

WELLCOME WITNESSES TO TWENTIETH CENTURY MEDICINE

TECHNOLOGY TRANSFER IN BRITAIN: THE CASE OF MONOCLONAL ANTIBODIES

SELF AND NON-SELF: A HISTORY OF AUTOIMMUNITY

ENDOGENOUS OPIATES

THE COMMITTEE ON SAFETY OF DRUGS

WITNESS SEMINAR TRANSCRIPTS EDITED BY:
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Key

Front cover photographs, L to R:

Monoclonal Antibodies: Dr Georges Köhler (1946–95), Sir Christopher Booth, Dr César Milstein (1927–2002)

Endogenous Opiates: Dr Derek Smyth

Endogenous Opiates: Professor John Hughes

Back cover photographs, L to R:

Self and Non-Self: Professor Peter Campbell, Professor Richard Batchelor, Sir Christopher Booth

Committee on Safety of Drugs: Dr Tilli Tansey, Dr Stephen Lock, Mr Wilfred Turner,

Professor Owen Wade (1921–2008)

Committee on Safety of Drugs: Dr Josephine Weatherall, Professor Miles Weatherall, Professor David Finney

Self and Non-Self: Professor Deborah Doniach (1912–2004), Professor Ivan Roitt

Endogenous Opiates: Professor Lesley Rees, Professor Howard Morris

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WHAT IS A WITNESS SEMINAR?

Advances in medical science and medical practice throughout the twentieth century, and especially after the Second World War, have proceeded at such a pace, and with such an intensity, that they provide new and genuine challenges to historians. Scientists and clinicians themselves frequently bemoan the rate at which published material proliferates in their disciplines, and the near impossibility of 'keeping up with the literature'. Pity, then, the poor historian, trying to make sense of this mass of published data, scouring archives for unpublished accounts and illuminating details, and attempting throughout to comprehend, contextualize, reconstruct and convey to others the stories of the recent past and their significance.

The extensive published record of modern medicine and medical science raises particular problems for historians: it is often presented in a piecemeal but formal fashion, sometimes seemingly designed to conceal rather than reveal the processes by which scientific medicine is conducted. As Sir Peter Medawar suggested, in his famous article, 'Is the scientific paper a fraud', much scientific literature 'misrepresents the processes of thought that accompanied or gave rise to the work that is described ...',¹ not deliberately intended to deceive, but structured and arranged in a rigid format that allows for little individual expression or amplification. Recourse to unpublished archives for elucidation can introduce additional difficulties. Official archives may have limitations on access: in the UK public records are subject to a restriction that keeps papers hidden for at least 30 years. Equally, specialist archives can present problems: the survival of personal papers can be erratic, many are lost during the lifetime of an individual, as space constraints or relocation demand the jettisoning of material without proper regard for its significance. Probably even more papers are wrongly discarded as worthless and uninteresting by their owners, or by relatives acting immediately after a bereavement.²

Thus historians of contemporary medicine and science are increasingly turning, or returning, to the traditional technique of oral history to supplement, or extend, existing records, and to create new resources.³ Recognizing that many of the principal sources of contemporary medical history are still walking around, although on increasingly elderly and fragile legs, they are attempting to hear, and record, their accounts. A particularly specialized form of oral history is the Witness Seminar, where several people associated with a particular set of circumstances or events are invited to meet together to discuss, debate, and even disagree about their reminiscences. Originally developed by the Institute of Contemporary British History (ICBH), this format attracted the attention of the History of Twentieth

¹ Medawar P. (1990) Is the scientific paper a fraud? In Pyke D. (ed.), *The Threat and the Glory: Reflections on Science and Scientists*. Oxford: Oxford University Press, 228–233.

² See Booth C C, Sheppard J G, Tansey E M. (1990) Archives of contemporary medicine and science. *British Medical Journal* 301: 1408.

³ See Tansey E M. (1995) Telling it like it was. *New Scientist* 148(2008): 49.

What is a Witness Seminar?

Century Medicine Group, which was inaugurated by the Wellcome Trust in 1990, to bring together clinicians, scientists, historians and others interested in contemporary medical history. An initial experiment was to organize a meeting with the ICBH on the subject of 'Monoclonal Antibodies', which was held in September 1993. The response from those taking part or attending that meeting, and subsequent requests for the transcript, convinced the Steering Committee of the History of Twentieth Century Medicine Group that this forum should be developed. During the following summer a meeting on 'Renal Transplantation' was organized, and in the academic year 1994–1995 a number of smaller 'mini' Witness Seminars were included as part of the routine programme of the group.

Since then Witness Seminars have become a regular feature of the Group's activities, and subjects are usually proposed by, or through, members of the Steering Committee of the Group. From 1990–1995 this comprised Sir Christopher Booth (Chair), Dr Tilli Tansey (Secretary), Professor Bill Bynum and Dr Stephen Lock. They were joined in 1995 by Dr Lara Marks and Professor Tom Treasure, and in the following year by Dr David Gordon. Meetings already held or planned for the current academic year are listed opposite.

Once a suitable subject has been agreed, we try to identify and invite participants, and to plan, in conjunction with the meeting's chairman, a flexible outline plan for the progress of the meeting. Occasionally we have had to abandon or postpone meetings at this stage if key people are unable to attend. This is a constant problem when many we invite are elderly. Similarly, some meetings can be disrupted at the last minute by accidents or ill-health: sadly the late Professor Charles Fletcher suffered a bad and incapacitating fall just days before he was due to join Dr Philip D'Arcy Hart as one of the two principal witnesses at the 'Pneumoconiosis' meeting. Invitations inevitably lead to further contacts, further suggestions of people to invite, and we rely heavily on such recommendations. As the organization of the meeting progresses, we ask some participants to be principal witnesses; to speak for a short period of time to initiate and stimulate further discussion. Again, these arrangements differ from meeting to meeting, although all speakers are asked not to prepare formal presentations or to show slides, as these disrupt informal interchange. Thus by the time each meeting is held, it has already developed its own particular shape determined by the participants. For example, no one could dispute that 'Endogenous Opiates' would undoubtedly have been a different kind of seminar, not necessarily better or worse but different, if Hans Kosterlitz had been able to attend; or that 'Monoclonal Antibodies' would have been markedly different if the National Research Development Corporation had sent a representative who had been personally involved with the patenting issues that were raised.

As each meeting proceeds it also develops its own kinetics, largely dependent on the personalities of the chairman and the participants, and the relationships among those taking part. No two meetings have ever been the same.

Each meeting is fully recorded, and the tapes are transcribed. The Steering Committee then decides whether the transcript should be edited for publication. This decision is informed by two main factors – the overall coherence of the meeting, and whether the transcript will contribute new material to the published

History of Twentieth Century Medicine Witness Seminars, 1993–1997

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

historical record. Of the meetings held so far, we decided not to publish the proceedings of 'Renal Transplantation' because many of the speakers repeated well known anecdotes and accounts, adding little fresh information or interpretation; 'Pneumoconiosis' was handicapped by the absence of Professor Fletcher; we have yet to come to a final decision about 'Oral Contraceptives'. All other meetings will be published in this format, apart from 'Ashes to Ashes', which forms part of the proceedings of a symposium that will appear under that title in the Wellcome Institute's History of Medicine Series published by Rodopi.

What is a Witness Seminar?

Once the decision has been taken to prepare a transcript for publication, a first editorial pass is simply tidying-up. Infelicities, the ‘ums’ and ‘ers’ are removed, and a copy then sent to all participants for them to correct, if necessary, their own contributions. Such amendments are principally stylistic, occasionally misremembered facts – names or dates – are corrected. When all these are returned, which can take several months, all the comments are usually incorporated into the master text. Extensive alterations, or the submission of fresh material, are confined to explanatory footnotes. At the same time, we begin to annotate the major reference points alluded to in the seminar, to add biographical and bibliographical details and to continue, if necessary, to edit the text. When this stage is completed the transcripts are again sent to every contributor, for his or her comments on the complete text. Once more, any subsequent comments, usually few, are incorporated if appropriate, or otherwise footnoted. Throughout we are keenly aware that our responsibilities are as editors, not censors, and that our aim is to make the substance of these meetings available to the informed non-expert.

What then do Witness Seminars contribute to the historical record? At a fundamental level they can, and frequently do, serve to guide professional historians through the morass of published and archival sources already referred to, and to alert them to subject matter and sources of which they were unaware; conversely they emphasize to the scientists and clinicians taking part that ‘history’ embraces their working careers. This realization has a number of results – before, during and after meetings we are frequently given documents that are not preserved or accessible elsewhere, and in such instances we always suggest the proper conservation and archiving of the material. Perhaps understandably, it is the less well-known areas that have generated such responses, and many of our witnesses express astonishment at our interest! All such materials will, if not deposited elsewhere, be archived with the records of the meetings and eventually deposited in an appropriate archive for consultation by other scholars.

There are also obvious disadvantages to this format. Primarily, the balance of participants is crucial, and there is little we can do if potential contributors are unable or unwilling to attend. Those who do attend may not contribute much, others may deafen with their axe-grinding. One check on the conduct and content of the meetings is the presence of other participants – a Witness Seminar can be seen as a form of open peer review, with all remarks and opinions immediately susceptible to rejoinder, agreement or dispute. Sometimes too, the frailty and variety of individual memory is all too clearly highlighted: an amusing but thought provoking illustration is provided by the differing accounts that emerged during and after the meeting of the ‘Committee on Safety of Drugs’ of the evolution of the yellow card for reporting adverse reactions.

Acknowledgements

Many people assist in the organization, recording and publication of these meetings. The contributions of Mrs Lois Reynolds and Dr Daphne Christie far exceed the editorial tasks that are acknowledged in the individual transcripts. They have jointly worked, as well as two people job-sharing one position can, on every document, standardizing, reformatting, and indexing the text. The attractive appearance of the finished product is almost entirely due to their efforts. They have been advised by staff of the Information Systems Department and the Publishing

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Department of the Wellcome Trust, and we thank them for that assistance. Throughout, Mrs Wendy Kutner has helped organize and run all the meetings of the History of Twentieth Century Medicine Group, and I am enormously grateful to her. I would also like to thank the staff of the Wellcome Trust's Audiovisual Department who are responsible for setting up and recording the meetings, Mrs Jaqui Carter our transcriber, and Mr Chris Carter for taking the photographs. I would particularly like to thank all those who have participated in our Witness Seminars, who have contributed so freely, corrected their drafts, and often provided additional material and memories. Finally, I gratefully acknowledge the Wellcome Trust for its financial support.

Tilli Tansey
Wellcome Institute for the History of Medicine

Technology Transfer in Britain: The Case of Monoclonal Antibodies¹

The transcript of a Witness Seminar held at the Wellcome Institute
for the History of Medicine, London, on 24 September 1993

Edited by E M Tansey and P P Catterall²

¹ We are grateful to Frank Cass for permission to reprint this article, which has already appeared in (1995) *Contemporary Record* **9**: 409–444. A paper on the discovery of monoclonal antibodies has appeared as Tansey E M, Catterall P P. (1994) Monoclonal Antibodies: A witness seminar on contemporary medical history. *Medical History* **38**: 322–327.

² Dr E M Tansey, Wellcome Institute for the History of Medicine; Dr P P Catterall, Institute of Contemporary British History.

Technology Transfer in Britain: The Case of Monoclonal Antibodies

PARTICIPANTS:

Dr Ita Askonas (London)
Dr Basil Bard (London)
Sir Christopher Booth (Chair) (London)
Dr Robert Bud (London)
Dr John Galloway (London)
Sir James Gowans (Oxford)
Sir John Gray (Cornwall)
Dr Georges Köhler (Freiburg, Germany)
Dr César Milstein (Cambridge)
Mr John Newell (London)
Dr David Owen (London)
Dr David Secher (London)
Dr David Tyrrell (Salisbury)
Dr Guil Winchester (London)
Professor Miles Weatherall (Charlbury)
Dr Peter Williams (Oxford)

Monoclonal Antibodies

In 1975 two Cambridge scientists published a short article in *Nature* which announced the discovery of monoclonal antibodies. The article concluded 'Such cultures could be valuable for medical and industrial use'. The interest which developed by the end of the decade in the industrial and financial possibilities of the new prospects opening up in biotechnology was to throw the apparent 'failure' to follow-up the potentialities of this discovery into a public prominence rarely achieved by scientific discoveries. By the time Mrs Thatcher came to power it had become a scandal, another example of Britain's apparent inability to exploit effectively the brilliance of its scientific base. It was to explore both the process of scientific discovery and the conditions in Cambridge which nurtured it, and the issues which this particular discovery raised in the area of technology transfer (and the changes of policy that ensued), that the Wellcome Trust's History of Twentieth Century Medicine Group and the Institute of Contemporary British History organized this special witness seminar. It was held at the Wellcome Trust in London on 24 September 1993. The seminar was chaired by Sir Christopher Booth and introduced by Dr Robert Bud of the Science Museum. Those participating included the two authors of the *Nature* article, Dr César Milstein and Dr Georges Köhler, who received a Nobel Prize for their research, Dr Basil Bard (National Research Development Corporation (NRDC) 1950 to 1974), Sir James Gowans (Secretary of the Medical Research Council (MRC) 1977 to 1987), Sir John Gray (Secretary of the MRC 1968 to 1977), John Newell (BBC World Service science correspondent 1969 to 1979), Dr David Owen (MRC), and Dr David Secher (Laboratory of Molecular Biology (LMB), Cambridge). There were also contributions from Dr Ita Askonas (former head of immunology at the National Institute for Medical Research), Dr John Galloway (former member of MRC headquarters staff), Dr David Tyrrell (former Director, MRC Common Cold Unit), Professor Miles Weatherall (Head of Therapeutic Research Division, Wellcome Research Laboratories 1967 to 1975), Dr Guil Winchester (post-doctoral fellow, Wellcome Institute for the History of Medicine), and Dr Peter Williams (former Director of the Wellcome Trust). The organizers would like to thank the Wellcome Trust for hosting and sponsoring the seminar. We would like to dedicate this publication to the memory of Georges Köhler, who sadly died in April 1995 before this could appear.

Dr Robert Bud: The study of contemporary history provides a rare opportunity for the active and self-conscious interaction of subject and viewer, which can be as daunting as it is exciting for the historian. Historians of the nineteenth century can rest assured that none of their subjects can say that it was not like that. At the same time it provides an opportunity for all of us to have a much more interesting interchange and identification of what are already understood to be momentous and important changes and developments. Already it is clear that the emergence of biotechnology as a whole is one of the big shifts in late twentieth century

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technology and in the future and industry as a whole.³ Of course it is a topic that has benefited from hype as well as reflection on its real and great importance in technological development, and that hype has been very important in understanding, interpreting and indeed generating some of the changes which have occurred. After all, Genentech the first biotechnology company, had shares which benefited not from deep understanding of the technology, but also a sense of great excitement. That hype has been associated not with the long-standing category of biotechnology, of making things through living processes in general, but from association with a category which in the mid-1980s came to be called the 'new biotechnology', a phrase which I believe was launched in the 1984 Office of Technology Assessment Report, *Commercial Biotechnology*, and this category, the 'new biotechnology', was seen to stand distinctively on three legs. One, which was quickly forgotten, was new fermentation technologies engineering. The other two were much better known; one was recombinant DNA and the other, which is what we are studying today, was hybridoma, specifically monoclonal antibody technology.⁴ So even then in 1984, still less than a decade ago, monoclonal antibody technology was seen to be one of the engines of the West's industrial and technological renewal. Now this startling claim is observation and highlights for us all a remarkable process in which a scientific paper published in *Nature* in August 1975⁵ could be translated into a Nobel prize, into a British achievement, the potential basis for biotechnology and indeed, as we shall explore later, also a scandal.

Three radically different contexts have been brought together for such a rich brew to emerge from a piece of science. First, the scientific history: developments in immunology, tissue culture, work with myelomas and the techniques of cell-fusion in one of the world's premier laboratories, the Laboratory of Molecular Biology (LMB) in Cambridge, a large laboratory with a sequence of significant people there – César Milstein – working with a series of other collaborators in a large scientific community. This had to be translated into an achievement for somebody having done something, and early in the 1980s when the significance of what had been achieved became clear there was a debate about who had done it. How do you translate the complexity of real science into the simplicities of the discoverer? That perhaps is something that we will reflect upon today, how the public can understand the complex nature of modern science.

Secondly, all this happened at a time when many other exciting things were happening in biotechnology. In February 1975, the Asilomar meeting had considered how one could control the safety of work on the recombinant DNA technology.⁶ By June 1976 the US National Institutes of Health had identified regulations by which this work could happen, and by 1976 onwards enormous amounts of commercial enthusiasm went, particularly in the States, into

³ Bud Robert. (1993) *The Uses of Life: A History of Biotechnology*. Cambridge: Cambridge University Press. On the perceived economic possibilities of new biotechnology industries see p. 190f.

⁴ Antibodies are the proteins produced by lymphocytes that recognize and bind to foreign substances or antigens in the blood and neutralize them. Each antibody is specific for one antigen, and is produced by a particular kind of lymphocyte. Hence the latter are immensely diverse, and purifying or extracting a single, defined, antibody was practically impossible. Monoclonal antibodies are just one, defined and pre-determined kind of antibody, produced from a pure single-cell culture line.

⁵ Köhler Georges, Milstein César. (1975) Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256: 495–497.

⁶ Op. cit. See note 3, pp. 175–176.

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biotechnology, the recombinant DNA technology. The outcome were many companies, Genentech was one, Biotech another.

So, the conjunction of the August 1975 paper, César Milstein, happened at a time when many other things were causing technological excitement and this had particular meaning in Britain because there was a local history to the idea of technological excitement over a scientific breakthrough. There had been here the memory of the discovery of penicillin and the subsequent apparent failure of Britain to cash in on it. I am not talking about the realities of the contributions of the British scientists and of the many American scientists and engineers, but a very important national mythology. At school my Latin teacher would break off from telling us about Latin to attacking the incompetents who had failed to make this country rich through penicillin. It seemed that monoclonal antibodies was a rerun. Here were 'British scientists' who had written a paper which said at the end, very clearly, that this work has got industrial and medical significance, having indeed written to MRC saying that this work might have significance, the work was not patented. Americans were getting patents; in the early 1980s the Wistar Institute indeed tried to get a British patent for work which was perceived to have originated from this country. A British patent was not, in fact, granted. Typical was David Dickson in his 1978 *Nature* article.⁷ The net result is that, like penicillin and other similar stories, monoclonal antibodies may join the list of the ones that got away from the UK.

1979 was a critical year for such excitement to be occurring in this country. It was a time when the whole organization of biotechnology was being considered by the so-called Spinks committee, and also by the new government of Margaret Thatcher. In his history of Celltech, Mark Dodgson points out that the importance of the affair, as far as he could see it, was its acquired, symbolic significance, which highlighted the importance of technological transfer to the new Conservative government and sustained the development of this new company, Celltech.⁸

So, out of this conjunction of three, quite separate, phenomena, the science, the technological excitement over biotechnology and the symbolic significance of Britain, we can, perhaps, identify a series of questions which will be touched upon, I hope, through the meeting, and where we will be richer in our understanding of the answers than we were before.

The first one, perhaps, is what happened scientifically and the nature of the collaboration. Each of the participants has published their understanding of the developments. Perhaps we can hear a bit more about that and the nature of a single breakthrough event. How legitimate is it to translate a complex process into a single paper and a single experiment? What is the relationship between the people? Can you even identify single discoverers? Second, in time, and perhaps we can identify it, is the failure to patent. Was it the result of an accidental failure? Sometimes it is seen as the incompetence of an individual, or was it a structural problem in technological transfer in this country. Thirdly, we can think of this not as a problem of technology transfer but of the nature of political scandal in this country. When did it come to be seen as a scandal? There was no excitement in

⁷ Dickson David. (1978) NSF encourages more university/industrial collaboration. *Nature* 271: 396–397.

⁸ Dodgson Mark. (1990) *Celltech: The First Ten Years*. Brighton: SPRU.

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1976 and the first article I have been able to find, in 1977, still made no mention of patents.⁹

And in retrospect, do we still think of it as a disaster, with the benefit of being in 1993 rather than in 1983? Was it a disaster that this was not patented? And indeed, is there such a thing, if one is talking about scandals, as British science? In what sense was this a 'British discovery' at all? Of course, one of the exciting aspects of the whole monoclonal antibody excitement and one of the reasons that people felt it was a disaster was that there were enormous hopes for the technological significance, very large numbers of noughts were attached to estimates of the commercial exploitation by the mid-1980s, and we can reflect now to what extent the enormous hopes of 1980 were justified in terms of short-term commercial advantage. How much of those hopes could be attributed just to this discovery and how much to the entire context of what was happening in the late 1970s and the hyping up of biotechnology? And perhaps, to end on a more sober note, what have been the technological outcomes and what do we now see as the implications? I hope this provides us with some tags to which we can attach much of the rich discussion which I am sure will follow.

Sir Christopher Booth: Thank you for a characteristically provocative introduction. I think the first words must go to César Milstein and Dr Köhler, so perhaps I could ask Dr Milstein to continue the discussion.

Dr César Milstein: I really am impressed by the introduction. There are indeed the points which you have mentioned and perhaps those are the most interesting. There were perhaps some other issues which I would like to glance over, at least some of them, without getting into any detail, but I think there are some other issues as well which perhaps you did mention in a way but perhaps not focusing on them. One is the scientific atmosphere, and particularly technical background, which you did mention, particularly things like the fact that myelomas were in culture, that some of the cell-fusion methods were beginning to come out which were used and that were recent, and perhaps about previous attempts at getting monoclonal antibodies. Whether there was an interest in producing them and whether those which were interested were approaching the problem in the way which eventually came to be considered to be the best. There is also the problem of the local atmosphere, which again you did mention, but there are more details about the atmosphere which refer to methods and materials which provided, for instance, the impetus to develop those methods. Issues which had nothing to do with the development of hybridoma, but more with the concepts of basic immunology, like allelic exclusion, somatic mutation and so on, which were, in fact, the interests of my laboratory at the time and the reason why Georges Köhler came to the lab. Perhaps even more important is an issue which you did not mention, and is with hindsight why the experiments worked so smoothly and so successfully. To what extent there were elements that were coincidental, just pure luck, and to what extent they were done correctly. Both, I think, are true. On the other hand there is the question of to what extent were some of the hybridomas applications, which came later and which were shown to be critical, clear in our own minds or indeed in the minds of most investigators at that time; and the issue

⁹ Anon. (1977) Spin-off from cell fusion. *Lancet* i: 1242–1243.

