12 to 18 hours of discontinuing *Sativex*.

**Holdcroft:** I think activism played an important part in recruitment into our clinical trial. The positive activism by patients was very important to recruit people onto the study, but, on the other hand, there was also the negative activism, as Willy Notcutt has suggested, that patients who have had a bad experience, presumably by overdose, can influence other patients, who then refuse to go into clinical trials, particularly if they have not taken cannabis before. I can remember one particular time when a patient on our clinical study was saying how they felt and their partner came along and said: 'Oh, you'll feel differently, you'll actually feel better, if you think this way.' So there was one person altering the effect on another. I think that's something to be discussed out in the public arena: how one person influences the pain of somebody else, or even influences consent to these types of studies.

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[142] Notcutt (1993).

**Berridge:** There's almost a sense of a group of people already quite knowledgeable, who were then recruited onto trials? Patients who had experiences.

**Holdcroft:** Yes, grannies and granddads who had missed the hippie culture in their youth were having second thoughts when their sons and daughters came along and said: 'Oh, you must go on this study, you know, if you missed it when you were young, have it now!' [Laughter]

**Mechoulam:** Let me tell you how we solved this problem, partially solved, of course. There was pressure on the Israeli parliament from patients to allow them to use cannabis. There was a committee appointed by parliament (around 1995). I was the head of the committee, the others were people from the various ministries and I was the only one who came from the outside. There were a lot of things that we suggested: one of them was that medical cannabis should be allowed. This was never discussed in parliament because members of parliament, of course, didn't want to appear in the newspapers: 'They are for illicit drugs.' But the Attorney General apparently accepted it, passed on his approval to the Ministry of Health, which has, for the last couple of years (since 2006), allowed the use of medical marijuana from a standardized source to patients. There is a committee with which I am partially involved, which has approved it for about 300 patients. We think that we shall reach the number of 1000 patients within the next few years. The physician of each patient has to apply to the ministry, describing what the treatment has been so far, and that he recommends the use of medical marijuana. Then the committee or the Ministry of Health has to approve it. As I said, we have about 300 patients, mostly for Crohn's disease, MS, bone marrow replacement therapy, post-trauma and rheumatoid arthritis. We get feedback from these patients and on the basis of this feedback, we shall allow more patients to go ahead. We've not solved the problem, but I think that we are moving in the right direction.

**Guy:** I want to address two points: one that Anita Holdcroft brought up, of course, is to do with consent. It's true to say that there are very few patients, if any at all, who go into a trial of a cannabis-based medicine and don't have an opinion about what they're about to take. Now, that's very different from other pharmaceutical trials where you're giving them a coded drug and the patients generally have little in the way of expectations. What you'll find, and what we have certainly found in our trials, is that we have very, very high placebo rates in the placebo group, but also overall, and our experience now is over 3000 patients in randomized trials, that there isn't unblinding, except in the end points that you're looking for. There's no unblinding in terms of the patient being able

to determine whether they're on active or placebo. That actually extends to both cannabis-naive and non-cannabis-naive patients. We don't really see any difference in those. All we saw, I think, in the earlier studies was the cannabis-experienced patients would titrate up to their optimal dose about a day earlier; in about seven days compared with the non-experienced, but they'd still end up on the same dose. So, the placebo experience is something you have to deal with and we've dealt with in more recent trials in a fairly special approach to the way we obtain consent.