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to which I refer most particularly is the issue of the development of the hybridoma technology as a way of describing cell differentiation antigens, which I think is a very important issue in the application of technology and something which might be worth exploring. This is something which I have not discussed with Georges at all but did we think about it seriously? It was perhaps in the back of our minds.

Then, of course, there is the issue of the ownership and the patenting and what you call the scandal and the controversial issue of why the patent was not taken. Not less interesting perhaps at the time is what was the patenting atmosphere in this country and indeed elsewhere, particularly in the emerging field of biotechnology, and I am not referring to whether we thought it was good patenting or whether it was bad, whether discoveries should be given to the world or patents were morally justified or not, but rather what was the attitude towards genetic engineering patents themselves and what were the conditions, the incentives, the involvement of scientists themselves, or indeed research institutions, in Britain for patenting issues.

So, when we talk about monoclonal antibodies we have to keep this background in mind. The problem of patenting or not patenting monoclonal antibodies is also somewhat confusing because the atmosphere, as I remember it, changed so rapidly, so by 1980, when the first official *post mortem* analysis started, already the attitude was beginning to change and probably that report was part of the change itself. In those days, when I read that Spinks report, my attitude towards the whole process was shattered and I realized somehow that until then I had said nothing at all about the process of the patenting and at that moment I realized that I could not remain totally silent, and perhaps, since your talk was provocative, we should continue somewhat in that vein, I would like to read what made me change my mind in that respect and why I became more interested in having my say in this story, and the injurious sentence in that Spinks report – the Spinks report, I should say for those who don't know about it, was a joint report of a working party of the Advisory Council for Applied Research and Development, the Advisory Board of the Research Councils and the Royal Society.

Booth: And let's be clear. Spinks himself had been director of research at ICI before becoming a member of the Advisory Board for the Research Councils – that is correct, isn't it?¹⁰

Milstein: I think so.

Booth: So he had a very industrial background.

Milstein: Yes, and there is a point at which it reads:

There appears to be a lack of awareness in practice of the obligations on recipients of government money and of the rights of NRDC. (I will add

¹⁰ Advisory Council for Applied Research and Development (ACARD)/Advisory Board of the Research Councils/Royal Society. (1980) *Report of the Joint Working Party*. London: HMSO. Op. cit. See note 3, page 158. Alfred Spinks was Research Director of ICI from 1970 to 1979 and Chairman of ACARD from 1980 to 1982.

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parenthetically that in those days, NRDC was the only organization which was allowed to take patents on behalf of scientists working for government organizations, including the MRC, so neither of us, me, Georges, or anyone working for the MRC, or the MRC itself, was allowed to take patents, so these were the rights of the NRDC, they were the owners or discoverers.) This must be remedied. We are concerned (and this is the critical sentence) that a lack of appreciation of NRDC, particularly by young scientists, may continue to result in situations such as that which occurred of monoclonal antibodies where patent protection was not sought early enough and British advantage was reduced.

I would like to divide the sentence into two parts. It says patent protection was not early enough, on the one hand, and that the British advantage was reduced for that reason. In other words, it was the fault of young scientists that patent protection was not sought. Now, I must say from the beginning that when we wrote the paper, and please do correct me Georges if I say something with which you disagree and of course you will, but I seem to remember quite clearly that when the paper was written we were considering this last sentence, which eventually went into the paper, we felt somewhat shy, as if we were blowing our own trumpet too much by putting that sentence at the end. In the end we decided we should because we were convinced that that was going to be true, and I am not now arguing about how many zeros we put in the equation. I must confess that I clearly remember that I would have never dreamt the number of zeros that actually went in, probably neither did Georges. We were rather shy about the issue of the patenting therefore. However, when an officer of the headquarters of the MRC heard the story which I presented to an internal meeting of the MRC on (an occasion when there were discussions about the safety of genetic engineering experiments, a meeting in Oxford), when he heard that he approached me and said that perhaps they should do something about it, so I sent the paper to him and that was almost a month before the paper came out and the letter he sent to me a few days later reads as follows:

Thank you very much for your letter of 10 July (remember the *Nature* paper came in August 1975) and for your kindness in letting us see the preprint of your paper. I was interested by your talk in Oxford and reading your paper confirms my feeling that this approach to antibody synthesis has great commercial implications. It is most important that action is taken as soon as any exploitable idea gets to the stage where patent protection can be applied for. I have therefore taken the step – and I do hope that you will forgive me for acting without consulting you first – of drawing the attention of the National Research Development Corporation to your reprint. It may be they will contact you direct to discuss whether to take any formal steps.

So, although perhaps initially we might have been accused of not taking the right step, this accusation is rendered void by the action of the contacts between the MRC headquarters and the scientists themselves, which is the correct way that these things should happen anyway, in my view. So, the issue of the Spinks report now, for reasons which are not very clear to me, choose to ignore those facts.

Now, was the NRDC in a psychological position to exploit this idea? Were they prepared to exploit the idea? I would argue that they were not and that is the second part of that sentence. The reason I am saying this is as follows. Even though

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nothing happened for a period (which is something I don't quite understand), just over a year after the paper was published the NRDC had an opportunity to discuss the contents of the paper. In a letter which the NRDC sent to the MRC, dated 7 October [1976], just over a year after publication, (so NRDC had the benefit of hindsight of almost one year) and they say I quote, 'Although they also suggest that the cultures which they have developed, or rather similar cultures, could be valuable for medical and industrial use, I think this statement should be taken as a matter of long-term potential, rather than immediate application', which is of course true in my view, depending on what you call long-term potential. However, then it adds:

It is certainly difficult for us to identify any immediate practical applications which could be pursued as a commercial venture, even assuming that publication had not already occurred. I would add the general field of genetic engineering is a particularly difficult area from the patent point of view and it is not immediately obvious what patentable features are at present disclosed in the *Nature* paper. In summary therefore, unless further work indicates a diagnostic application or industrial end product which we can protect, despite the disclosure in the *Nature* paper, we would not suggest taking any further action ourselves.

Booth: What date is that letter?

Milstein: This letter is dated 7 October 1976, thus it is clear that in the minds of the patenting people in the NRDC, the idea of patenting an idea does not cross their minds, and that is the whole thing in the area of genetic engineering patenting. I think for starters perhaps I should stop now.

Booth: Dr Milstein, that was a superb account of the opposition at that stage. I think we want just not to get stuck with patenting. I think the scientific background is very important too. Perhaps I can ask Georges Köhler to continue and then throw the discussion wider. Why did you go to Cambridge? What were you after and what happened? How was this discovery made?

Dr Georges Köhler: It is the story of a young scientist looking for a good laboratory, which is approximately what I had in mind and that was exactly what happened in Cambridge in César Milstein's laboratory. He was working with myeloma cell-lines, which were growing in culture and had, I believe, the first mutants of these immunoglobulin-producing cells, and I was in Basle at an immunology institute and there were big ideas about how the multitude of different antibodies could be generated and one of these ideas was that they might be generated somatically and I took up a thesis in Basle and I worked with the heterogeneity of antibodies and found myself that what scientists say is true, that they are heterogeneous and you get multitudes and you can find a thousand different antibodies against one particular determinant on protein. I was fascinated by the idea that you could generate a diversity of antibodies by starting with one gene and diversifying it by mutation and I thought we should try to find such mutation and this is the application I made to come to César Milstein's lab. Actually it is only a little story but César Milstein came to Basle and we met there

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for the first time, and I was very proud at that time that I could make isoelectric focusing plates with a new method, not putting two plates together, but putting one on the table and spreading out the material which had to solidify, and I could do not only one plate at once, but four. I knew that César Milstein was using this technique and I thought that it might impress him, so I told him that I had this wonderful method of using not two plates but one plate and that I can make four plates in one go and he looked at me and said that in Cambridge they were making 20 plates at one time! So I knew I went to the right place. So that was the set up, to study somatic mutation in antibody genes. We did not even know whether there was one single gene; there were rumours that there might be two genes, a bit like that. So that was the start. Do you accept that? [to Milstein] I had come because this was such a nice method to make the plates.

Milstein: Can I interrupt you because there is another side. Why did I accept him, because I had two candidates from that visit, and the reason I accepted him was because it was quite clear that there was something communicating in our minds. Somehow I felt that we were talking the same language.

Köhler: That turned out to be true and very important. That was the pleasure of the two years in Cambridge. It was easy to communicate, and usually it is not easy between two people, but with César it was easy.

Booth: You felt the same about César.

Köhler: Yes, I felt the same. That was a luxury and we felt this and we would have felt this with or without monoclonal antibodies. I was happy to have been accepted in César's laboratory – actually I had three other offers and I accepted your offer – and the setting was that I was looking for some somatic mutation that meant that I had to learn to cultivate cells, which I did not know how to do. My PhD dealt with immunizing mice and analysing the sera with isoelectric focusing, and David Secher was instrumental in that. There was Shirley Howe, the technician, who taught me how to culture cells and we tried to find some mutants, but the idea, the new thing that I wanted to do was to find mutants not anywhere in the gene but in the part that makes the contact to antigen, that was in the variable region, but for that you needed a specific antibody which bound to antigen but the immunoglobulins of most myelomas didn't bind to antigen, so we were a bit stuck; so I could either continue to make the same sort of mutants which had already been generated by David Secher or we should find a myeloma which had specificity, and they existed, so I think that was the start to get other myelomas with specificity into the lab and trying to grow them. Apparently I was not good enough at that. In my hand they did not grow, so I had to think about another project. I am just telling you that. I don't know whether that is of any importance. It may give you the set up. It is the story of a young researcher coming to an established laboratory. It is the same story all over the world. So, I turned to cell hybrids, because that was the other thing that went on in César Milstein's laboratory that he was known for, that he had published a paper on, and we thought maybe we should make a better hybrid between two myelomas than the

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one he had already managed to make in his lab and so I went into fusion and indeed that worked out very nicely. I could fuse cells, I could generate hybrid myeloma cells. We found out some things about their properties that had something to do with allelic exclusion, (I won't explain that) so I was happy that I could fuse but I remember that the original project was to find somatic mutations in the variable region of antibodies and I was unhappy that I could not do the job I wanted to do. So was César. So we thought maybe we should find a specificity for the myeloma which worked, which I could grow in the laboratory and there were methods to find the specificity to the unknown immunoglobulin, but I was not happy with that and in my view it was this combination of knowing how to fuse cells and wanting to get specific lines which produced specific antibodies which made the idea that maybe we can make our own fused cell-lines which make antibodies with that specificity. This has been reported in an interview with Nicholas Wade but incorrectly.¹¹ The nice thing with César, and I think I should continue to say this, is that he listens and we could talk to each other and he never dismissed an odd idea, so when I came with the idea that we should fuse a myeloma with a normal spleen cell he did not dismiss it as something out of reach, the strange idea of a post-doc., but he sat down and asked let's see, what were the possibilities. How many hybrids was I going to be able to get? Between one and ten we would be happy per fusion, so what is the specificity? How often would you get the specific cell in the spleen, from one in a thousand to ten thousand, so we made a little division and said okay. I had to do a hundred fusions to be able to find one of the kind that I was looking for and that would take a lot of time in the lab. That was a bit depressing, I must say, but I said I would try. I wanted to see how it would work. Then I was lucky and it worked and that was the generation of hybridoma.

Booth: Let's stick with the science just for a minute. David Secher, perhaps you were a witness to these events, you were there at the time. Would you like to comment on the discussions of the events of the discoveries that we have made so far?

Dr David Secher: I think it is very interesting to note the point that both the speakers have made about how important it was that there were the techniques available in an established lab that were there at the time, that somehow came together to enable the new idea to be put into practice. I think it is very interesting and very typical of many cases, the way in which new scientific discoveries build on the previous work of the scientists, so I think that is a very interesting aspect of the way in which the discovery was made. I think to the other points that have been made about the Spinks report I would also add that that was 1980. In 1993 the general view of the history still has not been corrected and I think that really is the job of historians – and a real challenge for the historians here today – to somehow, listen and examine the evidence today, really get that right in terms of the history. I will just quote to you two sentences of an article that comes from the journal *Scrip*, which is probably the most respected pharmaceutical journal internationally – it is a British journal – and the two sentences in an article in their April 1993 issue are:

¹¹ Wade Nicholas. (1982) Hybridomas: the making of a revolution. *Science* 215: 1073–1075.

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It seems incredible that in the mid-1970s the two British scientists [!] who discovered how to make monoclonal antibodies decided not to patent their invention. In accordance with a long scientific tradition they felt they had no right to try to benefit commercially and personally by obtaining a patent.¹²

I find that amazing, absolutely astounding, and so whereas perhaps the parts of the history as to how this scientific discovery came about are fairly typical and well and accurately documented, the story of how the technology transfer then happened from the invention to commercial exploitation is one that is equally fascinating but still, nearly 20 years later, enveloped in a totally incorrect history and myth that it is the job of the historians to put right.

Dr David Owen: My point is a very narrow one – but I am not sure that it is not the time for a technical one, after what has been said – and is that in the whole of this debate you [Bud] have just talked about an American perspective. I have been at the MRC for three years and have to deal with these things and this history permeates what we do today very much, but one of the dimensions has been this thing which is sometimes explicit, usually rather more hinted at, that somehow or other they would have done better had it been in the States, had it been somewhere else. My point is also not original, but it is usually overlooked. Dr Bud made reference to what I would call gene-splicing, recombinant DNA and monoclonal antibodies and there we have two very fundamental molecular biology advances which have proved subsequently to be of great commercial worth. One, the monoclonal antibodies, and the message is not patented, the other gene-splicing, patented, the so-called Cohen and Boyer patent.¹³ If you actually start looking at things, and this is again a point you make, was it structural, was it cultural, I would make the judgement that there is a cultural element but I would argue that there is factual evidence that there are structural disadvantages in this country and I think that this is a thing that needs to be looked at. Within US patent law there is this period of 12 months, the so-called grace period, which is allowed between the first publication on the topic and the latest date at which a patent application can be filed, which allows consideration and it allows discussion, it allows discussion above and beyond the inventors. In non-US patent law, which applies to us, there is no opportunity for any public disclosure, and indeed people are often amazed how readily something can be called a public disclosure, going and giving a lecture and speculating on some idea, and can be used against you. If we actually examine the Cohen and Boyer patent which existed at this time and I have a first-hand account, the key publication was made in the *Proceedings of the National Academy of Science* in November 1973,¹⁴ and the first debate about whether patenting should even be considered was in May 1974, and the prompting of that was as much as anything else in relationship to speculation in the *Wall Street Journal*. At the time, and this is an area where the Americans might be said to have been ahead

¹² Schwartz Harry. (1993) Talking Points: American protectionism – the Schwartz view. *Scrip Magazine* (June): 6–7.

¹³ Stanley Cohen (1922–) and Herbert Boyer (1936–) in California in 1973 discovered a recombinant DNA technique which was patented in 1980, the same year that Genentech was floated on Wall Street.

¹⁴ Cohen S, Chang A C Y, Boyer H W, Helling R B. (1973) Construction of biologically functional bacterial plasmids *in vitro*. *Proceedings of the National Academy of Sciences USA* 70: 3240–3244.

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of us, there was somebody in Stanford University who had responsibility to do these things, and we obviously had NRDC, but in all fairness I suspect having somebody reasonably local is helpful. So there was a responsible individual who was actually prompted to do this not by his local *Nature* but by reading the *Wall Street Journal* and the first thing he ran into was that the inventor did not want to patent, he thought it was wrong, we have heard the arguments. But that is in the States, not here, and also there was no precedent for such a patent, no one quite knew what you could claim, which is a point that César has touched on, but the reality was that some arm-twisting was done and a patent was filed, but a considerable time after the original publication. I would take the view that the subsequent exploitation was done very prudently and by the end of 1981 there were 73 companies as licensees and now there are 200. The licensing income to Stanford University, and indeed there was an additional equal share to the University of California in San Francisco, exceeds \$50 million to each, but perhaps far more fundamentally in this notion of national culture was the stimulus to company and job creation in the States. If you actually stop and look at things, and one can say something absolutely dogmatically, had the same patent law prevailed in the US as prevails in the country, there would not have been the Cohen and Boyer patent, so this adverse comparison would not have existed. Now, we can speculate, and César has given me his answer, whether had we had the benefits of US patent law, would we have filed the patent or not? César, I think, feels probably not, but that is a speculation. The other is that there would not have been a Cohen and Boyer patent. That is factual. Just going back to my position at the moment, because I, within MRC, have responsibility not to make sure these things never happen, because that is unrealistic, but to minimize the probability. The fact is that this piece of structural advantage still exists in the States and I have to ask myself what will be the next example of something where we miss an opportunity in comparison with the States simply because we don't have a common sense of criteria which surround us. This is a very technical point, it seemed the right time. It is part of the fair discussion of this debate.¹⁵

Booth: Thank you. I think we will come back to that, and we no doubt will need more on that, but following up on Georges Köhler's point and David Secher's, for someone who is not an immunologist what I would like to know from the immunologists is how sudden this discovery was. Was it something that other immunologists were working on? Did you feel that you were, as obviously Jim Watson¹⁶ did, in immediate competition with someone else who was going to make the discovery quicker than you if you weren't very sharp about it? Where are all the immunologists who were thinking about what you were thinking about, or

¹⁵ This was an issue David Secher drew attention to in a personal submission to William Waldegrave, then Chancellor of the Duchy of Lancaster, in the wake of the May 1993 science White Paper, *Realising Our Potential* (Cm 2250). This White Paper began by expressing concern that the excellence of British science had not benefited as far as it might the economic fortunes of modern Britain (p.3). Secher in his submission ('Is Innovation Really Lacking in Britain?'), however, pointed to the fact that patenting procedures were not addressed in the White Paper, and called for action to give the same kind of protection as that already available in the USA.

¹⁶ Jim Watson FRS (1928–) and Francis Crick FRS (1916–) discovered the structure of DNA at LMB in 1953. They were jointly awarded the Nobel Prize for Physiology or Medicine for this achievement in 1962.

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was it, as appears to me as a non-immunologist, something that came out of the blue from you entirely, or were there lots of other people.

Köhler: We naturally thought we were the only ones thinking about it!

Milstein: We were afraid that Matty Scharff¹⁷ was exactly after the same thing. Don't you remember that?

Köhler: I don't remember that.

Milstein: Yes, well I do.

Köhler: Because he was a competitor in your field.

Milstein: I remember very clearly, and later on he was asked about that, I read it somewhere, and it is in the letter. He said they had never thought about it, absolutely. When the paper came out, when he heard about it, he really was caught totally unawares. But we were afraid.

Köhler: That was because they were the only others working in that area.

Booth: What about the other immunologists here present?

Milstein: Before we go into that I would like to get one thing out of the way which I am sure you have hinted at and on which I never said anything. This time I would like to say something. When I read the account of Georges about him having had a dream about this I was taken totally aback because until that moment I was completely convinced that the one who first thought about the experiment was me and when I read that I said: 'My goodness, this must be true!' and then I started to think about how the two accounts can clash so badly. I have a very clear memory, having this conversation in the morning, next to the water bath, which was in the corridor incidentally, outside the lab because we were not allowed to have water inside the laboratory, I remember that I suddenly had this idea and I said something like: 'Bloody hell, if we can't get a myeloma with an antibody activity we should make it.' And I have that sentence in my mind. But now, after I read it, [G.K.'s account] I asked what happened in the five minutes before that, and that I cannot tell. Maybe he was beginning to tell me – I don't think he told me 'I had a dream' because that, I think, I would have remembered – so maybe he came and started mumbling something or other and I immediately realized what he was going to say and I thought I thought about that first!

What I can say is that, as soon as that idea came about, whichever way it was – and I have no reason to disbelieve his dream, which will put him ahead – that I was

¹⁷ Yelton D E, Scharff M D. (1981) Monoclonal antibodies: a powerful new tool in biology and medicine. *Annual Review of Biochemistry* 50: 657–680.

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very keen on analysing this. I was very realistic, and what he is saying I remember too, and we said we must have a method which will detect one in very, very rare events, and that is why we did the thing with red cells and the way the experiment was done, which now with hindsight perhaps was not even necessary. We could have done it in a different way, although that was the best. Probably it was necessary because of the problems of clonal instability, which at the time we did not understand. This experiment was going on at the end of the year, and the first hybrid has an interesting story. The first hybrid was going well and we were at the first cloning step and then he had to go on holidays or something – you remember that was in the Christmas period, or something like that – and I was left taking care of that hybrid and I tried to reclone it. It was with Shirley Howe, and the clone disappeared. I thought my goodness Georges is going to kill me! Then I had this idea of putting the clone together with red cells to see whether the antigen, (the red cell was the antigen), whether the antigen would bring the clone back and lo and behold it did, and I thought when Georges arrived back I was going to shatter him with this piece of news that the clones can be antigen-stimulated. But before he arrived we repeated the experiment and it was not true, so I could tell him that I thought it was, but it wasn't.

Anyway, this issue of who did the experiment was a bit traumatic for me because of this conviction I have had before and because I never said anything and I did not want to say anything because I did not want to contradict Georges at all. Then, when the Nobel prize was announced, and at the same time there was a Lasker Award and so on, I was really nervous about what to say if the issue came about in the press interviews, and as a consequence of that we got together in the airport after quite a number of years to discuss what to do, and we came round to write a joint account which I would like to read because I think that that will end that story. I really think that in the way I look at it that this is how I felt before, and I still feel like this, even if my account was tinted by him telling me something or perhaps even giving me the gist of the experiment and my not noticing it directly, but indirectly. On that occasion we wrote a document which sounds a bit legalistic because perhaps that is the way we felt at the time. I was under some strain. I don't know if Georges was. Perhaps, no longer?

Köhler: No longer.

Booth: You agree with what has been said?

Köhler: I think it is a perfect way to explain our discrepancy. I think we have understood each other so quickly that who said what first may ...

Milstein: I could give another anecdote demonstrating that fact, but perhaps later. The document reads:

Questions have been raised about the relative contributions which each of us made to the design and execution of the experiments described in the paper published in 1975 in the journal, *Nature*, entitled 'Continuous cultures of cells producing antibodies of predefined specificity'. We wish to make the following statement: We agree that both conception and

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execution of the work was the result of close collaboration between us with the skilled technical assistance of Shirley Howe. We are further convinced that the combined effect which resulted from such close collaboration was of a synergistic nature. Synergistic effects taken to mean – as with monoclonal antibodies – effects which result from the combined action of two but which cannot be produced by the two separately. We both have a most pleasant memory of an exciting period in which a word, a comment or a passing remark made by one, had a resonant effect on the other. We do not want such happy memories which have sealed a close friendship to be disturbed by superficial interpretations of our individual recollections. It was a collaborative work, it was a collaborative paper. We are happy to share this Lasker Award and we wish to make no further comments on this matter.

Booth: That is a very generous statement by two scientists!

Milstein: I stick by that and I am very glad that is the way things happened.

Booth: Can I just come back to the question of the state of immunology at the time. Sir James Gowans, you were directing an MRC unit at that time before you became secretary to the MRC, I think, two years later. Was this a discovery that came as a shattering revelation or was it something you were expecting as an immunologist?

Sir James Gowans: I don't remember being shattered. I think I was actually at the meeting where you [Milstein] gave the paper and where the MRC official was also present, which you spoke about, and came to you afterwards about the paper. I remember the paper. I remember being mighty intrigued. I thought it was extremely ingenious and very very interesting and one went away and talked about it and told one's friends what César has been up to, but some time later when a little of the light of the history that you have been telling us was known, I remember thinking back to those days when I listened to the lecture, when the message that came away was that you could break allelic exclusion, heavy and light chains on the same chromosome. These were all the scientific spin-offs as it were. One was not thinking at the time when one was in the lecture that there was a vast catalogue of diagnostic reagents just waiting on the horizon, or perhaps even therapy. It was a very, very interesting, very biologically-illuminating bit of science, but also a method for producing extremely pure antibodies, which of course one could see would be important. Once you had shown you could break allelic exclusion, you had a method for studying mutants, you could assay them and you developed techniques to study the questions you had asked yourselves. It was a beautiful piece of science. So it is everything you say but we all know that science does not work by breakthroughs and disasters, science is usually the slow chipping away and every now and again there is a mighty big chip and this was a big chip which we all sat up and took notice of.

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Booth: Would any other immunologist in the audience like to comment on that particular issue as to what it felt like to be faced with this?

Dr Ita Askonas: I would like to comment because I remember the excitement, in fact, it was also Max Perutz¹⁸ who told me when I bumped into him somewhere. You ask whether it was shattering and I would say that it was not shattering, just like Jim [Gowans]. It was not the first time that people thought about trying to do it but I think we have to say that this was the first time it was successful and the only thing that was really surprising was the fact that it worked so well. I have to admit – and I think César could tell this story too – that Alan Williamson and myself had been working some years before, trying to get monoclonal antibodies but by transferring clones *in vivo*, and that worked very well through quite a few generations and then all of a sudden the clones started to go off – we call it senescence – it had actually divided many, many times, and so very rapidly we said we need this antibody, we have got more work to do on it, let's try and fuse. Now, we were not prepared at all to fuse and the only thing we had in house that was growing well was the Littlefield cell line, the fibroblast – was it A9? We rapidly tried to fuse but of course it did not work because that fibroblast line probably never would have worked because it was not expressing IG. So as I say, I was absolutely thrilled to hear that it was working and even more thrilled to see that it was working reproducibly, but I think it was obviously not the first time that anyone wanted to make monoclonal antibodies by fusion. I think there were some groups in the States other than Scharff out West, I am not quite sure.

Milstein: There were others but the one we were afraid of was Scharff.

Booth: Anyone else in the audience like to comment, sticking on the science and scientific background just for a moment. No, well David Secher, as a witness of the situation do you agree with what you have heard?

Secher: I think that with hindsight one can focus back on a shattering invention, but there was doubt as to how easy it would be to reproduce, how easy it would be to translate into an industrial process. There was even, and Georges and César will be able to describe many examples of this, there was even doubt as to how easily it could translate to another laboratory or to another month. Remember, early on the first experiment worked but then there were experiments that did not work, for reasons that were not so obvious, and then there was quite a long time when it did not work and so I think, with hindsight of course, there was a single shattering moment when the paper was published, but of course, had it not turned out to be reproducible or had it not turned out that the importance in medicine and technology would be so important we would not now be looking back and saying when was the single moment, we would say that there was a period over which it happened. Of course, there was a prophetic and true claim in the paper, because literature is full of claims that turn out not to be so true, and I think there was a period over the following year or two when people on the one hand were

¹⁸ Max Perutz FRS (1914–) was Nobel Prizewinner in Chemistry in 1962 and Chairman of the LMB from 1962 to 1979.

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speculating about what it meant commercially but also other people were busy working to see how it was going to turn out and how do we make it reproducible and translate it into a practical proposition. Even at the end of 1976, a year later, there were still questions about how widely applicable it could be and the reason I mention the end of 1976 is because that is when Derek Burke and I began a collaboration to try to make a monoclonal antibody to a soluble antigen that was itself very impure. In 1976 it was a very unknown protein called interferon which I had never heard of and most of us had not, although it was an MRC invention from 20 years previously, but it was a particular interest of Derek Burke who was at the University of Warwick and it was an anti-viral protein and we worked on that from 1976 to 1979 and then published that when we were eventually successful after a really quite long collaboration in 1980 and were still then the first people in the world to have made a monoclonal antibody to interferon and perhaps the first people to make a monoclonal antibody to any cytokinal, lymphokinal, any soluble protein that was only available in a very impure state. That now is really a very important class of compound for which monoclonal antibodies are important. I think that shows there was a time in which the generality of the technique and the reproducibility and the practicability became established.

Booth: Thank you very much indeed. Any other comments?

Milstein: Could I add one comment? Since we are talking about the technical aspects and the problems which were involved, I think one of the aspects which to me is one of the most fascinating ones is the cell partnering fusions. Which cell is used to fuse? A point which Ita brought in and of course we now more or less realize that the obvious best partner is a myeloma, but there is something else. Not all myelomas proved to be adequate, and other people tried other myelomas and in general found that none of them were very good, so one of the questions I have been giving some thought to over the years is what was special about our X63. In fact, looking more carefully at the genealogy of the line it is not only X63 but also NS1, which derives from X27. These Xs were the consequence of massive cloning experiments which I am sure David will remember very clearly and I should mention another name which should come into this is Richard Cotton, who was the one who was largely involved in the development of these techniques in the laboratory and he was the one who trained Shirley Howe, who was the bearer of the technology over the years, much better of course than I could do. I was a bit of a red fingers, if you like, in contrast to her green fingers. But what was special about X63, or indeed X27, is that they both derive from the same myeloma, so perhaps that one original myeloma was important but I rather think that what was important was something else and it was that both clones were derived from very long-term cultures which were kept under continuous growth in a spinner and the reasons we were doing that were precisely the experiments we were doing with David and I was responsible for the spinners in which the cells were growing continuously.

Booth: So they were robust.

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Milstein: They were extremely robust. They were cells which had been growing for three or four months continuously and the clones were derived from those spinner cells and I think that was probably the reason. Of course at the time it was totally unpredictable – perhaps it was predictable but for us it wasn't – and no one ever thought that this was the way to do it. Later on, when we tried to fuse a rat cell line and we failed we started to think about that and we did with that rat line exactly what we had done before; put it in a spinner, grew it for several months and then took clones from that and did it again and eventually we got a clone which was a useful clone and I think that was an important piece of serendipity of which we had no clue.

Booth: Sir John Gray, you were secretary to the MRC at the time all of this was happening.

Sir John Gray: That was not a remark I was going to make at this moment. Perhaps that could come later. I was merely going to say that as a scientist in a totally different field, not immunology, nearly every one of the papers that I have published during my career have been collaborative papers and I do not think I could tell you or anyone else who made what contribution to those papers. I appreciated very much the document that you [Milstein] read out just now as your joint thing. It is almost impossible, I think, in scientific collaboration to say who has done what. It is an interactive thing all the time and I suspect that my experience in neurophysiology is no different from that of scientists in other fields.

Booth: Having said that, you were Secretary at the time. Did you hear about this work because Georges Köhler or César Milstein or Max Perutz told you about it or did you just read it in a lecture? There are many villages throughout the country who still remember how news of the battle of Waterloo reached their village. How did the news of this discovery reach Head Office?

Gray: I don't think I can remember to be quite honest. My memories are very vague. I certainly remember a visiting group to your [Milstein] lab which must have been just before that, but I can't remember its date. It must be in the MRC files but my guess is that it must have been somewhere around 1974–75. I remember everyone being very impressed with what was going on. I am not an immunologist but obviously it was exciting, good science, which we thoroughly enjoyed. I certainly have no recollection now of feelings that we were on the brink of some great technological discovery of great commercial importance. It was quite clear it was of great scientific importance, really following very much the line that Jim [Gowans] said earlier. I am guessing, but I guess it was probably John Duncan who wrote to you, [Milstein] about the patent.

Booth: John Duncan was the administrative secretary of the MRC.

Gray: He was the administrative secretary when I was Secretary. A lawyer by background. Of all of us working at Head Office at that time, he was the one

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person who really was keen on patents. By that time we had all accepted that there were such things as patents and we probably ought to take them out. To say that we were emotionally keen on them is certainly not true. Of the scientists among us, this sort of commercial background to science and medicine was not something that we morally rejected like the Council formally did before in 1940 or whatever it was, over penicillin, that era had gone, and we certainly accepted that, but there is a big difference between making a total moral rejection and still being interested in the science and the medicine and feeling that commercial implications are a secondary matter. Yes, fine for John Duncan to go writing to directors and telling them about it. I suspect that what I am saying was a fairly general attitude among scientists at that time, in other words that we accepted the existence of patents but they were not the first things that would come to our minds in any consideration of science. To come back to answering your specific question, I really do not remember at all the question of this important scientific advance being likely to be of great commercial importance coming up. Someone obviously did because you have quoted the letters to the NRDC and my suspicion is that it was probably John Duncan who did that.

Booth: I think we will come back to patenting science later, but Robert, you had a point.

Bud: Yes, a question about when this becomes defined as the seminal event and the seminal paper. After all for Georges Köhler, this was originally an experiment as a means to an end. When you did the experiment did you think that you could then go back to Basle because your life there was finished or did you see this would be a good base for something which would be really important?

Köhler: I knew at the end of my stay at the MRC that it was an important discovery, but I knew that only because I was able to repeat it. That was the first fear we had. We had the success with one of the first fusions and so we tried to repeat it and that worked and we tried to repeat it with another antigen, a soluble antigen, and it worked. Only at that time did we start to be sure that it was a matter which at least we could do, and only at that time could I be sure that it was something of more general importance. I must say that there was a long time where experiments did not work and that is reflected by the nomenclature we gave the fusions, they were called spleen 1, 2, 3, and suddenly at 7 it stops and starts again at 25. So there was a big gap in between where ...

Milstein: Six and 7 worked just.

Köhler: They worked. We were very concerned that we had created something important which could not reproduce and then we were concerned that we could reproduce it but could someone else reproduce it and it took more than two years

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and we were very happy to hear that Klaus Rajewsky could do it as well.¹⁹ Only then was the method one which we could think of to be of some importance.

Milstein: The reason why the method did not work for so long and it did not work in our laboratory, it didn't work in your laboratory when you left for Basle and we were on the phone all the time and exchanging serum, I think, or perhaps preparations of the virus and the reasons actually probably were different in both cases. And in our case it was quite an unbelievable situation, but we were using something called HAT medium which is a medium specially for the selection of hybrids and in preparation of this medium we had this in concentrated form.²⁰ Now just before Georges left the lab, or maybe at that time, the concentrated solution was finished and one of my students prepared a new solution, so this was a concentrated solution, so from there dilutions were prepared here and there in several stages and it transpired six months later – it took us six months to find out – that that solution, for some reason which we never found out, was toxic, so instead of selecting cells we were killing them and that certainly was not the case in your lab. I don't know why in your case it didn't work, it must have been something trivial like that. That does not change the fact that we were afraid.

Booth: Now, there are some questions from the floor. Firstly, Peter Williams.

Dr Peter Williams: I wonder if I could pick up on this name of the person who wrote that letter to César Milstein because if it was John Duncan it was a lawyer, but I got the impression that it was someone from the scientific staff who had been to the meeting and who had therefore understood the implications which John Duncan would not have. Now, that could be a very important point because it shows the significance of someone of that type at the meeting who would take it back to the Head Office, not tell the Secretary but go ahead with it himself, by the sound of it, and I think – is there any reason why we should not know the name of that person? It is not the same as the civil service at the MRC I am always told.

Milstein: I prefer not to say names, actually, if I may.

Williams: Could you tell us if it was a medical person.

Milstein: It was and it was not John Duncan.

Williams: So it was a medical person.

¹⁹ Lemke Hilmar, Hämmerling Günter J, Höhmann Christine, Rajewsky Klaus. (1978) Hybrid cell lines secreting monoclonal antibody specific for major histocompatibility antigens of the mouse. *Nature* 271: 248–251.

²⁰ HAT medium, containing hypoxanthine, aminopterin and thymidine, is a medium for growing tissue cultures.

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Gowans: It was a scientific person, not a medical person, a scientific person, a member of the office staff who was at the meeting as a scientist listening to what was going on at the MRC who picked it up and then took it back to headquarters and then wrote the letter that you heard. He spotted something that César had said at the meeting and that had appeared in the paper, the manuscript of which had been sent to this person at headquarters. So there we are. It was a scientific person.

Williams: I do think that was important because it was not simply John Duncan being keen on patenting, it was someone in the office who saw the implications.

Gray: That is a very good point, Peter.

Booth: We have another witness here from Head Office. John, you were there at the time.

Dr John Galloway: I am John Galloway, and at about that time I joined MRC Head Office as a scientific administrative officer and I did not have responsibilities connected with the Laboratory of Molecular Biology, but what I can say is that the idea that the science might be patentable and commercially usable was around. I worked for the Medical Research Council at Head Office from 1975 until 1987. I arrived at 20 Park Crescent at almost exactly the time that César Milstein and Georges Köhler published their paper in *Nature*. I have a few comments on the relationship for example with the Laboratory of Molecular Biology, which might be useful to this seminar.

The first thing to say is that the recollection by Sir John Gray, that the member of Head Office who was responsible for the Milstein and Köhler discovery was not, in the part of my memory, John Duncan, although it could well have been, I think. Certainly, my recollection is that John Duncan was sensitive to the widely believed and, I think quite falsely believed, idea that penicillin as a commercial venture had in some way been lost to Britain because of carelessness or lack of foresight. I think that is not true. Penicillin as I understand it, sort of went over to the States at the beginning of the War for two reasons: the first is that I think it was part of a deal that was done between the United States and Britain, by which they gave us arms in exchange for such things as islands in the Caribbean and as it turned out, the opportunity to manufacture penicillin.

The second reason was, of course, as I understood it, that British pharmaceutical companies were not in a position to produce penicillin on the scale that it would have to be produced. American pharmaceutical companies, there were a number, did seem to be in a position to gear up to large-scale production in a short time, so there was a practical reason as well. Nevertheless, my guess is that John Duncan would have been sensitive to what people had said about penicillin and therefore might well have been the person who would pick up on the Milstein and Köhler discovery. I am absolutely certain in fact, that that was not the case and that the person who did it was a member of the scientific staff, not the medical staff, of MRC Head Office, and was actually the person with whom I worked when I first joined MRC head office in 1974. Since Dr Milstein doesn't wish to

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give the name of that person, I will also follow his wish and I won't say who I *know* it to have been. He is not here today, by the way.

There are two other things I would like to add. The first is that it is not true that the MRC didn't have a keen awareness of the need to try and make sure that its discoveries/inventions should be exploited in the public interest and that meant, if necessary, commercially exploited. And I think that, certainly given this experience with penicillin it would have been astonishing if they had not done. I have some personal experience of that, since the first job that I did when I joined the MRC was to try and steer through the Committee and grant-giving structure the newly discovered idea of using nuclear magnetic resonance as a means of imaging the human body. And certainly it was made clear to me by my section head that part of my job was to ensure that the NRDC were kept fully informed about what was going on and that there should be no suggestion that the MRC had neglected its duty in respect of NRDC's position in both respects of the public funding of research and so on, and I certainly did that. And in the fullness of time nuclear magnetic resonance imaging actually did become a commercial proposition and if it did not make large sums of money for the United Kingdom that was no fault of the inventive scientists who did the work, nor of the MRC I think, nor of NRDC, but was almost certainly a problem of marketing, which organizations like EMI had already experienced in developing the CT Scanner (computerized tomography); they just did not have the access to the big markets of the United States and as far as I could see, they could not get it. It was a weakness of British industry and marketing, not a weakness of the earlier stages in development.

It is worth also saying here that some years later, when I acted as Editor of *MRC News*, I used to try and run in each issue a small historical piece, which I thought might be of interest to readers, and one of the ones that I did run was about the discovery of interferon by Alick Isaacs and Jean Lindenmann, in about 1957.²¹ Jean Lindenmann wrote a small piece for me, a rather nice piece, in which one of the things he said was that there had been great stress laid on the need to patent interferon when it was discovered, which they duly did and he added ruefully, 'I've never actually seen a penny of any money that was made from that patent. I guess none ever was.' I tell that story, because I think it puts events in the right perspective. My own view was that at the time, and it has never been changed since, certainly in that part of the office in which I worked, which was the part that served the Cell Board, or serviced the Cell Board, there was keen awareness of the need to keep NRDC informed about discoveries and to try and ensure that things were given an opportunity to be commercially exploited.

There is one final thing that I want to say, which has a number of parts to it. I think that one point that is not appreciated today, which was certainly very clear to me then, in 1974 was that the relationship of the Laboratory of Molecular Biology to the Medical Research Council Head Office, and the rest of the MRC was a very curious one indeed. My impression was that, to a large extent, LMB was actually a no-go area for MRC head office staff and certainly head office staff paid visits, but if you've read the minutes that they wrote, they seemed on the whole not to indicate a close relationship between the two. It's also worth saying that in America, for example, the MRC as an organization was not known, except through

²¹ On the discovery of interferon, which was in its time seen as a wonder drug, see Peters T. (1993) Interferon and its first clinical trial: looking behind the scenes. *Medical History* 37: 270–295.

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the Laboratory of Molecular Biology, indeed LMB and MRC were synonymous, as far as I could see, in large parts of the world, indeed they were actually synonymous within LMB itself. On a number of occasions, I talked to scientists who worked there and they were actually quite surprised to discover that the MRC encompassed units and research which had nothing to do with the Laboratory of Molecular Biology (LMB). Again, I think that is a useful perspective. Part of that relationship and the oddness of it was, I think, to do with the fact, and I do not know whether Sir John Gray would agree with me, but was actually part of an intention to perhaps preserve Nobel prize-winning scientists at LMB from being harassed about things that it was felt were simply a distraction to them. I mean the view was that it was their job to be interested in and solve big questions in science and really not to be concerned overly much with small questions. I don't know whether that is true or not, but again it was the impression that I had at the time.

[Sections of tape marked * – ** were damaged shortly after the meeting, and the gaps were filled immediately from the detailed notes of three participants. They are therefore accurate, but not *verbatim*, reports.]

Booth: David, did you have a point?

Dr David Tyrrell: I was involved in two bouts of patent applications for Common Cold vaccines using killed material. The MRC tried to get in early, and was involved with the NRDC in getting patents for a protective vaccine. The point was that it was premature because there was not one rhinovirus but hundreds, and it was a useless vaccine and therefore patenting was a wasted effort. You need finance and knowledgeable lawyers, which were not there. It was the same story with interferon, patenting was also premature, it was tried to provide a protective patent for this too as an anti-viral agent, without realizing that there were different interferons for different species. Leucocyte interferon was purified to homogeneity using the monoclonal antibody made by Secher but by then it was too late for the patent to be exploited. Only in the 1980s was the experiment done to demonstrate to the patent people that interferon did what it did. People need to understand (a) the science, and (b) the limitations and the possibilities of the technology. The lawyers who tried Common Cold interferon had got their fingers burnt, and were therefore cautious about not patenting monoclonal antibodies.

***John Newell:** I was then the Science correspondent for the BBC World Service, and there was no problem publicizing this. There was no *Nature* press release system at the time so you trawled through the issue of *Nature* by yourself, and immediately saw the Köhler-Milstein paper as a way of making antibodies in pure form outside the human body, and I therefore assumed the therapeutic potential. I rang and spoke to Milstein, who was very helpful, and wrote a report. I thought it was an obvious big advance.

Milstein: Why did you pick up on it?

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Newell: Because it was obviously a major advance. This reflects badly on the science reporters who did not pick it up. Mine was the only press report to appear immediately [on BBC World Service].

Bud: In April 1975 the American Cancer Society discovered that interferon was a cancer cure, and therefore big interferon stories were run. The scientific press were obsessed with interferon.