The other issue, and I know it's come up a few times about grannies revisiting their youth and whatever: I think it's very important for people not to leave with the thought that these patients are better because they're stoned or they're high. I'd use the word, disability,, and I know I got pulled up in the US for doing this, but I said: 'I don't want to swap one disability for another.' I think Victoria Hutchins's experience was that she found that she was – as she told me earlier – very incapacitated by some of the other medicines that she was on. What we have done in all these trials is to ask patients about the classic, cannabis-like side-effects, the ones that worry people; the reason why an enormous swathe of preclinical research is now looking at non-psychoactive or peripheral cannabinoids; strange really when most of their effects are central, of course. You may be interested to know, for example, if you take two symptoms, dizziness and euphoria – I think you'd relate those quite well to intoxication – you find overall, I think, that in *Sativex* trials the level of euphoria was about 3 per cent. So if we were looking to create a euphoriant, we wouldn't have done very well. In two trials the placebo was higher. In terms of dizziness: a lot of the drugs that patients would take for MS, gabapentin for example, cause dizziness, I think the average in the trials is around 34–35 per cent, a recent trial of *Sativex* we reported was 13 per cent with dizziness.[143] Those two classic, giggly-type effects you would expect from cannabis are very low. The third one is that we created a 100-point visual analogue scale for the patients to report on the extent of their intoxication. We used this in the early clinical trials, in the Phase I studies, where we did give some subjects some extremely high doses, and we also developed an inhaled route just to see if we could replicate the smoking route. Essentially, on a score of 0 to 100, if the subjects did not score above 80, then they didn't have any particularly strong subjective experience of being high. So 70 or 80 on that scale is into the high zone. I know that Philip Robson, when he gives lectures, says that: 'If you buy street cannabis and you only get to 70,

[143] Johnson *et al.* (2010). See also Rathbone *et al.* (2009).

you'll go and ask for your money back.' The patients who enter our studies are all on multiple therapies. They're on half-a-dozen drugs, some of them, and they will score at the beginning of these studies about six or seven out of 100. In the ensuing two weeks of titration where we're asking them to titrate as far as they can to obtain benefit, but not have excessive side-effects, so we'd expect them, in successful titration, to experience some side-effects, they score up to about 14 out of 100. By two months, they're down to about six, and by a year they're down to three out of 100.

One other thing I would like to say is that in thinking about cannabis-based medicines, I mean, thinking about other cannabinoids, the psychoactive effects, when used in the dosage and delivery regimen that we use, are simply not an issue, with regard to prohibition or with regard to not being able to proceed. There are a whole slew of other drugs that patients take, which will give far greater psychoactive effects on any particular day. You'll find that patients with these medicines are able to go about their normal daily work: teachers, lawyers, stockbrokers, and also adjust their dosage around it. There's an important message: although we know cannabis in very high doses can cause what we would call overdose, these psychoactive effects simply aren't an issue for patients in therapeutic doses.

**Notcutt:** To pick up on the titration: as time has gone by, one has learnt to titrate this medicine very accurately and very carefully, and to get to the point where the patients want to be. I'm going to go back and ask Victoria Hutchins: how easy did you find it to titrate and to get the response that you want?

**Hutchins:** With the others, with the tablets I was given [**Notcutt:** That's *Nabilone*], yes, I couldn't choose when to have side-effects. But with *Sativex* – maybe I get a greater pain at 11 o'clock in the morning than I did yesterday, so I take it then. So I can just work it around my day.

**Notcutt:** So you can fine-tune it and customize it to how you are, and to your activities in the day? I don't want to put the words in your mouth.

**Edwards:** Listening to this debate, I was wondering what the rules of evidence are; we haven't talked enough about that. The first use in this country of penicillin was the giving of it to a police constable who was suffering from sub-acute bacterial endocarditis. It was done in Oxford and the guy should have died, because people die of sub-acute bacterial endocarditis, but he survived.[144] It didn't

[144] See Fletcher (1984); Booth (1995).

need a controlled trial, people didn't say: 'Go away for ten more years, or, it's not really safe to give it: what are the side-effects?' So I don't necessarily believe that controlled trials are everything and sometimes persuasive evidence of another kind is there before one's eyes. And there are also, of course, quite bogus claims made on single cases. I deeply respect what our patients say, and I wish doctors would listen more often and more closely. But I also know that medicine was once founded on what doctors believed and patients told, and that really wasn't enough. We also need the evidence of science and control for the placebo effect.