Booth: I'd like to consider the point about the types of institutes from which Nobel Prize Winners come, on the scientific working environments. The LMB, Cambridge, the Max Planck, the Rockefeller Institute all dedicated to research, is that the answer – the ideal environment?*

Milstein: The functional role of institutes is critical. Laziness is the mother of good science. Creation comes from moments when you don't have anything to do. When you have no teaching, and basic admin, and extra commitments are seen to interfere with research, what if you have strong motivation, and don't know what to do? If you are teaching, you can fill your gaps by teaching, but researchers have to fill the gaps with thoughts. Applications of science are important and socially attractive but they detract from the single mindedness of research, and LMB has a tradition of allowing scientists to develop their own ideas.

*I came to the LMB to work with Fred Sanger,²² and chose a project out of three suggestions, and did an experiment suggested by Sanger which didn't work. On the side I did experiments of my own, which Sanger didn't discourage, and when these worked Sanger encouraged me to go on, he said 'Do good experiments and don't worry about anything else.'** I always felt that summarized it, one should do good experiments and not worry about anything else. Other factors were the general quality of the place and the non-restriction of the subjects: you were inventing subjects as you went along. and no-one stopped you crossing disciplinary boundaries. Once you were 'trusted' then you were free to develop ideas in the way you wanted.

Gowans: These are classic MRC views, like Mellanby and Himsworth,²³ you find a good man and then support him. It is also true that individuals are important in history – stars attract stars. But it is also important to preserve good institutions. What is good about the LMB? It is partly the stars, which attract young people, and partly the existence of scientific dynasties. Bright people want to go where the action is. But it's also the style of scientific management, the LMB management style includes two factors to add to the list from César (1) there is no pressure to publish, and (2) there is no empire building, even distinguished people still work at

²² Fred Sanger FRS (1918–), who won the Nobel Prize for Chemistry in 1958, and (jointly) in 1980, was then head of the Protein Chemistry Division of the LMB.

²³ Sir Edward Mellanby FRS (1884–1955) was Secretary of the Medical Research Council (MRC) from 1933 to 1949; Sir Harold Himsworth FRS (1905–1993) was his successor as Secretary from 1949 to 1968.

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the bench with a technician and a couple of post-docs, but this tends not to occur elsewhere.

Booth: Perhaps we should hear from Dr Bard about the NRDC's view of all this?

Dr Basil Bard: [Partly reading from a prepared paper] It is hoped to explore at this seminar the nature of ownership and scientific discovery and the relationship between academic research and its subsequent commercial exploitation. I have been concerned with this matter since 1945. In 1948 the Labour government passed the Development and Inventions Act under which in 1949 the National Research Development Corporation was set up. Its terms of reference were to develop and exploit in the public interest innovative work resulting from public research or any other research in respect of which assistance was provided out of public funds. In other words, its area of responsibility included government laboratories together with those of the various Research Councils, the universities and also industry, in so far as it was not able to carry out its own development and exploitation.

A Treasury circular (5/50) required government laboratories to transfer their invention results to the NRDC and discussions also took place with the BMA under which medical doctors were invited to transfer their inventive results to the newly formed NRDC, it being recognized that ethics in relation to medical research were the loftiest of any profession in the country. In other words, where there were employees of the government, the NRDC stood in the shoes of the government and similarly for all other research supported by public finance. The NRDC acted as the handmaid of the MRC, particularly in the fields of medical problems at that time which included ACTH (adrenocorticotrophic hormone), cortisone, the collection of certain glands from slaughter houses and later, the production of hecogenin, a precursor for cortisone, from the juice and waste of the sisal plant by sisal producers in Africa and Jamaica. The NRDC dealt with the innovative rights in the Melrose blood oxygenator and work by Tait and Dodds in aldosterone. Later, that is, by 1957, it took on the development and commercialization through licensing to the industry of cephalosporin. Some £150 million resulted to the NRDC from this work and all the scientists involved became rich men.

It is clear that there is a great deal of difference between a discovery and an invention. Penicillin was 'discovered' by Fleming but was converted into a practical and commercial proposition through the work of Florey and Chain. Patents could only be sought for 'inventions', not 'discoveries', that is, a novel manufacturing technology or product. I had left the NRDC before the work on monoclonal antibodies was considered. However, I have been able to secure from the representatives of the British Technology Group (BTG) (the privatized successors in title to the NRDC) their account of the facts. These are as follows:

An article appeared in *Nature* of 7 August 1975 about continuous cultures of fused cells secreting antibody of predefined specificity signed by Messrs Köhler and Milstein of the MRC's Cambridge Laboratory of Molecular Biology. Dr Milstein had sent the MRC a printer's proof of the article only a few weeks before it was published. A further 13 months elapsed before the MRC formally drew the article to the attention of the

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NRDC, and apologised for having failed to communicate it prior to publication.

In replying to this letter, the NRDC executive concerned reflected the general perception at that time in saying that the cultures developed by Köhler and Milstein could be valuable for medical and industrial use but their potential was long-term rather than for immediate application. Since nothing could be done to protect the general invention because of the disclosure in the *Nature* article he took the view that, unless further work indicated a more specific diagnostic application or industrial end product, there was nothing NRDC could do at that stage to take matters further.

With the benefit of hindsight Dr Milstein, the MRC and the NRDC were all at fault in failing to capitalise on the commercial potential of monoclonals and a number of conclusions can be drawn: No-one, including Dr Milstein, really appreciated the full commercial potential of a piece of outstanding academic work, and therefore the need to stop publication. The MRC's internal procedures for communicating inventions to NRDC failed to work. In any event, the considered view of NRDC patent experts was that Milstein's work as published was not patentable. Considerable further work would have to be carried out in conditions of secrecy to develop the invention to a state when it could have been adequately protected.

The conclusion is that much academic work is not of itself capable of patent protection at the time the academic desires to publish to establish his scientific reputation. It is necessary to persuade him to develop his work in secrecy, and to support this financially, often for several years. The BTG has adopted a more pro-active style in its relations with academics and has taken a number of initiatives here.

Monoclonal antibodies appear to have a political dimension, for example, the absence of basic patent protection. It would appear, therefore, that as the results of work on monoclonals is currently used for research rather than manufacture that minimal harm from a commercial viewpoint results. However, it seems clear that the procedures in operation at the time were not complied with. Patenting requires action before publication.

Newell: When I was science writer in residence at Loughborough University, the biggest problem in communicating research was not with scientists or engineers but, on occasion, with their industrial sponsors. But you can't get scientists to talk about their work because nowadays sponsors demand confidentiality. Therefore regardless of the situation, we now do have science careers interfered with. It also interferes with the scientists' relationship to the public (who pay for all this).

Secher: Since Isaacs and Lindenmann discovered interferon, there have been many changes from 1970 to 1975. The MRC has accepted patents as a means of protecting its inventions, which is true at the level of MRC policy. But at the lab level especially at Cambridge, the LMB was not favourable to patenting in 1975. Nor was it in 1980 when the monoclonal antibody to interferon patent was taken.

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Only with a change in the culture of science did I become liaison officer, and now all scientists are more aware, but the LMB was not in a patent culture in 1975. Dr Bard has spoken of BTG comments on patentability, and how to protect medical and academic inventions. The BTG says it was not patentable at the time. But my view is however, that there was the possibility of patenting at the time. I recently took professional advice about whether monoclonal antibodies were patentable at the time of the *Nature* article and was told yes. In 1980 (that is, five years after) we [Secher and Burke] succeeded in making a monoclonal antibody against interferon. But in order to avoid the criticism of the MRC over inventions and so on, we were concerned to follow official MRC Head Office policy. We submitted the note to *Nature* in manuscript well in advance to Head Office. The NRDC advice, and the MRC's, came through that the antibody advance was not patentable. I was relieved at the time, since it would have meant a delay in publication, and there was no incentive for the scientists concerned, and therefore submitted it to *Nature*, and then became uneasy it might be patentable after all, and filed a preliminary application in April 1980 without MRC approval.

Booth: How did you do it?

Secher: We didn't use a patent agent as we didn't want to spend any money, and paid only £5 to deposit the *Nature* manuscript only in the Patent Office.²⁴ We delivered the manuscript to the *Nature* offices on the same afternoon. The lawyers laughed, but it has held good. You can claim up to one year after application.

The point is that one can obtain patent protection without delay in publication and without further work in secrecy. The patent has now passed to Celltech who have derived quite a lot of money from it. Thirteen years later, after the patent was granted in GB, it was challenged by Hoffman la Roche in the US, but was not sustained. You can therefore get protection with publication and without secrecy.

Owen: If I can enunciate a policy, patenting is both an opportunity and an obligation, but inventors from wherever feel such objectives require much insight to recognise the commercial opportunities. Patents need not delay publication, but a claim for patent protection is limited if you do this. It obviously needs careful thought to work out what you are trying to cover. However there is a danger of over-filing. A patent needs a good patent agent to design a good submission. This is expensive, it can cost £1000 to employ a patent agent and most will have no commercial value. If I filed everything I would be accused of wasting the taxpayer's money. MIT are generally considered to have the best record and they think they are doing well if they successfully file one in three, which is outstanding. Last year the MRC filed 28 patents, but it would have been easy to file 128.

Gray: Scientists and Council members did not give patents a high priority, the science was everything. The NRDC says that the MRC was lax. If that was so, I

²⁴ The article was published as Secher D S, Burke D C. (1980) A monoclonal antibody for large-scale production of interferon. *Nature* 285: 446–450.

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was in charge of the MRC at the time so if the MRC didn't report monoclonal antibodies to the NRDC then I am responsible for that. Although I had no knowledge of the situation. But César's letter says they did, and the MRC did operate through a member of my staff. There had been a change in attitude between 1948 and 1975. By 1975 the MRC had accepted patenting but the culture among scientists at the LMB, and the systems which were in place, were not favourable towards patenting.

Bard: There was a problem throughout the world.

Gray: By the mid-1980s the systems began to change and the national and international culture among scientists also changed. But César is worried about the constraints on publication involved in patenting; there is a real incompatibility between commercial interests and scientific responsibility. It's an increasing problem, especially with regard to contract research, post-Rothschild.²⁵ Science is only science when it is published.

Milstein: Work in secrecy has been mentioned many times, and I think that in the minds of the people who rejected the idea of patenting monoclonal antibodies there was the belief that the work was not yet patentable and that it would have to be continued in secrecy. At the time I wanted to get mutant antibodies and the NRDC wanted antibodies against useful molecules. But what is useful? Was it the interferon antibody? Nevertheless it was patented in 1980. At the time I was worried by competition from Scharff and needed to publish to overtake them in science. But I did want to make human monoclonal antibodies and we tried but we failed. With hindsight, the most important practical application has been to apply the technology in developing a methodology of study of cell surface antigens. That has opened up a new world of molecules, not realized then, and CD antigens have become a large market now. That was definitely not in our minds and came later, from the work with Alan Williams.²⁶

Booth: [to Köhler] How many patents have you ever taken out? [Köhler made a zero with his thumb and forefinger].

Köhler: I'm surprised at all the fuss over patenting and the discussion here. Scientists are not the persons who should patent, some other mechanism has to be found, and the pharmaceutical industry have mechanisms. If the American system is better, why don't we have US system instead of the UK system?

²⁵ The key principle of Lord Rothschild's 1971 report on *The Organisation and Management of Government R & D* (Cm 4814). London: HMSO, was 'that applied R & D, that is R & D with a practical application as its objective must be done on a customer contractor basis. The customer says what he wants; the contractor does it (if he can); and the customer pays.'

²⁶ Professor Alan F Williams FRS (1945–1992) was Director of the MRC's Cellular Immunology Unit from 1977 until his sudden death in 1992.

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Owen: It's not necessarily a good idea for other users of the patent system, therefore it's a major political problem in getting major changes in law.

Professor Miles Weatherall: *I have spent half my research life in pure research and half in the pharmaceutical industry, where I worked at the Wellcome Foundation. I had patent experts just around the corner there, but in academia I could call on no specialist support.

Bud: Could the scientists comment on the changes in culture between Asilomar (where the idea of making money was shocking) and three years later we have the present situation where some scientists behave like venture capitalists. Pure science equalled papers but now seem to equal technological change. Was there a change in attitude at the LMB?*

Milstein: The monoclonal antibody story is important in producing changes in the attitude of the LMB between 1976 and 1978. We have already mentioned that it was in 1985 before David Secher was appointed as Scientific Officer in charge of patenting. There had been a slow change over ten years. In 1976 the LMB had received letters from the NRDC re their correspondence with the Wistar [Institute] and there was a list of things that could be patented at that time. The NRDC thought the Wistar patent would not be taken but it is valid in the States. In 1980 I strongly supported David Secher's patenting of the monoclonal antibody against interferon. I wanted a policy which would take into account the needs of the scientists and thought patents should be owned by the institutions which supported the scientists.

In 1980 Celltech was created, based on development of work that had been going on at LMB and my lab., and I was asked to be on the Council of Celltech and didn't want to do it but thought I ought to. But I couldn't accept the way Celltech were doing things and the atmosphere, and I resigned a year later. In 1985 changes in the law were made and the labs and scientists not the NRDC were allowed to take out patents. There was a conflict between Celltech and LMB and the LMB broke away from Celltech and did not use them as patent agents and took the first patent out on Greg Winter's work on human monoclonal antibodies. Winter wanted to follow up the work himself, he wanted to dictate the tune, and the interests of the scientist should be a major factor to keep control of the research. There should be rules based on: (1) the interest of the taxpayer, I mean responsibility to the public at large; (2) the interest of protecting the scientist; (3) making money must come last. This is the least important consideration.

Gowans: Celltech was set up by the MRC, when they found themselves confronted by the Spinks report. It was for the biotechnology patents, the pathway of British science to capitalism. At that time two young men from the National Enterprise Board (NEB) came to see me at the MRC and said they would like to set up a biotechnology company. They had no products and no science and the MRC did a deal in which the company would have first refusal on all products developed by the MRC – exclusive rights to MRC discoveries. They saw where the future was. That was Celltech, helped set up by the MRC and with little Treasury

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support, and it put Celltech in an advantageous position, but other companies hadn't asked. At the time the only dialogue we had with government agencies consisted of gloomy discussions about how to protect the taxpayers' money. Celltech depended on the LMB, and started by making monoclonal antibodies against blood grouping reagents, but it wasn't just the LMB that got fed up, later on it was felt that one company had had exclusive access for long enough to public work and Celltech could now fend for themselves. They agreed it was unfair, and the agreement was therefore renegotiated. I must say I thought Spinks was a terrific fellow and the report had resulted in a piece of action which was rare.

Booth: I think I remember Spinks saying that at ICI he had five times the research budget of the MRC.

Bard: The NRDC felt that Biotech was new stuff, and the old 1960s stuff was not applicable. It was left behind.

***Tyrrell:** I remember a lot of talk about the dangers of recombinant DNA; and very little about the possible benefits. I guessed then it would be ten years before there were tangible benefits; but in fact there was recombinant interferon within two to three years. Had there been any fears about monoclonal antibodies? About using retroviruses in mouse cell lines?

Newell: That atmosphere at the beginning has persisted in the public mind. The current atmosphere is pretty much the same: the public perception of genetic engineering is very bad. This is partly media concentration on negative matters. But as benefits have begun to appear public perception has begun to change.

Booth: The Royal Society and British Medical Association have been trying to reverse this. There has been a report by Anne McLaren and Mary Warnock on genetic engineering.²⁷ But journalists always produce scare stories, not success stories.

Gowans: The scientific media are at fault but the other point is that the public are scientifically illiterate. I've just spent three years in France and France is far more informed about science and engineering. Science reporting is better there and one was likely to sit next to an engineer at a party. Science ignorance is rife among the educated elite in this country.

Dr Guil Winchester: I would like to ask what was the reason why John Newell picked the paper up – was it in the *Nature* News and Views section?^{2**}

²⁷ McLaren A, Warnock M. (1992) *Our Genetic Future: The Science and Ethics of Genetic Technology*. Oxford: Oxford University Press.

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Newell: There was nothing done like that then. News and Views was not then focused on current publications, and there was no press release.

Milstein: *Nature's* reaction to the paper was not to the level of News and Views. It was submitted as an article, that is, longer and complex, but they replied yes, it was acceptable but not of real general interest, so they would not publish it whole. We cut it to 1500 words for a letter and it was a big problem cutting this down.

Also I think it was the NEB, not the NRDC, which was involved in the creation of Celltech, and Ben Lewin had been commissioned by the NEB to look at the possibility of creating a biotechnology company. The other point is the safety of monoclonal antibodies. That is an issue that was raised but it was never terribly important and the reason it was not important was (a) because no new technology was involved, essentially just tissue culture methods which were standard laboratory practice and to which nobody objected. Myelomas in cultures had been growing and this was potentially no different from that. However, when the issue of using monoclonal antibodies in therapy came, there were some worries about that, but that was much later, when the atmosphere was much more rational and it was treated in a much more rational way. The first experience of course, as far as I know – David Secher, you would have been aware of that situation – I think it was much more rational by the time. In the beginning there was never being able to use this and the other, but it never was an important factor, I think.

Booth: A final point, Georges Köhler.

Köhler: It is just a quick point. It was said before that with the patenting it is the scientists who should change. Now, with the advertisement of discoveries, it is again the scientist who should go to the public and be more open. I think that is wrong. You just have to keep the scientist a scientist and change things around him.

Booth: Well, that is a happy point of view. I think this has been extremely interesting. This is the first seminar we have had at the Wellcome Institute and I would like, on behalf of you all, to thank the witnesses who have so frankly and freely discussed what went on in that time when they were involved with this remarkable discovery and the remarkable things that went on. For myself, as an embryonic scientific historian, which I suppose is what I am now, it has been a fascinating story of an evolution of ideas and it is so easy to look back 15 years and say if only we had done it like that, but nothing happens that way and the story we have heard has been very much clearer than anything I have ever read in the subject of monoclonal antibodies and on the development of them, so may I thank everyone. To have two Nobel Laureates sitting on either side of me is an honour and distinction I have never had before, and to sit at the same table as two Secretaries of the Medical Research Council is equally outstanding. Finally I would like to thank the Wellcome Trust very much for supporting the whole thing.

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Self and Non-Self: a History of Autoimmunity

The transcript of a Witness Seminar held at the Wellcome Institute
for the History of Medicine, London, on 14 February 1995

Edited by E M Tansey, S V Willhoft and D A Christie*

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Self and Non-Self: a History of Autoimmunity

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Self and Non-Self: a History of Autoimmunity

Sir Christopher Booth:¹ Today, we are going to talk about self and non-self, about autoimmunity. At the table here beside me are several people who have been involved in that history; also there are many people in the audience who, equally, were important in this story, so we hope that you will speak whenever you wish. The idea is to promote reminiscence, discussion and debate about medico-scientific events of the recent past and this story dates from after 1950, essentially the latter part of the twentieth century. It has been an extraordinarily interesting and important part of medical scientific history, in terms of the basic scientific approaches to the immune system and the work of Peter Medawar, Leslie Brent and others.² Self-recognition and the failure to recognize self, which results in human disease is the subject under discussion. How is it that you are capable of maintaining a completely satisfactory immunological situation, as you sit there in your chair? Yet under certain circumstances that whole system goes wrong and you attack your own tissues to the extent that you produce a disease of some significance. That, basically, is the background that I should like to set and we have asked Professor Ivan Roitt who is a great pioneer in this field to start us off. I'll hand over to him at this stage.

Professor Ivan Roitt:³ Well, I'll kick off by trying to outline the conceptual situation as it was when Deborah Doniach, Peter Campbell and I discovered thyroid autoantibodies, and go on from there to see how autoimmune disease and its study followed. I think we probably have to go back to that wonderful man Ehrlich, at the turn of the century. He appreciated the fact that the body had to be able to distinguish between self and non-self molecules in terms of the production of antibodies, and he coined the term that many of you will know, the *Horror Autotoxicus*, in which he could see that the body would control the production of antibodies to itself which would be self-poisoning.⁴

¹ Sir Christopher Booth was the first Convenor of the History of Twentieth Century Medicine Group, Wellcome Institute for the History of Medicine, from 1990 to 1996; and is Harveian Librarian at the Royal College of Physicians.

² Sir Peter Brian Medawar, shared the Nobel Prize for Medicine in 1960 for the discovery of immunological tolerance with Macfarlane Burnet. See Mitchison N A. (1990) Peter Medawar (1915–1987). *Biographical Memoirs of the Fellows of the Royal Society* 35: 283–301.

³ Professor Ivan M Roitt FRS (1927–). Research Fellow Cancer Research Campaign; Professor and Head of Immunology and Rheumatology Research, Middlesex Hospital, London 1967; Emeritus Professor of Immunology at University College London since 1992. Discovered (with Deborah Doniach and Peter Campbell) the autoimmune nature of Hashimoto's disease.

⁴ Paul Ehrlich (1854–1915). Won the Nobel Prize in Physiology or Medicine in 1908, for his work on immunity. For his earliest discussion of *Horror Autotoxicus*, see Ehrlich P. (1957) Die Schutzstoffe des Blutes. In Himmelweit F. (ed.), *The Collected Papers of Paul Ehrlich*, London: Pergamon Press, Vol. 2, 298–315.

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We move on to the next really devastating insight that came from Sir Macfarlane Burnet.⁵ Around 1949 he considered a number of experimental findings. One of them was by Traub of the Rockefeller Institute, who showed that if you injected lymphocytic choriomeningitis virus into embryonic mice *in utero*, they grew up without making antibodies to it, even though it was very foreign.⁶ Also Burnet was struck by Owen's findings about dizygotic (non-identical) twin calves who shared a circulation in utero and grew up having genetically mixed red cells.⁷ Each had the red cells of the other, material which normally would have been looked upon as foreign because they were from a genetically dissimilar individual. I would just like to read from Macfarlane Burnet.⁸ He says that obviously you must try not to react against self, 'a concept basic to modern immunology ... [which] no one had applied seriously until 1949', which was when he applied it. In that year, and I'm quoting him again 'Fenner and I published a second edition of an Institute Monograph on *The Production of Antibodies* (that's the Walter and Eliza Hall Research Institute). In this there was the first clear recognition of the differentiation of self from non-self as being very important in immunology, and that to a large extent it was developed in birds and mammals during embryonic life.' That book is long out of print and has become a minor collector's piece, because of a prediction, as follows: '...if in embryonic life expendable cells from a genetically distinct race are implanted and established, no antibody response should develop against the foreign cell antigen when the animal takes on an independent existence.' In other words, antibodies recognize self and non-self as shapes, they don't recognize them as chemical entities, and as such they are not intrinsically different. The only difference between them essentially is that self molecules are in the body and non-self, most of the time, are not. It is that presence within the body that Burnet perceived as being the only way that evolution could develop a system in which you didn't react against self. There had to be something in the developing system that was triggered, or was made to learn self, because it was there in the body originally.

Medawar and Billingham read these seminal observations and realized they would explain why dizygotic twin calves could interchange grafts which normally they would reject! The other twin's blood cells were in the circulation, So they (and their very bright PhD student Leslie Brent, who's with us today) tested the hypothesis by putting foreign, in this case allogeneic CBA cells, into a neonatal strain A animal. When the A- strain animal grew up, having received the allogeneic CBA cells neonatally, it was then immunologically tolerant to further grafts from CBA donors. So if antigens are present during the early development of the lymphoid cells, they are recognized later as self.

Now I'd like to turn from my own story in relation to thyroid autoimmunity to when Peter Campbell and Ita Askonas were studying protein synthesis at the

⁵ See Fenner F J. (1987) Frank Macfarlane Burnet, 1899–1985. *Biographical Memoirs of the Fellows of the Royal Society* 33: 101–162.

⁶ See for example Traub E. (1939) Epidemiology of lymphocytic choriomeningitis in mouse stock observed for four years. *Journal of Experimental Medicine* 69: 801–817.

⁷ Owen R A. (1945) Immunogenetic consequences of vascular anastomoses between bovine twins. *Science* 102: 400–401.

⁸ Burnet F M. (1941) *The Production of Antibodies*. New York: Macmillan.

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National Institute for Medical Research at Mill Hill.⁹ They came under the very beneficial influence of John Humphrey.¹⁰ They were filled with the ideas of tolerance and Medawar's work and so on – it was all very exciting, and I believe that this broadened their concepts and made them interested in the ideas of self-tolerance. Let me just say that I think one of the fascinating things about people like John Humphrey was that he would just spread ideas around like confetti; you didn't have the present day situation where you are frightened of telling anyone anything, because they might crawl into a corner and patent it. In those days science was enjoyable, you really talked about it and you didn't mind giving someone else an idea – it didn't cost you anything, in fact you took a lot of pleasure from it. So I was working at the Courtauld Institute when Peter [Campbell] arrived to work on protein synthesis. I'll let him tell you why we decided that I should work on trying to autoimmunize animals against their own milk proteins, in fact β -lactoglobulin. The idea was to try to autoimmunize them, because taking the opposite side of the coin, if self protein is present during embryonic development of the lymphoid system to imprint tolerance, then absence of self protein during that time should make it potentially foreign at a later stage. So the idea was that in our model system autoimmunity or potential autoimmunity against milk proteins was induced and you saw whether that would attack the mammary tissue in any way. The idea was that ultimately you might be able to apply this to attacking tumours and, in fact, it is interesting the way in which we have gone a full circle, because we think we can do the same thing now.

While we were trying to do that, we had an extremely wise boss called Frank Dickens and he said, 'if you are looking for something that probably isn't available to lymphoid tissue as it evolves, why not try thyroglobulin, because that's imprisoned in the thyroid follicles'.¹¹ But as we were working on milk, and Peter [Campbell] knew what we were doing, we stayed with that – you generally stick with the system that you know how to pull the levers on.

Booth: For the record – can you put a date on that?

Roitt: This was late 1955. Then in March 1956 there came the annual ritual of the *Federation Proceedings*, which were two enormous tomes, the Abstracts of the Meeting of the American Federation of Scientific Societies; it was *de rigueur* to read this stuff and if you didn't Peter [Campbell] got very cross. When I was reading this, I saw two abstracts from Rose and Witebsky.¹² Witebsky was the great guru of tissue antigens and very highly respected; Rose was a younger guy working with him, testing whether the hypothesis concerning *Horror Autotoxicus* was correct or not. Witebsky had got Rose to take one lobe of the rabbit thyroid, emulsify it in Freund's adjuvant and put it back into the rabbit, and Witebsky, I'm sure,

⁹ Askonas B A, Campbell P N, Work T S. (1954) The biosynthesis of proteins. Synthesis of milk proteins by the goat. *Biochemical Journal* 58: 326.

¹⁰ See Askonas B A. (1990) John Herbert Humphrey (1916–1987). *Biographical Memoirs of the Fellows of the Royal Society* 36: 273–300.

¹¹ See Thompson R H S, Campbell P N. (1987) Frank Dickens (1899–1986). *Biographical Memoirs of the Fellows of the Royal Society* 33: 187–210.

¹² Rose N R, Witebsky E. (1956) Production of specific rabbit thyroid antibodies in the rabbit. *Federation Proceedings* 15: 609–610. Abstract presented at the American Association of Immunologists, Atlantic City, April 1956.

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expected nothing to happen because he believed in *Horror Autotoxicus*. Much to Rose's delight, he saw that the thyroid of the remaining lobe was attacked by inflammatory cells and that the animal had made thyroid autoantibodies.¹³ Our hearts gave a little leap when we read that, we thought, my God, Dickens put his finger on something important when he mentioned thyroglobulin.

The other strand in this story then emerges, which Deborah [Doniach] will tell you in much greater detail. She was working with Rupert Vaughan-Hudson, a distinguished surgeon, who specialized in thyroid disorders and had recruited, in his wisdom, Deborah as his clinical assistant.¹⁴ She developed the idea that the plasma cells in the thyroid gland were directed against something in the thyroid. We met one day and had a chat. It was Knudson in chemical pathology who suggested that you [to Deborah] come and talk to us. When the three of us were together, our mind sets were all tuned in, and it was obvious what our favoured hypothesis should be. Straightaway we said 'right, this has got to be the best hypothesis – these plasma cells are directed against the normal self proteins of the thyroid'. So we carried out some very simple studies, with a test tube and a Pasteur pipette, and layered some thyroid extract on the Hashimoto's patient's serum and lo and behold found the precipitins in the tubes at the interface where the antibodies in Hashimoto's patients had reacted with the thyroid extract. I must say we thought this was terrific, and that was how we found the thyroid autoantibodies. The *Lancet* accepted our paper within a week after we submitted it. That was in October 1956 and they published it in five weeks. We thought, 'gosh this is the game to be in, normally we have to wait several months before anybody publishes something'.

We looked a little further. Deborah had the benefit of having a husband who was not only an experimental thyroid pathologist, but also a practising histopathologist.¹⁵ I am sure, in your discussions together you suggested that other diseases might be autoimmune. I think we looked at Sjögren's syndrome¹⁶ and systemic lupus erythematosus (SLE),¹⁷ but we only had precipitation, since we weren't very technologically sophisticated in those days and we didn't find anything. Subsequently, it transpired that these two diseases were autoimmune. Interestingly at that stage, Witebsky very kindly invited me to go to his lab to learn their technique of tanned red cell agglutination. I must tell you – I got a very strong feeling and I am sure I was right – he was quite cross with us. There they were, these established immunologists who'd found this thyroid autoimmunity in

¹³ Witebsky and Rose published in a series of papers in the *Journal of Immunology* during 1955 and 1956. The work reported at the Atlantic City meeting (*ibid.*) was published in full as Witebsky E, Rose N R. (1956) Studies on organ specificity: iv Production of rabbit thyroid antibodies in the rabbit. *Journal of Immunology* 76: 408–416, see also Rose N R, Witebsky E. (1956) Studies on organ specificity: v Changes in the thyroid glands of rabbits following active immunization with rabbit thyroid extracts. *Journal of Immunology* 76: 417–427.

¹⁴ Hashimoto's thyroiditis is a chronic inflammation of the thyroid gland due to the formation of antibodies against normal thyroid tissue. Its features include a firm swelling of the thyroid and partial or total failure of secretion of thyroid hormones.

¹⁵ Professor Sonny Doniach contributes later in the seminar.

¹⁶ Sjögren's syndrome is a condition in which there is progressive destruction of salivary and lachrymal gland tissue.

¹⁷ Systemic lupus erythematosus is a chronic inflammatory disease of connective tissue.

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the rabbit, and here were these amateur upstarts from England who were really quite ignorant about immunology and had produced this paper.¹⁸

What is interesting is to appreciate how the scientific community decided to take on the idea that autoimmunity might be connected to disease. Robin Coombs will tell you about the way he had opened up the technology with the antiglobulin test and being able to demonstrate antibodies on red cells. That led Dacey in 1953 to show that what we know as autoimmune haemolytic anaemia *was* autoimmune, because there were antibodies on the red cells. You [Coombs] carried out some studies with immunoglobulin. However, it wasn't really until we produced the paper on thyroid autoimmunity which, together with the previous work, suddenly convinced the medical community that this was something serious, that maybe autoimmunity could be a pathogenic mode of disease.

The UK scientific community took it on board very rapidly, it wasn't rigid in its views, but opened up, was imaginative and had no difficulty in thinking it was reasonable. In the States, probably most of the scientists and physicians were okay, but the pathologists fought to the last drop of somebody's blood. It was not possible to get a grant from NIH if you wanted to work on human autoimmunity at that stage. They didn't believe in it. I think I have said enough now and leave it open for others.

Booth: Thank you very much for that introduction. Now Peter Campbell, what about the original work at Mill Hill?

Professor Peter Campbell:¹⁹ I would just say one thing to Ivan about the scientific community. Knudson, who he has mentioned, was the medical adviser to Charles Dodds at the Courtauld Institute. I remember going into the lab and explaining to him what we'd done – we had done some controls and so forth – he told me in no uncertain terms that we had made awful fools of ourselves. The other person that I was really more concerned with was Rodney Porter, who also told me politely on one occasion that I'd made a terrible fool of myself.²⁰ We had tried to counter this sort of thing, by going to the Wellington Pub near University College with Medawar, David Newth and Leslie Brent, I think, and asking them what they thought about it, before we sent the paper to the *Lancet*. Much to my surprise, Medawar didn't respond at all. He turned to Newth and asked him what he thought and he said it was okay, so we felt fairly reassured. It was interesting that Medawar didn't offer a view.

Just to go back a little – of course it's quite right, as Ivan has said, that we were very much influenced by John Humphrey at Mill Hill. I was working with Ita [Askonas] who is somewhere in the audience and, of course, we were working

¹⁸ Roitt I M, Doniach D, Campbell P N, Vaughan-Hudson R. (1956) Auto-antibodies in Hashimoto's disease. *Lancet* ii: 820–821.

¹⁹ Professor Peter Campbell (1921–). CRC Fellow of the Middlesex Hospital Medical School from 1954 to 1967; Professor and Head of the Department of Biochemistry, Leeds University from 1967 to 1975; Middlesex Hospital Medical School, London University from 1976 to 1987. Now Emeritus Professor.

²⁰ Rodney Robert Porter won the Nobel Prize in Physiology or Medicine in 1972 for his work on the structure and function of the immunoglobulins. See Perry S V. (1987) Rodney Robert Porter, 1917–1985. *Biographical Memoirs of the Fellows of the Royal Society* 33: 443–489.

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with Tommy Work²¹ on milk proteins and we were experts at milking all sorts of different animals.²² When I arrived at the Courtauld, we were still thinking about milk. It so happened that in 1955, the Bland-Sutton Institute of Pathology at the Middlesex was having an open day and an exhibition to celebrate the centenary of the birth of Bland-Sutton and I went to have a look. I was attracted by a surgeon from New Zealand, called Richardson, who had studied the prognosis of patients who had come to the Middlesex Hospital and received surgical treatment for breast cancer. He was particularly interested in the seven per cent with medullary carcinoma with lymphoid infiltration, and of the 117 patients with this type of tumour, he found a relatively favourable prognosis. He suggested that the inflammatory infiltrate could be a visible sign of some slight tumour antigenicity. Ivan and I spoke about this. We thought that it would be interesting as a model, to try to get animals with antibodies to milk proteins and then see how those milk antibodies reacted with the lactating mammary gland. That was our concept before we heard from Dickens, met Deborah and moved over from milk proteins to thyroglobulin.

Booth: Leslie Brent do you want to confirm that part of the immunology story and the meeting?

Professor Leslie Brent:²³ I can't say that I have any clear recollection of it. I used to go to the Wellington Pub, certainly, with Peter Medawar and Rupert Billingham and David Newth, who was an embryologist at the Department of Zoology at University College, but I have no clear recollection of that particular episode.

Booth: By then you had published your original work?

Brent: We published our *Nature* paper in 1953²⁴ and, at the time of which we are speaking, we were preparing our big paper which was published in 1956 in the *Philosophical Transactions of the Royal Society*.²⁵ I have been looking at these old papers and in the 1953 paper we do, of course, refer to Burnet and to Owen as well, and we say that acquired tolerance has implications beyond its experimental nature, but we didn't enlarge upon that in the *Nature* paper. In 1956 we discussed at some length the interaction or the connection between tolerance and autoimmunity and expressed the view that the *raison d'être* of tolerance was to prevent autoimmune responses in the body. We gave various examples, such as milk proteins and lens proteins and spermatozoa antigens, which do not normally

²¹ Dr Thomas Spence Work (1912 –) PhD Edinburgh, 1936. Appointed to Scientific Staff of NIMR, 1938. Head of Division of Biochemistry from 1956 to 1977.

²² Askonas B A. (1990) From protein synthesis to antibody formation and cellular immunity: A personal view. *Annual Review of Immunology* 8: 1–21.

²³ Professor Leslie Brent (1925–). Worked with Medawar and Billingham, University College London from 1954. Professor of Immunology at St Mary's from 1969; now Emeritus Professor.

²⁴ Billingham R E, Brent L, Medawar P B. (1953) Actively acquired tolerance of foreign cells. *Nature* 172: 603–606.

²⁵ Billingham R E, Brent L, Medawar P B. (1956) Quantitative studies on tissue transplantation immunity. III Actively acquired tolerance. *Philosophical Transactions of the Royal Society of London Series B* 239: 357–414.

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have access to the developing immune system in embryonic life. They are therefore exempted from tolerance production and have the ability to induce tolerance if they are introduced later in life. That was a fairly reasonable if brief discussion of the question of autoimmunity. Peter Medawar and I published a paper in 1959 in the *Proceedings of the International Congress of Microbiology* in Stockholm.²⁶ I gave this paper in 1958; it was specially devoted to the subject of tolerance and autoimmunity and went into considerable detail about the interrelationship of these phenomena.

Booth: Can I just tell you my bit before Deborah Doniach begins. What I remember about the 1950s is meeting you and of course I worked at Hammersmith, as a junior, with your husband. I remember you showing me a tube and at one end you'd put in some thyroid tissue and the other end you'd put in some serum and in the middle there was a precipitin line. I thought, 'how on earth can you discover major things by such simple techniques?' I was puzzled by the whole thing.

Professor Deborah Doniach:²⁷ My main interest was in endocrinology. In 1947 I had been qualified about three-and-a-half years. After the usual house jobs I worked as Assistant Medical Officer in London County Council (LCC) hospitals including one year in rheumatology at St James's under Dr Francis Bach.

A women could not easily aspire to become a clinical endocrinologist in those days, but clinical pathology was a less crowded specialty and I managed to obtain a junior trainee job in chemical pathology at the Courtauld Institute under Professor Charles Dodds.

I was put in charge of the basal metabolic rate (BMR) tests. This was the standard investigation for thyroid function. It was an excellent way to learn about thyroid disorders. Every morning between five and 12 patients rested on a couch for half an hour, then had their BMR tests and were interviewed. I examined them in some detail and obtained a personal and family history. After three years I passed my MD examination in Chem Path. I also did a six months voluntary training job in bacteriology at UCH with Dr Joan Stokes, which was particularly useful in view of our future research, and six months of haematology at the West Middlesex Hospital where Professor John Dacie, the visiting consultant, taught me a great deal.

I then became research assistant at the Royal Free to carry out a clinical trial of the antithyroid drug neomercazole (carbimazole). This had been developed in the UK and a research worker was wanted to study each patient with regular BMRs. Once again I had a good opportunity to increase my knowledge of thyroid diseases.

In 1952 I approached Mr Rupert Vaughan-Hudson and asked him if he would allow me to treat some thyrotoxic patients with neomercazole before deciding on thyroidectomy. He agreed and I became his clinical assistant. One of the surgical registrars also working in the thyroid clinic was Bill Richardson,

²⁶ Brent L, Medawar P B. (1959) Tolerance and autoimmune phenomena. In Tunevell G. (ed.), *Recent Progress in Microbiology: Proceedings of a Symposium*, 7th International Congress of Microbiology, Stockholm, 1958. Stockholm: Almqvist and Wiksell, 181–190.

²⁷ Professor Deborah Doniach (1912–). Professor of Clinical Immunology, Middlesex Hospital. Now Emeritus Professor. First demonstrated (with Roitt and others) autoantibodies in Hashimoto's disease.

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mentioned by Peter Campbell, with whom I often talked about the patients. In addition to the thyrotoxics I saw several new cases of Hashimoto's disease and later, I recalled all the ones who had been operated on in order to study the effects of thyroidectomy.²⁸

Booth: For the record, Hashimoto's is basically a thyroid disease, with an enlarged thyroid which was different from the ordinary thyroid deficiency which you see in older people. It's a specific type of disease. How many per cent of thyroid diseases in older people are Hashimoto?

Doniach: It is a very small percentage. The patients I collected were classical examples as mild cases could not be diagnosed preoperatively at that time.

Booth: But you were selecting a particular group of diseases – this is the important point.

Doniach: I began collecting the Hashimoto cases because in the early 1950s the flocculation tests of liver function and the electrophoretic separation of serum proteins became popular. When these tests were applied to Hashimoto patients²⁹ it was found that the abnormal flocculations were due to raised gammaglobulins on the electrophoretic strip.³⁰ I used these two methods on all the patients suspected of Hashimoto's disease and confirmed these new findings.³¹ There was talk of gammaglobulins being connected with antibodies, but immunoglobulins had not yet been identified and autoimmunity was not understood. A chance occurred to see the effect of operation on the gamma-globulin level when a Hashimoto patient with a large goitre was submitted to thyroidectomy. Repeated tests showed that when the goitre was removed the gammaglobulins gradually returned to normal within three months. This suggested that some agent in the gland was the stimulus for their initial rise. I was not totally unprepared immunologically speaking as Joan Stokes had taught me the new method of precipitin tests in agar.

I asked to be introduced to Ivan Roitt. That was how we met in the pub and talked about a possible collaboration. Peter Campbell and Ivan Roitt had read the *Federation Proceedings* but I knew nothing about that. In June 1956, Ivan showed me a picture in the *Journal of Immunology* of a thyroid gland from a rabbit immunized with thyroid extract.³² This showed a striking resemblance to human 'struma lymphomatosa'. Encouraged by Sonny Doniach I had been in the habit of

²⁸ Doniach D. (1953) Treatment of thyrotoxicosis with neomercazole, report of 120 cases. *Lancet* i: 873–879. See also Hashimoto H (1912) Zur Kenntniss der lymphomatösen Veränderung der Schilddrüse (struma lymphomatosa). *Archiv für Klinische Chirurgie* 97: 219–248.

²⁹ Fromm G A, Lascano E F, Bur G E, Escalante D. (1953) Tiroiditis cronica inespecifica. *Revista de la Asociacion medicina Argentina* 67: 162–170.

³⁰ Luxton R W, Cooke R T. (1956) Hashimoto's struma lymphomatosa. Diagnostic value and significance of serum flocculation reactions. *Lancet* ii: 105–109.

³¹ Roitt I M, Doniach D, Campbell P N. (1956) The nature of the γ -globulins in lymphadenoid goitre. *Biochemical Journal* 64: 54P. See also Doniach D, Hudson R V. (1957) Lymphadenoid goitre (Hashimoto's disease). Diagnostic and biochemical aspects. *British Medical Journal* i: 672–678.

³² Op. cit. note 13 above.

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looking at the thyroid glands of operated patients I had seen in the clinic, and to discuss the histology with the pathologists in the Bland-Sutton Institute. Ivan and I talked about Witebsky's experiments and what they could mean. He asked me to bring him a human thyroid from which to prepare thyroglobulin and the sera of patients with Hashimoto goitres. Over four years I had collected seven sera. Within a few days I was able to obtain a piece of thyroid gland from the operating theatre. Ivan made an extract of it, and set up the precipitin tests and obtained positive results.³³

Dr Witebsky was a distinguished haematologist and one of the first to investigate organ-specific antigenicity but he had never heard of Hashimoto's disease. He told me that they did their rabbit experiments for several years before examining the histology of the thyroid in their animals. When he showed these to his local histopathologist after hearing about Ivan's results the man said 'that is not like Hashimoto's', and Witebsky was a bit upset.

Roitt: That pathologist really held them up I think. But also they were quite happy to blame the pathologist for not seeing a connection. You have to have the right people from the right disciplines with the right knowledge together. That's why it is so important to be in the right sort of place, in a centre of learning like University College. They are a critical mass of people, who are multi-disciplinary and whose minds are not fixed on only their own subject.

Doniach: At about the same time, Adams and Purves³⁴ discovered the long acting thyroid stimulator (LATS) which later turned out to be an autoantibody to the TSH receptor and is probably responsible for the overactivity of the thyroid seen in Graves disease.

During this exciting period, I read many of the early articles on lymphocytic thyroiditis. Hashimoto's own paper of 1912 is still a model of clear thinking and of stimulating scientific discussion. When I visited Japan in 1979, I met Hashimoto's son now a Professor of Toxicology. He told me that his famous father Hakaru, did his research in Tokyo as a young man but had to abandon it in order to take charge of the general practice of his own father in a small town. The only other paper he published was about erysipelas.