I am persuaded when Raphael Mechoulam tells me about 400 very ill children and no control.[145] I would accept that as evidence, and I don't necessarily accept controlled trials: they can be badly designed. At best, they will tell me about effect size and they'll tell me what the size is and not just if 'it works'. What worries me is the irrationality sometimes of the opposition to good research, with some weakening of standards on what we take as the evidence here. I am left puzzled that the controlled trials building on the brilliant laboratory work on endogenous cannabinoids etc., hasn't had its pinnacle in the application to clinical medicine. I feel it is a bit of a damp squib – well, that's too harsh – but the squib perhaps hasn't gone bang yet. I really would like to see more attention paid to the rules of evidence for our patients' sake.

Russo: I'd like to follow that with an effort to create a little more context about cannabis and how it works. What we've got is a situation where, for all intents and purposes, if we're talking about pain, everything we know about how to treat it has derived from plants. It may have started with *Salix* spp., salicylates, willow bark, which led to knowledge of the prostaglandins. We've heard about the opium poppy and then production of opiates, the discovery of endogenous opioids and enkephalins. The cannabinoids have led to the discovery of the cannabinoid receptors and the endocannabinoid system, which turns out to be a major homeostatic mechanism in the body. Just for context, people need to understand that there are more cannabinoid receptors in the central nervous system than there are for all neurotransmitters put together.[146] In the nervous system, it is a modulator; it's not a neurotransmitter per se, but works on other systems to modify them. Going from a concept, a beautiful concept, that Raphael Mechoulam introduced about ten years ago, called the 'entourage effect': this was the fact that there are many seemingly inactive things that structurally resemble

[145] See page 59.

[146] See Pertwee (2002).

endogenous cannabinoids, but have no direct apparent effects themselves.[147] However, when they're present with other active endocannabinoids, they can synergize to a great degree. An example would be palmitoyl-ethanolamide, which increases the analgesic effects of endocannabinoids 100-fold.[148] This is the kind of thing that we have to know to understand how the plant may work too. This is, again, speaking against the concept of single, molecular medicine and advocating synergistic phytomedicine. I think we're beginning to see more examples. One from a current clinical trial with *Sativex* would be in a cancer pain clinical trial that happened some years ago.[149] At that point, a high THC extract was being tested and *Sativex*, with THC and CBD, as well as the other components, versus placebo, because at the time no one was sure which preparation would be best. In fact, it was thought that both would probably work. What turned out to be the case for people with severe intractable cancer pain was that the placebo didn't work. Surprisingly, the high THC extract didn't work any better than placebo, but *Sativex,* with THC and CBD together, as well as other components, worked quite well.[150] In fact, about 43 per cent of patients who were previously intractable had a 30 per cent or better decrement in their pain, and this is the current gold standard for regulators.[151] We're beginning to see a situation in which it can be proven that sometimes nature does it better even than our biosynthetic chemists, who for a long time have had this lock-and-key model, where we know the receptor and what we therefore do is design a molecule which binds to it with the highest possible affinity and the greatest possible potency.[152] That isn't the way nature works: we're dealing with a system that has a certain static level of activity and if it is out of balance, too high or too low, nature will try to bring it back into the middle. This is what we think phytocannabinoids also are capable of doing on a therapeutic level.[153]

Robson: Could I directly address Griffith Edwards's point?[154] I think that the standard has to be consistent, and I agree with you that that standard has to be

[147] Ben-Shabat *et al.* (1998).

[148] Calignano *et al.* (1998).

[149] Johnson *et al.* (2010).

[150] Russo and Guy (2006).

[151] Russo (2008).

[152] McPartland and Russo (2001).

[153] Russo (2004a).

[154] See pages 66–7.

approached and it hasn't been fully reached yet, for very good reasons. I think that if you take the areas in particular that have been looked at for cannabinoid medicine so far; let's take spasticity, for example: if you look at the level of evidence that supports the drugs that are currently prescribed for this, you'll find they're surprisingly weak. Several of the drugs that are licensed in this indication haven't been proved against the so-called gold standard measure in spasticity and it's quite shocking to see how weak the evidence is for those drugs. In terms of large-scale, well-planned clinical trials on cannabis-based medicines, these are very early days. I think GW is a very innovative company, if I could say that, but it's a very small company and the level of resource that has been available to carry out clinical trials has been, to some extent, limited. The measures, the outcome measures, that we are dealing with are very inexact. There are many difficulties in the basic design of these studies. This, I think, explains why it's taking seemingly a long time to match in the clinical context what we've seen in the laboratory, but I'm absolutely confident, based on the results that are now emerging, not just from GW but from elsewhere, that these data will come. And I agree with you: there should be no lowering of the requirement of proof for these medicines.

Hodges: I would like to ask everybody about the downside of cannabis, because I've become more and more aware of the downsides, as we can see with young teenagers, because I can see that it's affecting my mind; not that it's making me psychotic, but I'm very conscious of it affecting my mind as well as helping my body. Has anyone studied this?

Robson: As the token psychiatrist, perhaps I could mention, what has happened is that there have been a number of long-term, well-planned studies which have identified children before they start using a drug, followed them through to adulthood and tested the correlation or the link, or the increase in risk, of a psychotic episode later in life, which is associated with smoking cannabis at a young age. There has been a fairly consistent demonstration that that risk is increased.[155] However, it has to be said that the methodology of all of those trials is, to some extent, questionable. There are great complications in carrying out such studies, not least in terms of confounding factors, outcome measures, the difficulty of relying on self-reported, subjective information about the drugs that are being taken and whether people are still continuing to take cannabis, when in fact they're saying they're not, at the outcome stage. So, although the general consensus is that smoking cannabis, especially at a very young age,

[155] See Moore *et al.* (2007).

increases the risk of developing a psychotic condition in later life, the level of risk as assessed, for example, by an independent body such as the ACMD, is low. It's important to bear in mind that the doses being used by people in the recreational context, as has been touched on before, are much higher in terms of brain levels than those being used by medical patients who are doing their very best to avoid intoxication and, as we've heard, have very low levels of so-called psychotic, unwanted effects such as hallucinations, paranoid ideas or indeed psychotic states. I think, again, that we have to separate recreational use from medicinal use. I think the answer is that the evidence suggests that in the recreational area, there is a risk, albeit a small one, and that the risk is likely to be much lower in the medicinal field. I would also say that when one is assessing risk it should never be in a vacuum. In the case of recreational drugs, one should always look at the relative risk of other drugs for causing the same effect, and it's certainly by no means just cannabis that may be associated with the risk of developing psychotic illnesses. Stimulants and hallucinogens have been investigated in the past. There are many other recreational drugs which carry, I suspect, an equal or greater risk than cannabis and, equally, in the medicinal context one shouldn't look at the risk of cannabis in producing psychiatric or any other adverse event in a vacuum, it should be relative to the risks of other medicines that are currently licensed.

Guy: Two little points there: you may be interested to know that a major global research collaboration we have with cannabis extracts is actually looking at the treatment of schizophrenia at the moment, so it goes both ways actually, that issue.[156] Can I just address the question? If I understood, what you proposed is that perhaps with all of the stigma around cannabis, people's standards and the hurdles may have been dropped or confused a bit. I think, actually, from our point of view, having dealt with regulators in most continents, with clinical trials at the moment running in 18 countries, so we have a lot of experience in most countries throughout the world, *Sativex* is being used in 22 countries, it's absolutely the opposite. If anything, the hurdles have been raised, because any of the regulators' decisions to do with *Sativex* are very, very public, even to the extent that, as you know, a year and a half ago, the MHRA took the unprecedented step of publishing a public information report on *Sativex*, on a medicine which was not under application at the time, and this is absolutely

[156] See Roser *et al.* (2008). Dr Geoffrey Guy wrote: 'My reference to collaboration is our global research collaboration with Otsuka Pharmaceuticals from Japan, which covers the research and development by GW of a range of our cannabinoids in the fields of neuropsychopharmacology, oncology and pain.' E-mail to Ms Stefania Crowther, 25 March 2010.

unique.[157] The basis was that of the great amount of public interest and the extent of usage. So, I can absolutely assure you that there are no short cuts; there are no easy ways. Having spent nearly six years trying to get *Sativex* approved in the UK, I can guarantee that the quality of data required by the regulators and/or indeed the publishers of the journals in which the study has been published, has, in our mind, not been lowered in any way whatsoever. In fact, possibly raised slightly.