Another important author from the distant past was Morris Simmonds of 'Simmonds disease' fame. He was interested in focal lymphocytic thyroiditis and its relation to clinical diseases.³⁵ Seventy-four per cent of thyrotoxic glands had areas of lymphocytic infiltration and only 15 per cent of other goitres. In *post mortem* material the most common associated disorders were diabetes and pernicious anaemia. In a later generation Paul Bastenie of Brussels extended Simmonds's work

³³ Doniach D, Roitt I M. (1957) Autoimmunity in Hashimoto's disease and its implications. *Journal of Endocrinology* 17: 1293–1304.

³⁴ Adams D D, Purves H D, Sirett N E, Beaven D W. (1962) The presence of long-acting abnormal thyroid stimulator in the blood of a thyrotoxic patient. *Journal of Clinical Endocrinology and Metabolism* 22: 623–626.

³⁵ Morris Simmonds (1855–1925). See Simmonds M. (1923) Über chromische thyroiditis und fibrose atrophie der thyroidea. *Virchows Archiv Pathologische Anatomie* 246: 140.

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and found connections with adrenal atrophy and chronic hepatitis.³⁶ His work prompted us to start an extensive collaboration with Sheila Sherlock at the Royal Free who gave us unparalleled cases of liver diseases and this led to the discovery of the mitochondrial antibodies which are important for the diagnosis of primary biliary cirrhosis.³⁷

Booth: So it's fairly clear that Hashimoto's thyroiditis, thyroid inflammation, was due to an autoantibody of some sort and the way in which that was recognised was from the clinical studies by Deborah and the basic scientific studies that had been carried out in the laboratory by Ivan, Peter Campbell and others. Is that a fair statement? I remember that period because the idea of autoimmunity was laughed at by many people at the time. People didn't really believe in it, they were very suspicious about it. In haematology there had been enormous developments as well. I wonder if we could bring Robin Coombs in at this stage. Can you tell us something about the recognition of the Coombs test and what impact that had on the recognition of autoimmune haemolytic anaemia?³⁸

Coombs: I don't want to talk about the test particularly, I think it's found its level.

Can I turn to something else? There are four things I want to mention very briefly. One is this word autoimmunity, secondly a recollection on autoallergic thyroiditis, thirdly a reminder that not all autoantibodies are pathogenic, and finally a comment on what we have already heard today – *Horror Autotoxicus*. I think this calls forth a preliminary lamentation on the usage of this quite misconstrued, absurd, and extremely confusing word 'autoimmunity'. I have the greatest respect for clinicians and a very learned and distinguished physician, medical teacher and writer, Dr Clarke-Kennedy³⁹ came up to me one day in Cambridge and he said 'Coombs, you immunologists are quite absurd. How can you have autoimmune diseases? How can you be immune to yourself? Well, of course, Dr Clarke-Kennedy, as quite often was the case, was absolutely right. But this was hard on me, as over many years I have tried, and still do try, to get my colleagues to talk of autoallergic diseases and not autoimmune diseases, which just doesn't make sense. but I've given up now. Philip Gell and I, with the enthusiastic support of Carl Prausnitz, a very distinguished allergist, tried to correct this absurdity in an appendix to the first three editions of *Clinical Aspects of Immunology*.⁴⁰ We returned to the teaching of Von Pirquet in 1907, who actually

³⁶ Bastenie P A, Neve P, Bonnyus M, Van Haelst L, Chailly M. (1967) Clinical and pathological significance of asymptomatic atrophic thyroiditis. *Lancet* i: 915–919.

³⁷ Walker J G, Doniach D, Roitt I M, Sherlock S. (1965) Serological tests in diagnosis of primary biliary cirrhosis. *Lancet* i: 827–831.

³⁸ Coombs R R A, Mourant A E, Race R R. (1945) A new test for the detection of weak and incompatible Rh agglutinins. *British Journal of Experimental Pathology* 26: 255–256. *ibid.* Detection of weak and 'incomplete' Rh agglutinins; new test. *Lancet* ii: 15–16.

³⁹ Dr A E Clarke-Kennedy, Dean of the London Hospital and Fellow of Corpus Christi College, Cambridge.

⁴⁰ Gell P G H, Coombs R R A. (eds) (1963) *Clinical Aspects of Immunology*. Oxford: Blackwell, appendix A, 850–907.

'The vaccinated person behaves towards vaccine in a different manner from him who has not previously been in contact with such an agent. Yet he is not insensitive to it. We can only say of him

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coined this word 'allergy', which only means altered reactivity, with no connotation as regards protection or immunity or clinical hypersensitivity and producing disease. Allergy was really the biological response which, depending on circumstances, could lead on one hand, to protection or immunity or, on the other hand, to harmful reactions and clinical hypersensitivity. We've all been talking today about autoimmunity. It doesn't make sense, whereas autoallergy is perfectly in order. When you inject egg albumin into a rabbit, you don't immunize that rabbit, you don't do anything to protect that rabbit from egg albumin, you just inject it to produce antibodies, and it has an allergic response. I read just recently a chapter on post-transfusion purpura by Muller Eberhard in 1994, and he and his colleagues write 'post-transfusion purpura is a serious adverse reaction, it affects mainly women beyond the age of fifty, who have been pre-immunized by pregnancy or blood transfusion'. What a silly way to say it. They'd been pre-sensitized, but they are not immunized, they are made susceptible to the disease. I'm not going to go further into that because I have written about it and if anybody's interested I can give them chapter and verse. So, I can't bear this use of autoimmunity, and I shall go down fighting it to the end.

The next thing, Mr Chairman, is autoallergic thyroiditis. As this is a witness seminar, I would like to comment on how fortunate Ivan Roitt has been with having such wonderful collaborators in Deborah and her learned husband. Their help in unravelling the phenomenon was absolutely indispensable. I'm going back here to Witebsky who was not so fortunate with his colleagues, as you have so rightly said Ivan. I think he must have been working on experimental autoallergic thyroiditis in rabbits for well over two years before he published. My wife and I were in Buffalo in December 1953, as Witebsky had asked us to take over the tanned red cell test, so that he could adapt it, harness it, to use antibodies to thyroglobulin or thyroid extract in his experimental animals. He was working at this time on organ specific antigens, thyroglobulin and crude extracts of the thyroid, and was asking the question 'could these organ-specific antibodies be autoantibodies?' Well, now you were quite right Ivan, I won't mention the pathologist by name, he worked on the other side of the corridor and was not the slightest bit interested at all. And Ernest Witebsky was perhaps to blame for not making sure that the pathologist did something. Nor were the clinicians particularly interested. His historic papers, which were on the experimental generation of the thyroid lesions in rabbits by injecting thyroid extract, were published in June 1956.⁴¹ They had been submitted in January 1956 and all I can say was that we were early witnesses of those – you were very fortunate, Ivan, with your wonderful colleagues.

Doniach: May I say something else. Witebsky told me that they did not look at the thyroid glands for three years. They injected the antigen and they did blood tests for the antibodies. It was only when they wrote the paper that came out in June 1956 that they started looking at thyroid sections.

that his power to react has undergone a change...For this general concept of changed reactivity I propose the term Allergy. ...The term Immunity must be restricted to those processes in which the introduction of the foreign substance into the organism causes no clinically evident reaction, where, therefore, complete insensitivity exists;

[from Pirquet, C Von (1906) *Allergy. München Medicinische Wochenschrift* 30: 1457]

⁴¹ Rose and Witebsky (1956), op. cit. note 13 above.

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Coombs: That was probably submitted in the January 1956, the experimental work finished in late 1955.

Booth: Let me ask Professor Coombs something. When you were in Cambridge and you read that *Lancet* paper by Roitt and Doniach, what was your reaction to reading that paper? Were you at once excited?

Coombs: Yes, delighted. In those days the more people who came up with encouraging things, confirming things, was wonderful. The question of priority never came up, and one never raised such questions then.

Booth: The other chap who was in Cambridge at that time was Peter Lachmann. I'm not sure whether you were actually a young research fellow at that time, but you were in the pathology department in Cambridge?

Professor Peter Lachmann:⁴² You overestimate my age, Chris. I didn't go back to Cambridge until 1958. In 1956, the year we're talking about, I was just qualifying in medicine. If I may I would like to comment on the use of the term 'autoallergy'. Robin, of course, is quite right on its true meaning, but English is a living language and there comes a point when one has to accept the majority usage and accept 'autoimmunity'. Whereas Robin will go on fighting until the next millennium, I am afraid I gave up a decade or two earlier. But he's absolutely right.⁴³

There were several strands of work on autoallergy. You've heard about the organ-specific thyroid disease and you've also heard something about haematological autoallergy and that goes back to 1904 and the Donath–Landsteiner antibody.⁴⁴ After the Second World War, and even before the thyroid work, the real recognition that autoallergic reactions and autoantibodies were likely to be important in tumour disease came from the studies of SLE. It was in 1948, (I'm not talking here about my personal recollections, because I was still at school), that Hargreaves *et al.* at the Mayo Clinic described the 'lupus cell' (lupus erythematosus cell).⁴⁵ It's worth recounting why this happened, because others had been examining bone marrow smears from patients with lupus for many years without seeing the 'LE cell'. The conventional technique was for the technician to draw the bone marrow and make the smear immediately by the bedside, and under those circumstances LE cells are not found. In the Mayo Clinic it was the practice for the technicians to go round the wards, take the marrow aspirate into heparin

⁴² Professor Peter Lachmann FRS (1931–). Sheila Joan Smith Professor of Immunology at Cambridge, since 1977– ; Hon. Director MRC Molecular Immunopathology Unit.

⁴³ Note by D Doniach. Clinicians prefer 'autoimmune disease' because allergy is a separate clinical specialty from thyroidology, endocrinology, rheumatology, hepatology and other branches of clinical medicine where patients with autoimmunity are treated.

⁴⁴ Donath J, Landsteiner K. (1904) Über paroxysmale hämoglobinurie. *München Medicinische Wochenschrift* 51: 1590–1593.

⁴⁵ Hargreaves M M, Richmond H, Morton R. (1948) Presentation of two bone marrow elements, the 'Tart' cell and the 'LE' cell. *Proceedings of the Staff Meetings of the Mayo Clinic* 23: 25–28.

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(which is also very important; if they had taken it into EDTA it wouldn't have worked either), to put them into their pockets and by the time they had wandered round the Mayo Clinic, the marrow had been incubated for some considerable period at a temperature approaching 37°C. When the bone marrow smears were then made in the laboratory, there had been enough time for what is an *in vitro* phenomenon to have occurred and they found these strange inclusions inside polymorphs which are altered nuclei from other polymorphs.

Booth: Basically the LE cell is what sort of a cell?

Lachmann: It is a polymorph that has phagocytosed the nucleus of another dead polymorph.

Booth: Specific to the disease of lupus erythematosus?

Lachmann: In large numbers typical LE cells are pretty much specific to the disease. I'll tell you in a moment the antibodies they are really specific for, as I worked on that ten years later.

Booth: So recognition of the LE cell was early recognition of something immunological happening?

Lachmann: That was in 1948. In 1950 Haserick and his colleagues, also in the States, showed that they could get LE cells to form *in vitro* if they took normal bone marrow and serum from the patients with the disease.⁴⁶ In 1954 Peter Miescher showed, that if he absorbed lupus sera with normal cell nuclei he abrogated this capacity of the serum to form LE cells.⁴⁷ Therefore he recognized that the factor in the blood of patients with systemic lupus that was responsible for this *in vitro* phenomenon might be an antibody to cell nuclei. That aroused very considerable interest. Two or three years later, a number of groups, including Cepellini, Polli and Celada in Italy,⁴⁸ Seligman in France⁴⁹ and Kunkel's group in New York⁵⁰ showed that among these antibodies were antibodies to naked DNA. At that time this was regarded as extremely unusual and, in fact still is, because

⁴⁶ Haserick J R, Lewis L E, Bortz D W. (1950) Blood factor in acute disseminated lupus erythematosus. I. Determination of gamma globulin as specific plasma fraction. *American Journal of the Medical Sciences* 219: 660–663.

⁴⁷ Miescher P, Fauconnet M. (1954) L'absorption du facteur 'LE' par les noyaux cellulaires isolés. *Experientia* 10: 252–254. See also Grabar P, Miescher P. (eds) (1959) *Immunopathology*. Basel: Benno Schwabe.

⁴⁸ Cepellini R, Polli E, Celada F. (1957) A DNA-reacting factor in serum of a patient with lupus erythematosus diffusus. *Proceedings of the Society for Experimental Biology* 95: 572–574.

⁴⁹ Seligman M. (1957) Mise en évidence dans le serum de malades atteints de lupus erythemateux disséminé d'une substance déterminant une réaction de précipitation avec l'acide désoxy-ribonucleique. *Comptes Rendue de L'Academie de Sciences* 245: 243–245.

⁵⁰ Robbins W C, Holman H R, Deicher H, Kunkel H G. (1957) Complement fixation with cell nuclei and DNA in lupus erythematosus. *Proceedings of the Society for Experimental Biology* 96: 575–579.

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unlike the antibodies which Ivan has been talking about, you can't raise antibodies to double-stranded DNA by conventional immunization. These are antibodies that are formed only in disease, and there is still great argument about why this should be so.

This non-specific autoimmunity or autoallergy was thus being recognized, as were the organ-specific reactions, and these gave rise in the late 1950s (when I was first with Robin Coombs and then with Henry Kunkel at the Rockefeller Institute) to the very interesting question of what it was that these antibodies actually reacted to. The antibody that gives rise to the LE cell is an antibody to what, in modern parlance, would be called the native nucleosome. It then became clear that antibodies can be found to every piece of the nucleosome: the DNA, the histone, the non-histone protein, and the LE cell factor itself, which is the antibody to the native structure. That is what I showed in about 1960.

At that time there was a great argument which long persisted, and in some peoples' minds may never have stopped persisting, of how these antibodies actually come about; to what extent they are driven by the autoantigens themselves; to what extent they are driven by antigenic mimicry from outside antigens, particularly infective agents; and (a little later) to what extent they are driven by the idiotype system (which we haven't yet discussed) that is whether their formation is driven by the variable regions of immunoglobulins; or finally whether they are driven by polyclonal activation. The answer for systemic lupus to my mind has always been – and I think few people would now disagree – that the antibodies are stimulated by antigens. The main reason for so believing is that if you have a particle to every piece of which an antibody is made, it's very difficult to conceive any other way of doing this other than stimulation by the antigenic particle; especially if antibodies are also made to its native configuration. It does therefore seem that even these strange antibodies are driven by the autoantigens themselves. In the case of lupus, the damage is not done by the antibodies reacting with the antigens in their native sites, but by immune complexes damaging small blood vessels.

Coombs: Could I just add there that I think lupus or the LE cell will be one of the major components in the formation of immunohaematology.

Booth: I wonder if we can just pause here. We've got a situation where thyroid-specific antibodies have been demonstrated to show a particular form of thyroid disease called Hashimoto's thyroiditis which, we know from what Deborah has said, was associated with other diseases. Equally, the lupus cell seemed to occur in some other, particularly liver, types of diseases. If I remember rightly the clinicians in the Walter and Eliza Hall group of which, of course, Macfarlane Burnet was the head, had described a condition called lupoid hepatitis. Now Peter, can you tell us where that comes in?

Lachmann: I think lupoid hepatitis was discovered in the early 1950s by Slater, Kunkel and Bearn.⁵¹ Their patients were hirsute young women with antinuclear

⁵¹ Bearn A G, Kunkel H G, Slater R J. (1956) The problem of chronic liver disease in young women. *American Journal of Medicine* 21: 3.

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antibodies, and a bad prognosis. Some had full blown lupoid hepatitis with involvement of the liver. The disease I think you are describing is 'autoimmune' chronic active hepatitis, and the patients have antibodies to a variety of antigens including antinuclear antibodies.

The immunological function of the liver is to remove antigens that come either from the portal vein or the hepatic artery. Normal livers contain no lymphoid tissue. If 'shunting' of blood from the portal circulation into the systemic circulation occurs then antibodies to all sorts of antigens that come from the gut are made as are certain sorts of autoantibodies. A finding which came to be of great interest to me later was first made by Ralph Wright at Oxford: patients with autoimmune hepatitis manufacture very high titres of antibodies to the measles virus and sometimes to the rubella virus.⁵² This finding drew attention to the role that viruses may play, in either a direct or indirect way, in the pathogenesis of these diseases.

Booth: You worked with Kunkel, a very distinguished immunologist, in New York at the Rockefeller Institute. What was his reaction to the idea of autoimmunity that Ivan and others were putting forward at the time?

Lachmann: By the time that I knew Henry Kunkel in 1960, it was all entirely accepted. He was extremely interested in the idea, and also he was one of the early immunogeneticists. He was very interested in the genetic predisposition to these diseases and I am sure Richard [Batchelor] will tell us about all that in a moment. Henry studied the autoantibodies in rheumatoid arthritis as well. This was one of the early contributions to the understanding of rheumatoid factors which also go back a long way – before the Second World War, Rose and Waaler and René Grubb had described autoantibodies that reacted to other antibodies. Robin [Coombs] will probably tell you about antibodies to bound complement that were described before the First World War.

Coombs: We didn't quite understand how they got there, but, yes, they had that sort of activity. But in fact Kunkel even accepted that they were physiogenic. So not all antibodies are pathogenic. These people, and Ingram, who was working with us in the lab at the time, showed that immunoglobulins, which are antibodies like the rheumatoid ones but to fixed complement, actually aid in protection from disease.

Lachmann: Pierre Grabar, who was another well-known immunologist, became enthusiastic about the idea that some of these ubiquitous and apparently non-pathological autoantibodies play a necessary role in tidying up the body after cell death, and he wrote extensively on this.⁵³ I must confess I have never found this argument compelling, because subjects who are totally agammaglobulinaemic have

⁵² Triger D R, Kurtz J B, MacCallum F O, Wright R. (1972) Raised antibody titres to measles and rubella virus in chronic active hepatitis. *Lancet* i: 665.

⁵³ Grabar P. (1975) Hypothesis. Autoantibodies and immunological theories: an analytical review. *Clinical Immunology and Immunopathology* 4: 453–466; *ibid.* (1975) The 'globulines transporteurs' theory and autosensitization. *Medical Hypotheses* 1: 172–175.

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no trouble in 'tidying up' after their dead cells. Although such autoantibodies may play some role in the process, it is not a necessary role. However, as we know, nature often uses belts as well as braces. Grabar was very keen on the idea that we make autoantibodies for a good purpose.

Booth: Richard Batchelor you are an immunogeneticist and Peter Lachmann has already raised this question of the relationship of genetics to autoimmunity. Would you like to say something at this stage about your memories of that period?

Professor Richard Batchelor:⁵⁴ Well, I'm about the same age as Peter, so I can't really tell you many stories about the early fifties from early experience. But I can tell you one to link John Humphrey, who was mentioned earlier on with my mentor, Peter Gorer, which has both a slightly sad but also funny side. It was in the very beginnings when immunology was becoming a sort of semi-respectable subject and the *Annual Reviews of Immunology* had just started, I think largely due to John Humphrey. He was certainly one of the editors but I've forgotten the others. Anyhow, John asked Peter Gorer to write about the antigenic structure of tumours. He wrote a very scholarly review about the work he had been doing, trying to define tumour-specific antigens in a series of chemically-induced leukaemias and other forms of tumour. Unfortunately he was struck down with carcinoma of the bronchus just as he'd finished his chapter. John Humphrey had the proof in his hands, but nobody to correct the proof. I should say in parentheses that at the time I used to see Peter Gorer with a cigarette hanging out of his mouth, working at an open balance, weighing out carcinogens without gloves or anything, putting his cigarette down and picking it up again. It was quite horrifying. But, that was a diversion. John Humphrey, when he had nobody to correct the proof, wrote to me about a particular element in it which worried him. There had been a lot of work on antitumour antisera in humans, an awful lot of half-baked work was going on and hitting the headlines, as anything to do with cancer always does. Gorer thought that he would do a demolition job on this, and started a section of his review by saying 'anticancer sera, like the poor, are always with us, but unlike the poor, they cannot be made to work'. I thought that was a very witty remark. John, I'm afraid though it wasn't acceptable and so in the end he said 'Look I don't think we ought to have this'. I consented, I think somewhat weakly.

Anyway, John deserves mention in the early work of immunogenetics and its relationship to autoimmunity, because he and a famous immunochemist, Michael Sela, got talking.⁵⁵ At that time John Humphrey was interested in tolerance, he wanted to have some artificial antigens where the structure was absolutely known which could be labelled and kill perhaps the cells that were responding to that particular antigen. So he talked to Michael Sela and Michael said 'I'll send you some synthetic polypeptides and you can immunize with those, you know exactly what they are'. John immunized rabbits with these materials at Mill Hill and got absolutely no antibody response at all. So he wrote back to Michael Sela saying 'I

⁵⁴ Professor J R Batchelor FRCPATH FRCP (1931–). Professor of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital from 1979 to 1994; now Professor Emeritus.

⁵⁵ Sela introduced the use of antigens composed of polymers of L-amino acids. Sela M. (1966) Immunological studies with synthetic peptides. *Advances in Immunology* 5: 29–129.