**Berridge:** I think on that point, bringing in the dual nature of cannabis, which is where we started, we will finish and we'll see how that duality develops in future years. Thank you all very much indeed for coming and for giving us what I think has been an excellent discussion and we look forward to seeing the transcription.

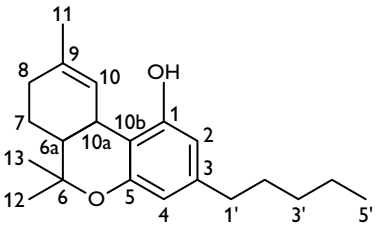
**Tansey:** I would like to add my thanks to all of you for coming here today. I hope you will now join all of us, the team, Virginia, Suzanne, and Lois, Ania and Wendy, who have been manning the microphones, for a glass of wine.

[157] MHRA (2007).

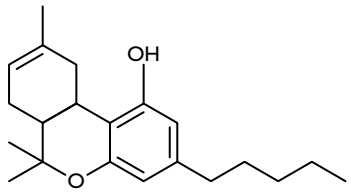
# Appendix 1

## Diagrams of the structures of some major plant cannabinoids and of certain structurally related synthetic cannabinoids

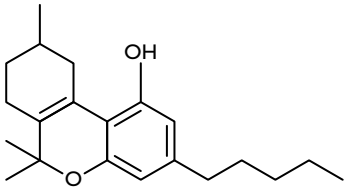
Adapted from Pertwee (2006): 165 and Pertwee (ed.) (2005): 3.



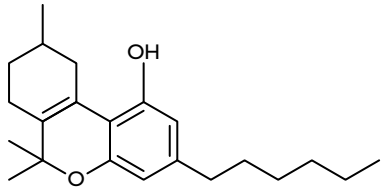

Delta-9-THC



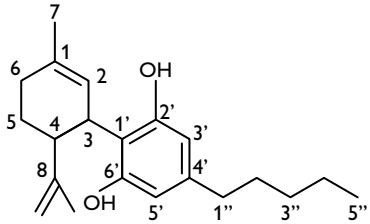

Delta-8-THC



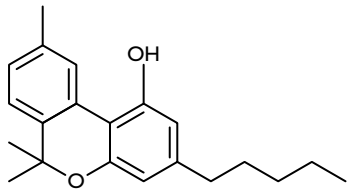

Delta-6a, 10a-THC



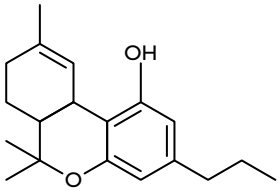

Synhexyl



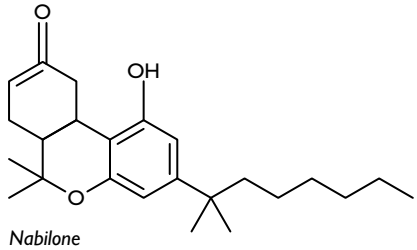

Cannabidiol




Cannabinol




Delta-9-THCV




*Nabilone*

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# Biographical notes*

### Professor David Baker

PhD (b. 1962) gained a first degree in zoology at Bedford College, London, before beginning his research career at the Royal College of Surgeons of England in 1983, where he was awarded his PhD in 1987 for work on delayed-type hypersensitivity. He developed a research interest in multiple sclerosis (MS) and was awarded the Angela Limerick MS Society Fellowship/lectureship. He moved to the Institute of Ophthalmology (1994) and Institute of Neurology (1999), UCL, where he became professor of neuroimmunology in 2005. His research group moved to Barts and the London School of Medicine and Dentistry, Queen Mary, University of London in 2006, where he is part of a translational neuroscience group. He has published over 130 papers and has been grant reviewer for many charities on diverse subjects related to MS, neuroimmunology and cannabinoid biology.