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think something has gone wrong with your stuff, can you send me some more'? A second batch appeared and precisely the same result occurred. No antibody formation at all. So John sent back some of the second batch to Israel and Michael Sela used it to immunize his rabbits there and sure enough it produced a response as they normally did. So the conclusion that they reached was that perhaps there must be some difference, presumably genetic, in immune responsiveness between the rabbits at Mill Hill and those in Israel. About that time, Hugh McDevitt had a travelling fellowship and was not really sure what he wanted to study. John said, well what about this? He thought it was a very good idea, but, rabbits don't breed very fast and it all turned out to be extremely difficult. I don't think Hugh got very far in that first year or two that he was at Mill Hill. He went back to the States and, as everybody here knows, subsequently made several discoveries; first of all that the mice of different strains responded differently to these polypeptide antigens, and then later on, he demonstrated that this was linked to H2.⁵⁶ Inevitably, of course, that raised the question – is the same thing true in man? There was then a relatively small group of people round the world working on human leucocyte antigens (HLA)⁵⁷ of which I was one, and we all I think simultaneously started studying the various diseases in which we were interested, and their associations with HLA. At about this time, Ian McDonald wrote to me and said we ought to talk about multiple sclerosis. There was a school of thought that considered MS might be driven by an immune process, but equally there was quite a large number of people who believed that the basis of MS was some abnormality in the cerebral lipid metabolism. Whether the pendulum had swung more in favour of immunity and against the lipid metabolism theory, I would probably have to ask Sidney Liebowitz, but certainly it was quite a respectable theory. The evidence that came out over the ensuing five years showed quite categorically that all chronic autoallergic diseases, I have to be very careful to use the right term, were in fact HLA associated.

Booth: So they had a genetic basis?

Batchelor: Absolutely. We know a great deal more about it now of course, but things got rather stuck between 1975 and 1985. Ita [Askonas] may disagree, but it really wasn't until we got down to the detailed biochemistry of the HLA molecules themselves. The three-dimensional structure of the class I and indeed the class II HLA molecules has been worked out in the laboratories of Jack Strominger and Don Wylie by X-ray crystallography.⁵⁸ I was down at East Grinstead, investigating HLA polymorphisms by serological techniques and there was a chap called Arnold Sanderson working with me who really had a lot to do with developing the chromium-51 lymphocytotoxic test. He was a very good membrane chemist and

⁵⁶ McDevitt H O, Chinitz A. (1969) Genetic control of the antibody response: relationship between immune response and histocompatibility. *Science* 163: 1207–1208.

⁵⁷ HLA (human leucocyte antigens): these are molecules, coded by different genes and present on the surface of many cells, that are essential in mounting a normal immune response. For a description on the immune system and how it works, see Isenberg D, Morrow J. (1995) *Friendly Fire: Explaining Autoimmune Disease*. Oxford: Oxford Medical Publications.

⁵⁸ Brown J H, Jardetzky T S, Gorga J C, Stern L J, Urban R G, Strominger J L, Wylie D C. (1994) The three-dimensional structure of the human Class II histocompatibility antigen complexed with superantigen. *Nature* 368: 711–718.

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Jack Strominger knew absolutely nothing at all about mammalian cells, he was a bacterial cell wall man.

Booth: What was Strominger trying to do?

Batchelor: He really didn't know but he knew Arnold Sanderson, I can't quite remember what the connection was. I think it was from the bacterial cell wall genetics days, because Arnold was originally a bacterial cell wall genetics man. Strominger invited Sanderson to visit his lab to teach him about mammalian cells. So Arnold went over, and taught Strominger all the basic tools – the chromium-51 test, showed him how to extract HLA molecules etc. He learnt all these basic tools but thought you couldn't get anywhere unless you grew large quantities of cells bearing the HLA molecules, and then learn about their structure by X-ray crystallography. He had a series of postdocs who worked on this who didn't really get anywhere and then this amazing girl, Pamela Björkman, who had patience and green fingers, decided that she was going to take it up and succeeded in growing crystals of class I molecules, which no-one else had done before.

Booth: Could this be related to human disease?

Batchelor: No. But it enabled Don Wylie to make the X-ray crystallography pictures, and the three-dimensional structure was then worked out. That immediately suggested that certain HLA molecules, could accept certain peptides but not other peptides. Presumably, that was the reason which connected the HLA genotypes with susceptibility to a human autoimmune autoallergic disease.

Booth: Thank you very much for that point. Deborah Doniach earlier referred to the relationship between thyroid disease and pernicious anaemia. I think we ought to just get that on the record. Pernicious anaemia is due to an autoimmune abnormality of the lining of the stomach, which means that you can't secrete intrinsic factor, you can't therefore absorb vitamin B12 and you get anaemia. The man who really started that was Michael Schwartz in Copenhagen. He started treating pernicious anaemia patients in Copenhagen with desiccated hog's stomach, which was a treatment in those days, or one of the treatments people talked about. He found that the hog's stomach became ineffective after a while, and associated that with an antibody in the serum to the hog's stomach. But what was then surprising was that you [Doniach] and Keith Taylor in Oxford showed that you could get a spontaneous antibody which was nothing to do with hogs, nothing to do with pigs' stomachs, but which was an autoantibody to the stomach and you did it, if I remember rightly, Deborah, using a similar technology to that which you'd used for looking at the thyroid. Is that right?

Doniach: Yes. Keith Taylor had a good collection of cases of pernicious anaemia and we started working on that because Bastenie's thesis had described the connection with thyroiditis. Also the work of Schwartz suggested that there was an antibody against the intrinsic factor. We started to do the double-layer fluorescence

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test with the serum from patients with pernicious anaemia and we found antibodies, which were not against intrinsic factor, but were against the cytoplasm of parietal cells.

Roitt: Keith Taylor had done feeding studies with human pernicious anaemia patient serum and intrinsic factor, and I think he had indicated that there was likely to be an antibody. Then I think Irvine's⁵⁹ people, and Goudie had had some complement-fixation with stomach extracts. So by that stage we have a whole series of diseases which were becoming generally accepted as being autoallergic, autoimmune, whichever way you like to call it. That had become fairly clearly established by the middle 1960s. Now, I would like very much to get a general discussion going here. There are many people in the audience who can comment. I think the person who should have first voice is Professor Sonny Doniach?

Professor Sonny Doniach:⁶⁰ I want to say a word in defence of the poor old histopathologists. You see, in those days, right up to the early 1950s, we were all used to seeing lymphocytes, plasma cells and histocytes in almost every chronic disease, from cirrhosis to syphilis and in cancer. Therefore, we almost had a rubber stamp which the surgeons used to call round-cell infiltration. The concept of this round-cell inflammation being specific in say, an adrenal gland in Addison's disease, was a little hard to take at first. Admittedly, we were very ignorant of immunology, as were many clinicians. The concentration had been really on phagocytes as immune defence.

Brent: Perhaps I can make two very brief points. One is in connection with what Peter Lachmann was telling us. He was talking about antibody-forming cells as scavenger cells. Interestingly enough, that concept was very much taken up by Burnet and Fenner in their 1949 monograph and they actually talked about antibody-forming cells as scavenger cells.⁶¹ Now we all realize that the 1949 monograph was critically important in the history of modern immunology, partly because of the hypotheses put forward, and partly because of the attention paid to Owen's work, which had been buried in *Science* since 1945 and no-one had paid any attention to it.⁶² In that connection, I think Ivan referred to the work of Billingham and Medawar and their colleagues on the cattle dizygotic twin story, and you might easily run away with the impression that they knew of Ray Owen's work and that was why they studied cattle dizygotic twins. In fact, during the course of writing my *History of Transplantation Immunology*,⁶³ I unearthed the fact that they didn't know about Ray Owen's work until way into their cattle work. Had they known about it, they probably would never have started, because Owen's very highly discriminating anti-red cell sera would have been far more easily applied to the problem they had set themselves, which was to find out whether they could

⁵⁹ Professor W J Irvine, Endocrine Clinic and Department of Therapeutics, Medical Research Council Clinical Endocrinology Research Unit, Edinburgh.

⁶⁰ Professor Israel Doniach FRCPATH, FRCP (1911–). Professor of Morbid Anatomy in the University of London, London Hospital, from 1960 to 1976; now Emeritus Professor.

⁶¹ Burnet F M, Fenner F. (1949) *The Production of Antibodies*. 2nd edn, New York: Macmillan, 33.

⁶² Op. cit. note 7 above.

⁶³ Brent L. (1996) *A History of Transplantation Immunology*. London: Academic Press, 488.

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distinguish dizygotic twins from monozygotic twins. This was a problem put to Medawar at a congress in Stockholm, by a Scottish veterinarian who thought this was a very important agricultural problem because of the sterility of the female dizygotic twin. And that is how Billingham and Medawar first decided to study this problem; and they didn't discover Owen's paper until they had read the Burnet monograph, and that was read by Peter Medawar in 1950, when they were well on the way towards completing their initial study. I am glad to hear that the 1949 Burnet and Fenner monograph is a collector's item, because I have Peter Medawar's copy of it, which he gave to me. I have looked through it and it is annotated by him because he was asked by *Nature* to review it. The review appeared in 1950. The English edition didn't hit this country until 1950, although it was published in Australia in 1949. So you might think that Medawar would have made a special note of the reference to Owen's work, but he didn't – it was totally ignored in his annotations. He made all kinds of other interesting annotations and in his review in *Nature*, which is unsigned but unmistakably Medawar (I have had this confirmed by the Editor of *Nature*), he doesn't refer to the Owen work at all, nor to the tolerance work. He refers to all kinds of other ideas which he was looking forward to investigating, but not to that. So I think this is rather an interesting historical snippet, because if Peter Medawar had known of Owen's work he probably wouldn't have started the cattle work which led directly into the tolerance work in mice.

Now, another interesting historical point: in 1950, a year after Burnet and Fenner had published their monograph, a couple of Russians published a very lengthy and discussive theoretical paper. One, an embryologist was quite well-known at the time. He was G V Lopashov and he, with a colleague, O G Stroyeva, published in a Russian journal a paper of which I have had bits translated. In that paper, interestingly enough, they are groping their way towards a self non-self hypothesis, very much on Burnetian lines. It's totally incorrect in many respects, but it was a muddled attempt to explain the difference between self and non-self on the sort of lines that Burnet had in mind. I think historically that is of some interest.

Professor Sidney Liebowitz: I should like to draw attention to another interesting aspect of the history of autoimmunity, namely the year gap between the formulation of the concept of autoallergy in the years 1900 to 1910 and the discovery of so many autoimmune diseases in the years after 1950. Why the 50-year delay? At least half a dozen auto-allergic phenomena were described in the early years of the century, including the Donath–Landsteiner and Wasserman antibodies. If you read the literature of the time it is clear that people were well aware of the possible existence of diseases due to immunity to self-antigens. The question is, why did it take half a century to discover them? I suggest that the answer lies in advances made in the technical and not the conceptual field. It is true that the work of Medawar and Burnet (and others) on the nature of self-tolerance exerted a profound influence on later developments in autoimmune research, but I suggest that the discovery of so many autoimmune diseases in the 1950s and 1960s was not primarily due to new theoretical insights, but to practical considerations and advances in technique. Take experimental allergic encephalomyelitis. In 1959 Kies and Alvord published a report of a meeting on the subject in which the word 'allergic' was in inverted commas, and those commas did not disappear until well

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into the 1960s.⁶⁴ I suggest that three significant advances contributed to the final recognition that this was an autoimmune disease. The first was the discovery of Freund's adjuvant which allowed the phenomenon to be reproduced reliably for study. It 'beefs up' immunological reactions – particularly cell-mediated reactions. They are exaggerated by Freund's adjuvant. That was the first advance. The second was the discovery that you could transfer the disease from one animal to another by sensitized lymphocytes. It was here that the work on transplantation and tolerance exerted an influence, on the practical, not the conceptual, level. And then finally there was the development of chromatographic techniques which allowed the myelin antigens to be characterized. A similar sequence of events can be demonstrated in the case of myasthenia gravis. The point I wish to make is that the discovery of so many autoimmune diseases in the 1950s and 1960s was not due to the development of new conceptual insights, but the cumulative effect of years of technical advance in immunology and chemistry.

Doniach: There was an interesting phase of research around 1905, when the Wasserman reaction was introduced and the complement fixation test (CFT) became available. Fiessinger and several other authors found that the serum of some patients with chronic liver cirrhosis reacted by CFT against human liver extract. Not many people believed in autoallergy or autoimmunity but they discussed this possibility.

Coombs: If I can just go back. Quite a few people have mentioned *Horror Autotoxicus* today, but I am afraid they have got it wrong. Ehrlich did not say you should not produce autoantibodies against yourself. He said just the opposite. He said a body does not usually allow autointoxications and that sounds sensible enough. And how do they do that? Well, once you have a sort of autotoxin, you have another autoantibody and another autoantibody, and now you are exactly down to the idiotypic anti-idiotypic network, which you only took up 100 years later.

Booth: I think you are getting a bit complicated for me.

Lachmann: I was just going to comment on what Sidney [Liebowitz] said: the whole of immunology went into considerable decline between the end of the First World War and the end of the Second World War. People got interested in other things and I think that in discussing the history of that time people do tend to forget how very little was actually known about the chemistry of it. Antibodies were only really recognized as chemical entities by Marrack in his famous report in the late 1930s.⁶⁵ Electrophoresis, which was the basis of showing there were gammaglobulins, wasn't introduced by Tiselius I think until 1939.⁶⁶ It was really

⁶⁴ Kies M W, Alvord E C. (1959) *Allergic Encephalomyelitis*. Ohio: Springfield.

⁶⁵ See Marrack J R. (1934) *The Chemistry of Antigens and Antibodies*. London: HMSO.

⁶⁶ A W K Tiselius won the Nobel Prize in Chemistry in 1948 for his work on blood proteins and for developing the technique of electrophoresis for their study. See Tiselius A, Kabat E A. (1939) An electrophoretic study of immune sera and purified antibodies preparation. *Journal of Experimental Medicine* 69: 119–131.

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only after the Second World War that immunological technology of understanding in the modern sense really appeared. And progress then happened very quickly, because there was this great resurgence of activity, associated with Robin Coombs; with John Humphrey, and with Robert White in this country (the founders of the British Society for Immunology) and with people like Henry Kunkel and many others in the United States.

Brent: I wouldn't at all disagree with the idea that technological advances were very important after the War. I would take issue with the suggestion that theoretical advances did not affect the attitude of people to the study of autoimmunity or to allergy, or whatever you like to call it – autosensitization perhaps, Robin – because there is no doubt that the concept of tolerance had a very profound effect on those interested in these phenomena. I will give you just two examples here of the impact it had. In our 1959 review on tolerance and autoimmunity, Peter Medawar and I wrote that there were two ways of testing the autoimmunity tolerance hypothesis that we put forward.⁶⁷ One, we said, was barely feasible, and that was to eliminate from the embryo some native antigenic substance that normally produces tolerance, and then challenge the animal later in life with that substance. If tolerance was really an insurance against autoimmunity, then that animal should respond against an antigen which had now become an autoantigen. And indeed, an American called Triplett actually did that experiment in tree frogs very successfully and this had a great impact at the time, showing that an antigen normally present can act as an autoantigen.⁶⁸ The other interesting point is that Patterson did some experiments in 1958 on allergic encephalomyelitis in rats, and he was able to induce the condition in adult animals by appropriate means, using, I think, Freund's adjuvant. He showed that by injecting the animals repeatedly in neonatal life with the antigen he prevented this autoimmune response. The animals had become tolerant to what was potentially an autoimmune antigen. So I think these concepts were milling around in the late 1950s and I am quite sure they had a powerful influence on the development of the field of autoimmunity.

Booth: Ivan Roitt would you like to comment?

Roitt: Yes. We know that there are a very wide range of autoantibodies which are made as part of normal life, as part of normal physiology, and the distinction has been made quite properly by Robin Coombs that there are some autoantibodies that are pathogenic and some which are not. Those are presumably not pathogenic but a part of normal physiology. When in the early part of the century people were immunizing with different tissues and raising autoantibodies they did find autoantibodies, but they didn't necessarily have a hypothesis that would make them see where to go with it. It is very much a question, I believe, of events coming together to make you feel more confident about a hypothesis, that you are prepared to put your own resources and time into it. And when Dacie showed the autoantibodies to red cells, one had a feeling that those could cause the red cells to

⁶⁷ Op. cit. note 26 above.

⁶⁸ See for example, Claman H N, Chaperon E A, Triplett R F. (1966) Immunocompetence of transferred thymus-marrow cell combinations. *Journal of Immunology* 97: 828–832.

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disappear. When we showed the autoantibodies in Hashimoto's disease at the same time that Witebsky showed that rabbits could produce a similar lesion, this made the hypothesis seem more likely. It's actually quite true today, we still haven't got any experiments that tell us what causes the lesions in human Hashimoto's disease. We are fairly sure that it's TH1 type cells, but we haven't actually got that proof, and we are not likely to get it because we don't run concentration camps in which we can make transfers of syngeneic sensitized cells into unsuspecting victims. But we have enough surrounding circumstantial evidence to say this is a good hypothesis to work on, it enables us to design treatment that works, enables us to design all sorts of things, and I think that is the important thing. The only autoimmune thyroid disease where we really think we have got excellent evidence for pathogenesis, is the neonatal thyrotoxicosis – mothers with thyrotoxicosis, with transplacental passage.

Booth: Thank you. David Tyrrell, I think, is next.

Dr David Tyrrell:⁶⁹ As a side issue, I want to mention that I was in New York from 1951 to 1954 in a laboratory just a few yards from Henry Kunkel's. People who worked for him were my friends 'on the house'. It looked to me at that time as though Henry Kunkel was mainly interested in antibodies and characterizing them, using electrophoresis, and myelomas as a source of material. I think he got interested in those girls with their liver disease, mainly because of their hypergammaglobulin and anaemia. In view of what Deborah said about people not being quite sure that antibodies were gammaglobulin, I should say that it was Slater, whose name you mentioned, who showed me how to do starch gel electrophoresis. That sounds a terribly crude method, but it did enable you to take the gammaglobulin out of a serum and study it, and find out what it would do and what it was. I used it to identify an antibody against a virus. Alex Bearn, who of course many of you know, looked after Kunkel's patients, but I don't think they ever really sorted out what was going on and the role of immunity. I was very interested, because I thought there might be an infection of some sort but at the time never got anywhere. You mentioned the Australians and Burnet's group. I remember being in Australia, not that much later, and they introduced me to the idea, which I hadn't really thought of before, that liver antibodies can be considered as an epiphenomenon in most cases. They are an indication that the liver has been damaged, often by a virus or something like that – and whether they are beneficial or whether they are accidental was not understood, but that idea was developing over there in the 1950s. So my thoughts are that there was a gradual upgrowth of a number of views which became integrated into a clear concept in the course of perhaps ten years or more.

Doniach: We should also mention the role of the fluorescence microscope. Bob White⁷⁰ found out about it from its American inventor when they served together in the Navy during World War II. He had one of the first models at the London

⁶⁹ Dr David Tyrrell FRS (1925–) was at the MRC Common Cold Unit at Salisbury from 1957 and Director from 1982 until his retirement in 1990.

⁷⁰ Professor Robert George White (1917–1978). Reader in Bacteriology, The London Hospital Medical School, later Professor of Immunology, Glasgow University.

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Hospital. I remember two formidable electric poles on special stands, with carbon rods. The current passed from one pole to the other and produced a sparking light which was directed through the microscope from a distance. The whole apparatus was in a separate dark room. It was quite a performance to get it started and it emitted noxious fumes.

In 1959 we had our first commercial fluorescence microscope in which the ultraviolet (UV) light entered below the lenses. This meant that the higher the magnification the weaker the illumination. In the late 1960s the newer models had the UV lamp above the lenses so that the high magnifications showed brighter immunofluorescence on the section.

This is a good example of how research may be retarded by technical problems. I looked for islet-cell antibodies like many other people with the older microscope and could not make up my mind whether the islet cells were positive or not when stained with the sera of diabetic patients. When Franco Bottazzo came to study with us several years later the new microscope was installed and he was able to demonstrate that insulin-dependent diabetes mellitus is indeed an organ specific autoimmune disorder in the same class as thyroiditis and pernicious anaemia,⁷¹ thus confirming the *post mortem* findings of Simmonds and of Bastenie. The fluorescence microscope generally was a great advance for autoimmunity since tissues can be examined in detail in an unfixed state.

Lachmann: The fluorescent antibody technique was introduced by Albert Coons in 1942, but didn't come to Europe until after the War. John Marrack used a stain, Trypan blue, or something like it to label antibodies. He hadn't, at that time, got the fluorescence microscope, but the idea of tagging and looking goes back to Marrack in the 1930s.

Professor Ian McDonald: A very small point, which may be of a little historical interest and that is the origin of the NZB (New Zealand Black) mouse which, of course, played such an important part in the development of the Walter and Eliza Hall Institute in the 1950s. It's origin was from Franz and Marian Bielschowsky, who were part of the diaspora from Nazi Germany during the 1930s and went to my old medical school in Dunedin in New Zealand. They were interested in endocrine factors in carcinogenesis and Marian Bielschowsky was inbreeding mice serially, and the NZB mouse was one of many which was thrown up in the course of their looking for other reasons. It has a whole range of apparently auto-immune diseases. Macfarlane Burnet visited and, of course, appreciated the potential usefulness of this mouse. And the other final small historical point to make is that Franz Bielschowsky was the son of Max Bielschowsky, the great neuropathologist who had done so much to elucidate a number of the genetically determined diseases of the nervous system earlier in the century.

Booth: To what extent then did the recognition of the NZB mouse have on people like Ivan and Deborah Doniach and others who were working on autoimmunity. Did it impinge upon your thinking?

⁷¹ Bottazzo G F, Florin A, Doniach D. (1974) Islet cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet* ii: 1279–1283.

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Roitt: It was one of the first examples of a spontaneous autoimmune disease in experimental animals. Most of the autoimmune experimental diseases had been induced, as Sidney [Liebowitz] said, with Freund's adjuvant or some other means and it's one thing to try and cure an experimentally-induced disease, but it is quite another to take a model which more closely resembles a spontaneous disease. So that was extremely important. It's actually quite interesting that, even to this day, we still don't know why the tolerance mechanisms fail in the NZB and in its cross with the New Zealand White which mimics systemic lupus. It's quite fascinating.

Booth: What I am trying to get at is to what extent did the New Zealand animal, which has been such a widely used experimental model worldwide since then, influence the thinking at the time?