### Professor Virginia Berridge

PhD FFPH AcSS HonFRCP (b. 1946) is professor of history at the London School of Hygiene and Tropical Medicine and director of the centre for history in public health. She was appointed senior lecturer there in 1988 as co-director of the AIDS social history programme. She previously worked at the Institute of Historical Research (1979–88), the Economic and Social Research Council; (1986–90) and the addiction research unit, Institute of Psychiatry (1974–79).

### Dr Vincenzo Di Marzo

ChemD PhD (b. 1960) was awarded a ChemD from the University of Naples (1983) and a PhD in Biochemistry from Imperial College, London, (1988). He has been research director at the Institute of Biomolecular Chemistry of the National Research Council (ICB-CNR) in Pozzuoli, Naples, Italy, since 2002, coordinator of the Naples region endocannabinoid research group since 1995 and an adjunct associate professor in the department of pharmacology and toxicology at the Medical College of Virginia, Virginia Commonwealth University, Richmond, since 2000. He has been the recipient of numerous

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

research grants, including a Human Frontier Science Program research grant to study the biosynthesis, metabolism and structure–activity relationships of anandamide (1994); an INTAS research grant to study the immunomodulatory role of endocannabinoids (1997); and a three-year research grant from the VolkswagenStiftung in Germany (from 2006). He has served as president of the International Cannabinoid Research Society (ICRS) (2004–05). He is member of the board of the International Chair of Cardiometabolic Risk, Laval (since 2005) and was awarded the ICRS Mechoulam Award for 'outstanding contributions to cannabinoid research' (June 2007).

### Professor Griffith Edwards

CBE DM FMedSci trained in medicine at Oxford and Barts. He was director of the addiction research unit of the Institute of Psychiatry (1967–94) and assisted in the foundation of the National Addiction Centre (see Edwards (1972, 2002)). He was closely involved in the British drugs advisory system, advised the White House and was a member of the WHO expert advisory panel on drug dependence and alcohol problems (1969–2001).

### Professor John Galloway

BSc PhD MA LLM (b. 1942) was senior administrative officer at the MRC (1975–86); the Cancer Research Campaign (1986–89); Nuffield Foundation (1989–93); Eastman Dental Institute (1993–96); and has been professor of biology at UCL, head of the dental team studies unit, Eastman Dental Hospital and expert adviser at the joint UCL/UCLH Biomedical Research Centre, UCL, since 1996.

### Dr Edward Gill

DPhil (b. 1931) read chemistry at Corpus Christi College, Oxford, and then completed a DPhil in the pharmacology department with H R Ing before beginning a postdoctoral placement in the pharmacology department, Cornell University medical school, under W F Riker (1958/9). He returned to Oxford as an ICI research fellow in the pharmacology department, Oxford (1959/60) and was then successively research fellow and tutorial fellow (1965) in chemistry, Worcester College. He was a university lecturer in pharmacological chemistry in the pharmacology department, where he was responsible for a course in pharmacology for chemists (1960–99).

### Dr Geoffrey Guy

BSc (Hons) LMSSA LRCP MCRS MB BS DipPharmMed (b. 1954) gained a BSc in pharmacology from the University of London in 1976, an MBBS at St Bartholomew's Hospital, London, in 1979, a MRCS (Eng). and LRCP (London) in 1979, an LMSSA Society of Apothecaries in 1979 and a diploma of pharmaceutical medicine from the Royal College of Physicians in 1984. He was international clinical research co-ordinator at Laboratoires Pierre Fabre (1981–83); director of clinical development at Napp Laboratories, Cambridge (1983–85); founder of Ethical Holdings plc in 1985, of which he was chief executive director and chairman (1991–97); co-founder and chairman of the plant medicines company that became Phytopharm plc (1990–97). He has been executive chairman of GW Pharmaceuticals plc, since founding it in 1998. In 1996 he received 3i's 'Venturer of the Year' award in the science and technology category.

### Dr Clare Hodges (pseudonym for an MS patient)

(b. 1957) gained a degree in classics at Oxford University and worked for a magazine for doctors and nurses. She later worked for Yorkshire television and travelled to various countries making films about science. After being diagnosed with MS, she became the founding member of the Alliance for Cannabis Therapeutics in 1993.

### Dr Anita Holdcroft

MD FRCA (b. 1947) qualified in 1969 from Sheffield University where she started her career in anaesthesia leading to appointments of registrar and senior registrar at the Hammersmith Hospital, Royal Postgraduate Medical School, London (1972–77) and senior lecturer and honorary consultant anaesthetist at the Charing Cross Medical School (1977–80). She was professor of anaesthesia at the University of Jos, Nigeria (1980–87) and senior lecturer and reader at the Hammersmith Hospital and Royal Postgraduate Medical School, Chelsea and Westminster Hospital and Imperial College London (1988–2007), later emeritus professor of anaesthesia at Imperial College London (since 2008). She has been the workshop organizer for the International Association for the Study of Pain (IASP) World Congress meeting on cannabinoids (2000), scientific adviser to the Medicinal Cannabis Research Foundation (2000/01), co-chair of the IASP special interest group on sex, gender and pain (2002–05), anaesthetic lead for the Confidential Enquiries into Maternal and Child Health (2003–

07), co-chair of the British Medical Association medical academic staff committee (2007/8) and is the Royal Society of Medicine section of anaesthesia president elect (2009/10), a member of the Chief Medical Officer's working group on women doctors and treasurer of the Medical Women's Federation.

### Ms Victoria Hutchins

(b. 1977) gained a BA in business administration at Liverpool John Moores University in 1999 and worked as an administrative officer in the Civil Service until 2001. She was diagnosed with MS in 1996 and began participating in clinical trials of *Sativex* in June 2007.

### Professor Raphael Mechoulam

PhD (b. 1930) completed his PhD with Professor F Sondheimer at the Weizmann Institute, Israel (1956–58) and undertook postdoctoral research at the Rockefeller Institute, New York, NY (1959/60). He was a junior, and later senior, scientist at the Weizmann Institute (1960–65) before moving to the Hebrew University, Jerusalem, in 1966, where he became professor (1972) and rector (1979–81). He was visiting professor, department of pharmacology, Virginia Commonwealth University, Medical College of Virginia, Richmond (1993/4); member of the Israel Academy of Sciences (1994); president of the International Cannabinoid Research Society (1999/2000) and head of the natural sciences section, Israel Academy of Sciences (2007).

### Professor Tony Moffat

BPharm PhD DSc FRPharmS FRSC (b. 1942) qualified as a pharmacist from Chelsea College in 1965, continuing there to complete his PhD under Professor Arnold Beckett, and then became chief pharmacist at St Leonard's Hospital, London (1968/9) before moving to become assistant professor at Baylor College of Medicine, TX, US (1969/70). This was followed by 24 years in the Forensic Science Service where he had various roles: head of drugs and toxicology at the Aldermaston Laboratory, assistant director of the Huntingdon Laboratory and later its resources manager, head of quality management in London and research coordinator in Birmingham. He later became chief scientist at the Royal Pharmaceutical Society and professor of pharmaceutical analysis at the School of Pharmacy, University of London (1994–2007) where he is emeritus professor.

### Dr William Notcutt

FRCA FFPMRCA (b. 1946) qualified at Birmingham University in 1970 and after working as a

flying doctor in Lesotho, took up anaesthesia. He worked at the University of the West Indies, Kingston, Jamaica (1975–79), became a senior registrar in the Nottingham area (1979–82) and then consultant at the James Paget Hospital, Great Yarmouth. He was appointed honorary senior lecturer at the University of East Anglia, Norwich (1997). His main interest is pain relief and he started a palliative care service in 1985, introduced patient-controlled analgesia for acute pain in 1986. He started working with *Nabilone* for chronic pain in 1993 and organized the first clinical trials of *Sativex* in 2000 (Figures 2 and 3). He is chair of the ethics group of the British Pain Society (since 2005).

### Professor Roger Pertwee

MA DPhil DSc (b. 1942) obtained his degrees at Oxford University. He began research on the pharmacology of cannabinoids at Oxford in 1968 and continued when he moved to the University of Aberdeen in 1974, where he is professor of neuropharmacology. He is also director of pharmacology at GW Pharmaceuticals (since 2002), co-chairman of the International Union of Pharmacology (IUPHAR) subcommittee on cannabinoid receptors and a coordinator of the British Pharmacological Society's special interest group on cannabinoids. He has also served as chairman of the International Association for Cannabinoid Medicines (2005–07) and as president of the International Cannabinoid Research Society (1997/8 and 2007/8) and he has been the society's international secretary since 1992. He was the recipient of the Mechoulam Award for 'outstanding contributions to cannabinoid research' in 2002 and was recognized to be an ISI Highly Cited Researcher and hence among 'the world's most cited and influential researchers' in 2005 (see Pertwee at http://isihighlycited.com/). His research has played major roles in the discovery and pharmacology of endogenous cannabinoids and the endocannabinoid system, the discovery of a CB1 receptor allosteric site, the discovery that THCV is a plant cannabinoid and a cannabinoid CB1 receptor antagonist, the pharmacological characterization of THCV and other plant cannabinoids, the gathering of evidence supporting cannabinoids for the management of multiple sclerosis and the discovery/characterization of novel synthetic cannabinoids, including the first water-soluble cannabinoid (O-1057), the first CB1-selective

agonists (e.g. methanandamide) and a widely used CB2 antagonist (AM630).

### Dr Philip Robson

MBBS MRCP FRCPsych (b. 1947) qualified in medicine at the Royal London Hospital (1971) and spent several years as a hospital doctor, then as a clinical pharmacologist. After training in psychiatry he became lecturer in psychiatry at the University of Oxford (1985) and consultant psychiatrist (1990) and headed the Oxfordshire regional drug dependency unit (1990–2000). At the request of the UK Department of Health he conducted a critical review of the scientific literature regarding the therapeutic potential of cannabis and cannabinoids and gave evidence to the House of Lords select committee inquiry (in 1998). He served as medical director of GW Pharmaceuticals (2000–05) and retains a part-time role with the company, alongside a senior research fellowship within the department of psychiatry, University of Oxford.

### Dr Ethan Russo

MD (b. 1952) graduated from the University of Pennsylvania in 1973 with a BS in psychology, and qualified in medicine at the University of Massachusetts Medical School (1978). He has held faculty appointments in pharmaceutical sciences at the University of Montana, in medicine at the University of Washington, and is a visiting professor at the Chinese Academy of Sciences. He is currently senior medical advisor to GW Pharmaceuticals, secretary of the International Cannabinoid Research Society (ICRS) and chair of the International Association for Cannabinoid Medicines (IACM). He was founding editor of the *Journal of Cannabis Therapeutics,* selections of which were published as books: *Cannabis Therapeutics in HIV/AIDS* (2001); *Women and Cannabis: Medicine, Science and Sociology* (2002); *Cannabis: From Pariah to Prescription* (2004) and *Handbook of Cannabis Therapeutics: From bench to bedside* (2006). He received the IACM Special Award in 2009.

### Professor E M (Tilli) Tansey

PhD PhD FMedSci HonFRCP (b. 1953) is convenor of the History of Twentieth Century Medicine Group and professor of the history of modern medical sciences at the Wellcome Trust Centre for the History of Medicine at UCL.

### Ms Suzanne Taylor

BA (Hons) MSc (b. 1978) obtained a BA in history from UCL (1997–2000) and an MSc in economic

and social history, specializing in the history of medicine at Oxford (2001). She moved to the London School of Hygiene and Tropical Medicine in 2002 as a research assistant and later a research fellow working on a variety of projects. She is currently completing a PhD there, entitled 'Medicalising Cannabis: Science, Medicine and Policy, 1950–2003'.

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