Roitt: It strengthened the hypothesis that autoimmune processes could be pathogenic, because you could manipulate the animal, its genetics told you no matter how you bred it, as long as it didn't drift, that it was going to get autoimmunity; it's programmed to get autoimmunity. If you diminished the immune response in those animals by immuno-suppressants, you diminished disease. You were strengthening the hypothesis.

Booth: So we are not dealing with a seminal laboratory observation which then spread around. It's just part of a wider field of thinking?

Roitt: There aren't so many things that are seminal. I would say that Burnet's views in 1949, Medawar, Brent and Billingham's demonstration of tolerance, these were seminal. A lot of other things come together and build up. It's a question of building up a confident hypothesis that generally gets accepted.

Lachmann: John Humphrey once suggested to me (though I do not believe he put it forward) that the Jackson Laboratory should be given the Nobel Prize for developing inbred strains of mice. He pointed out, in my view, quite correctly that what really revolutionized animal immunology in the 1950s and 1960s was the development of inbred strains of mice. They enabled whole fields of immunology, which couldn't be done in any other way, to be developed.

Professor John Playfair:⁷² Following up what Ivan said about seminal discoveries, I don't think we should forget the work of people like William Weigle who was really the first person who systematically investigated the effect of injecting human thyroid into rabbits and pig into mice – showing you could induce an animal to lose tolerance to its own antigens.⁷³

⁷² Professor John H L Playfair, Chairman Department of Immunology, University College London Medical School, London.

⁷³ See Weigle W O. (1967) *Natural and Acquired Immunological Irresponsiveness*. Ohio: World Publications.

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Weigle was the one who had the idea. I remember this vividly, because at the time when I joined Ivan's lab, which was 1965, that was very much in the air. To mention another couple of names that might slip through the net otherwise – the book that influenced me most of all was by Glynn and Holborow because they used the Weigle type of experiment.⁷⁴ They were working at Taplow with the Medical Research Council at that time. They were groping for an explanation of why when you injected, for example, pig thyroid into a rabbit, the rabbit should start making anti-its-own-thyroid. It's very fascinating to read how they were groping towards the idea of two sub-populations of lymphocytes; they more or less said that the only way you can explain this is if there is one lymphocyte that recognizes one part of the protein and another one that recognizes the other part, and this was definitely before the T and B era. I think perhaps that Holborow and Glynn should get a bit more credit than they do.

Roitt: Lots of people have very good ideas and hypotheses, and lots of people really, had those ideas been put to experimental test, would have been Nobel Prize winners. This is the barren ground that has been fertilised by untested hypotheses and it is, I suppose, those who are in a position to be able to test the hypotheses, who reap the fruit in the end. It's only a very few theoreticians, like Burnet, who predicted what Medawar did. That was an excellent hypothesis for which he has got credit, but someone else tested it.

Booth: I remember Medawar once describing Burnet as 'that man that shared my Nobel Prize!' I think also there were clinicians involved in the Macfarlane Burnet unit and one man who deserves some credit at a clinical level is Ian Wood. He was the senior clinician in the Walter and Eliza Hall Institute at Melbourne Hospital and he collected together a whole group of patients with rheumatoid arthritis, liver disease, thyroid disease, or pernicious anaemia. He didn't do experimental work, he was purely a clinician who had trained with Russel Fraser at Bart's many, many years ago, and he described a whole lot of these things, and he had an impact on the thinking within that unit. It is a good example from what you have all described of the way in which scientists, clinical observers, clinicians with laboratories, altogether have brought an idea which comes up. I can well remember as a young worker at Hammersmith in the 1950s and even in the early 1960s, we were terribly suspicious about the whole concept of immunity and autoimmunity and I think those inverted commas you mentioned, Peter, [Lachmann] stayed at Hammersmith rather longer than they should have done. Who else would like to chip in?

Professor Maurice Lessof:⁷⁵ Just a reminder of the old idea that you need a bit of serendipity, but you also need the mind that is prepared. I was at Taplow in 1953, and Glynn and Holborow were then making very good LE cell preparations by putting paperclips in a heparinized bottle and shaking them up. They realized that if you could break up some of the polymorphs, the others would have an avidity

⁷⁴ Glynn L E, Holborow E J. (1965) *Autoimmunity and Disease*. Pennsylvania: Davis.

⁷⁵ Professor Maurice Lessof (1924–). Worked with Bywaters and Glynn from 1953 to 1935. Professor of Medicine at Guy's from 1971 to 1989, now Professor Emeritus.

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for the damaged nuclear material. But when they tried very hard to do the kind of analysis that Peter Lachmann did later, they either could not think it through or, perhaps, lacked the techniques that would make this possible.

Coombs: Could I just say one final thing? And this is really addressed to Peter Campbell because I think it is really a great shame that you gave up your studies on milk. It is not impossible that the milk proteins are a wonderful example which can give rise to neonatal tolerance: we certainly have evidence of that with cow's milk. If you feed it early enough, you don't get a response to it, but it makes me think that in fact perhaps that's why most infants don't respond to mothers' milk, because there's no reason why they should. As you know, in cows you can get a horrible autosensitization to the mother's milk, and it actually causes quite a bit of disease.

Campbell: Although I gave up that particular aspect of milk proteins, I went on with α -lactalbumin. There has been a lot of serious talk today, of course, giving the impression that people who do this kind of work know all the literature and so forth. I would like to say that Ivan and I were pretty ignorant people really. We were fools rushing in, and the work we did was not what we were being paid for by the Cancer Research Campaign; it was done purely on the side. We were very fortunate to have as our bosses, Dodds who only used to appear about one hour a day and Dickens, who did appear a lot, but was a very liberal-minded fellow who allowed us to do whatever we liked and was very encouraging. But I often think back. What would have happened if we had written a long grant application, where you had to mention every single pipette that you were using, what would have happened? We have important people here like Peter Lachmann, who I believe is now exceedingly influential in the scientific world.⁷⁶ I would just like to remind him and others, that they should allow fools to rush in and do very stupid experiments on occasions.

Booth: Well, at this stage we should draw the discussion to a conclusion, but I think Ivan Roitt ought to have the last word.

Roitt: First of all, I would like to say that it was an absolutely fantastic process and that the research life that I had with Peter [Campbell] and with Deborah [Doniach] was outstanding and I am very fortunate. I agree with Robin [Coombs] completely that one has to be fortunate in one's collaborators. I have been. And the other thing is that autoimmunity seems to get more and more complicated, in a way, in its aetiology. Take a model like the non-obese diabetic mouse, which spontaneously develops an autoimmune diabetes very similar to the human disease, both in terms of the pathology and the serology. One can map something like 12 different genes which are influencing the outcome, only one or two of which are within the MHC (major histocompatibility complex). This is an immensely difficult multi-factorial situation. However, if any one of those factors is important for the progress of the whole disease, you may only need to stop one of them.

⁷⁶ Peter Lachmann was then the Biological Secretary of The Royal Society.

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Booth: This has been a fascinating discussion of a concept that has influenced medicine, and to which Britain has made a very major contribution, particularly the individuals who are sitting beside me at this table today. It illustrates very clearly the ways in which clinical, scientific, and other developments all come together to bring a concept to fruition, to the extent that it is now standard textbook teaching. May I thank you all for your contributions tonight, thank the audience for coming along, and all those in the audience who contributed to the discussion.

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Endogenous Opiates

The transcript of a Witness Seminar held at the Wellcome Institute
for the History of Medicine, London, on 7 November 1995

Edited by E M Tansey and D A Christie *

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Endogenous Opiates

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Professor Lesley Rees:¹ Good afternoon ladies and gentlemen. Welcome to this Witness Seminar on Endogenous Opiates. The purpose of the Witness Seminars is really to stimulate debate and discussion of events in contemporary medical history, and are designed to encourage historians and scientists to consider the historical significance and context of recent advances in medical science. I am going to ask Dr Tansey to introduce the seminar.

Dr Tilli Tansey:² Before AIDS hit the headlines, there were few advances in biomedical science that resulted in immediate, full-length articles in *The Times*, TV documentaries or a successful paperback book.³ The work in the 1970s on endogenous opiates and their receptor sites achieved all those accolades. In 1973 three different research groups from Johns Hopkins, London and Uppsala, reported the existence of receptor sites in brain tissue that were specific for opiate molecules and to some investigators these findings raised an obvious question. ‘Why should such specific receptors for morphine exist in the animal brain?’ After all, morphine was a plant extract. The hypothesis was thus promoted that the body itself could produce a chemical substance which was similar to morphine that naturally stimulated these receptors, their activation by morphine merely being a fortuitous, if enhanced, mimicry of a naturally occurring reaction. And, indeed, there was already some evidence of such a substance, because the stimulation of pathways in the rat’s brain that resulted in analgesia could be reversed by the application of naloxone, a specific opiate inhibitor.

In Aberdeen there were two pharmacologists who had thought for some time that there might be an endogenous opiate. One was the Professor of Pharmacology, Hans Kosterlitz, an important, but now elderly and, unfortunately, incapacitated player in this story. He spent several years examining the pharmacology of the autonomic nervous system and in particular the effects of morphine.⁴ The second was his colleague John Hughes, a young lecturer in the department. In 1973 a specialized unit for research on addictive drugs was established in Aberdeen, with the recently retired Kosterlitz as its Director and

¹ Professor of Chemical Endocrinology and Dean of the Medical College, St Bartholomew’s Hospital, 1989–1995.

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³ Goldberg J. (1989) *Anatomy of a Scientific Discovery*. London: Bantam Books.

⁴ Professor Hans Walter Kosterlitz (1903–1996). In 1968 he became Aberdeen’s first Professor of Pharmacology, then in 1973 set up the Unit for Research into Addictive Drugs; one of its aims was to look for endogenous morphine. **In 1975 he was jointly responsible for the discovery of enkephalins.** In 1978 he was awarded America’s Albert Lasker Prize in Medicine and elected a Fellow of the Royal Society and won its Gold Medal in 1979. For a perspective on Kosterlitz’s career and the search for the endogenous opiates, see Kosterlitz H W. (1979) ‘The best laid schemes o’ mice an’ men gaft aft angley.’ *Annual Reviews in Pharmacology and Toxicology* 19: 1–12. Professor Kosterlitz died shortly after this meeting was held. See Hughes J. (1996) Hans Kosterlitz (1903–1996). *Nature* 384: 418.

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Hughes as his Deputy. It was Hughes who struggled in the abattoirs and labs of Aberdeen to extract from pig brain a morphine-like chemical. His efforts resulted in a paper, published in *Brain Research* in May 1975, in which he announced that he had indeed found a naturally-occurring opiate-like substance, but its chemical composition remained to be determined.⁵ This was to be the critical step, because after all it was one thing to report the discovery of a new substance, and an entirely different matter to say what that substance was.

Hughes needed help in upscaling his isolation and analytical techniques. The expertise of John and Linda Fothergill in Aberdeen's biochemistry department were added to the team, as was Barry Morgan from the pharmaceutical company of Reckitt & Colman, but the precise structure of the substance, which they called 'enkephalin', remained unknown. It was the further collaboration of Howard Morris, an expert on mass spectroscopy, that finally cracked the problem and in December 1975 a paper appeared in *Nature* announcing the identification of two different enkephalins.⁶ Both were short-chain peptides of five amino acids, the ultimate amino acid being leucine in one case and methionine in the other. The two became known as leu- and met-enkephalin. The paper was described in a *Nature* 'News and Views' feature by Leslie Iversen as 'a very important advance', and he predicted rapid progress in determining enkephalin's wide distribution, its physiological roles and in the development of further techniques and models to measure and assess it more accurately.⁷ These predictions became true almost immediately. Other labs, hot on the heels of the Aberdeen team, reported their own identification and synthesis of enkephalins and the structural relationship of enkephalins to other known biologically active chemicals, especially β -lipotropin, was elucidated.

The effect of that 1975 *Nature* paper can be measured by a number of conventional yardsticks of scientific discoveries – the numbers of papers on the subject, the citations of such papers, the national and international awards given to the scientists involved in the discoveries, and the numbers of specialist conferences and publications that increased rapidly during the following years.

But let's look a little at the historical context of that discovery. Despite some opposition to the idea of chemical neurotransmission, evidence during the 1950s and 1960s had emphasized the roles of two particular chemicals as neurotransmitters and, indeed, the orthodoxy had developed in some quarters that acetylcholine and noradrenaline were *the* transmitters in the mammalian nervous system. Increasingly evidence was accruing that other substances, such as dopamine and serotonin might also act in this manner. During the early 1970s there was an explosion of discoveries about the physiological function of small molecules that challenged those prevalent ideas about the role of chemical mediators in physiological functioning, discoveries greatly facilitated by technical advances in the use of radioisotope-labelling methods and in the development of more accurate and sensitive assaying techniques. Among those discoveries were the peptides as

⁵ Hughes J. (1975) Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. *Brain Research* 88: 295–308. *Idem.* (1975a) Search for the endogenous ligand of the opiate receptor. *Neuroscience Research Progress Bulletin* 13: 55–58.

⁶ Hughes J, Smith T W, Kosterlitz H W, Fothergill L A, Morgan B A, Morris H R. (1975) Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 258: 577–579.

⁷ Iversen L. (1975) Chemical identification of a natural opiate receptor agonist in brain. *Nature* 258: 567–568.

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hypothalamic releasing factors; single amino acids as neurotransmitters; a dazzling array of peptide hormones, especially in the gut; and the practically heretical suggestion from Burnstock in Melbourne that the purine ATP might be a neurotransmitter, and that the nerve terminals might contain a mixture of bioactive compounds involved in mechanisms of cotransmission and neuromodulation.⁸

So was the intellectual climate of the mid-1970s more appropriate and receptive, to the discovery and acceptance of new, unconventional, biologically active chemicals in a way that the preceding decade was not? With particular reference to the discovery of the endogenous opiates was it so much easier for these chemicals to gain acceptance after a receptor site had been identified rather than before? The use of relevant techniques is also of interest in this episode, because Hughes and Kosterlitz in Aberdeen were using what can only be described as a rather old-fashioned technique. They were using strips of smooth muscle to assay the morphine-like activity of their brain samples. It was a method used by Kosterlitz for many years and I think it was an important component of their success. Indeed after Hughes's first paper in 1975 a number of other labs started learning the method because they recognized its advantages over some of the more sophisticated binding techniques that they had used.

But there was more than that. The financial climate was also favourable. In 1971 President Richard Nixon, apparently horrified by the high percentage of heroin addicts amongst Vietnam combatants, declared a war on drugs. He coordinated all federal spending on drug abuse, thus making special funds available for research into drug addiction. Neuroscientists from other fields were encouraged to work in the area. One was Solomon Snyder, at Johns Hopkins. It was Snyder and his graduate student, Candace Pert who had been one of the teams to identify successfully opiate receptors in 1973.⁹ The Aberdeen unit had also benefited from some of the American money, although they also had funding from other sources such as the MRC.

We might well ask what was the effect of this American initiative? How much of the work on endogenous opiates and their receptors would have been done or accepted without it? Funding, of course, is a critical area of contemporary medical research. Other players in today's story were the pharmaceutical companies. For many years the hope of finding a non-addictive, opium-like analgesic had been a pharmaceutical company dream. All the major academic research teams I've referred to already, and others beside, had contacts, and in some cases contracts, with drug companies. The whole question of commercial exploitation that so bedeviled the exactly contemporaneous discovery of monoclonal antibodies, and which was the subject of our very first Witness Seminar in this series, seems to have been either absent or substantially diluted in the enkephalin story.¹⁰

And what about the idea of a critical mass of workers in the field? By the late 1960s there were several workers around the world studying the effects of narcotic

⁸ Burnstock G. (1972) Purinergic nerves. *Pharmacology Reviews* 24: 509–581. Burnstock G. (1976) Do some nerves produce more than one transmitter? *Neuroscience* 1: 239–248.

⁹ Pert C B, Snyder S H. (1973) Opiate receptor: demonstration in nervous tissue. *Science* 179: 1011–1014.

¹⁰ See Tansey E M, Catterall P P. (1994) Monoclonal antibodies: A witness seminar on contemporary medical history. *Medical History* 38: 322–327. Tansey E M, Catterall P. (1995) Technology transfer in Britain: The case of monoclonal antibodies. *Contemporary Record* 9: 409–444. The latter paper is reprinted with permission of the publishers, Frank Cass, in the present volume.

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drugs on the nervous system, but by international standards, they were not a large community. A small group of about a dozen interested researchers had met during the International Congress of Pharmacology in 1969 to form what became known as the INRC (International Narcotics Research Club). One of those founder members was Hans Kosterlitz. The club included pharmacologists from both academia and industry and it increased in membership during subsequent meetings, stimulated by Nixon's war against drugs in 1971, by the discovery of the opiate receptor in 1973, and by the Aberdeen results in 1975. A larger group of workers can have its own problems. Competition between groups becomes stronger, the race for results intensifies, and if anyone wants a readable and dramatic account of that race Jeff Goldberg's *Anatomy of a Scientific Discovery*, which describes the race to discover endogenous opiates, can certainly be recommended as a good read. Competition however creates its own problems. It raises questions about the roles of scientific communication and publication and who tells who, what, and when. This has been a very brief and necessarily curtailed introduction, but I hope it has provided a useful basis on which discussion and debate can now follow.

Rees: Thank you very much Dr Tansey. I'll now ask our first witness, Professor John Hughes, of the Parke Davis Neuroscience Research Centre, Cambridge for his comments.

Professor John Hughes:¹¹ I hope my memory serves me well – I see everyone else has brought sheaves of documents. It's really difficult to imagine academic research 25 years ago, and that Kosterlitz and I had our own particular interests, which coincided. We were interested in neurotransmission and how neurotransmission works. I was approaching it from the side of noradrenergic transmission and had been working in that area for a number of years, whereas Kosterlitz was more interested in cholinergic transmission. He had got interested in the mode of action of morphine, after Paton and Schaumann's seminal papers showing that morphine inhibits the release of acetylcholine in the myenteric plexus of the guinea-pig ileum.¹² That was really a very critical observation, because Paton never did anything nonquantitative, but that particular paper was semi-quantitative in the sense that Kosterlitz and his group took that preparation on and turned it into a highly quantitative assay for opioids of all sizes and descriptions.

It's very difficult to identify the point where one becomes obsessive about a particular idea and again one has to go back 25 years to the state of academic pharmacology and academic research, in general. When one met colleagues in the tea room, in the lab, when one had the time to exchange ideas, and wasn't afraid to reveal one's innermost scientific thoughts in those days, there weren't any scientific audits. Just before this meeting today, Howard Morris and I were talking about how academics spend all their time filling in forms these days, not talking in the

¹¹ Professor John Hughes, FRS, Lecturer in Pharmacology, University of Aberdeen 1969–1977. Now Senior Research Fellow Wolfson College, University of Cambridge since 1983. Director Parke-Davis Neuroscience Research Centre, Cambridge University since 1983.

¹² Schaumann W. (1955) The paralysing action of morphine on the guinea-pig ileum. *British Journal of Pharmacology* 10: 456–461. Paton W D M. (1957) The action of morphine and related substances on contraction and on acetylcholine output of coaxially stimulated guinea-pig ileum. *British Journal of Pharmacology* 12: 119–127.

tea rooms. I'm in the fortunate position of not having to do that, of course. It is hard to pin down when a certain idea or sequence of events hardens into a course of action. I joined the Department of Materia Medica, which was then incorporated into the Clinical School at Aberdeen in 1969, and shortly after that we split off into a separate Department of Pharmacology and it was sometime during 1970 that I think the idea began to circulate within the group of scientists, I wouldn't say just our group, because there were a number of groups of people working in the department, the idea that there has to be something more to morphine than just inhibiting acetylcholine release.

Later, as my PhD student Graeme Henderson showed, it also inhibited noradrenaline release from certain neuroeffector junctions and it was really that, the observation of morphine in action if you like that stimulated us. You refer to the importance of bioassay, Dr Tansey. Of course, binding assays are great, they have advanced the cause of pharmacology and our understanding no end, but, and I still say this to students, there's no substitute for seeing a drug working. You don't see anything working in a binding assay, I'm afraid not even with a scintillation counter these days, because everything is on line. To see morphine being added to a tissue bath, to watch it inhibiting the twitch of the smooth muscle, and then to be able to show that that the action is directly attributable to the inhibition of neurotransmitter release is a more powerful argument for something fundamental going on than anything else.

You [Tansey] also mentioned the landmark opiate receptor binding papers, because after the insulin receptor, of course, the opioid receptor was the first one to be identified in such a way. It's rather strange that although it was the first of the neurotransmitter receptors, if I can call them that, or endocrine receptors, to be identified in that way, the opioid receptors are one of the last to be cloned. It's a very strange sequence of events really. It went quite against expectations. I think we'd fastened on our ideas well before there was any hint of binding studies. I've often been asked this and Kosterlitz was asked it as well, 'how did this influence our thinking?' It influenced it in the sense that when I was writing the *Brain Research* paper where we first formally reported our observations, those papers were quoted as 'bricks in the wall', but the argument was already there before opioid receptor binding was established and really didn't influence us directly in terms of our research.¹³

From my personal point of view, I think that the reason I got interested in searching for an endogenous opioid-like substance is that I had been previously involved during my PhD student work in looking at non-adrenergic, non-cholinergic innervation of various blood vessels and that's what my PhD thesis was eventually written on. I didn't do any biochemical work on it, because at that time there didn't seem to be any way forward. Burnstock, as you mentioned, was publishing on ATP at that time, and ATP was one possibility.¹⁴ We now know, I think, that the neurotransmitter, or mediator, that I was working on at that time was probably nitric oxide. So I am glad I didn't go on searching for it! But, you know, the idea was already there, that there were unknown substances in the nervous system and it would be nice to identify some of them.

¹³ Op. cit. note 5 above.

¹⁴ Burnstock G, Campbell G, Satchell D, Smythe A. (1970) Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. *British Journal of Pharmacology* 40: 668-688.

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The other argument that was put forward at the time – lots of things went backwards and forwards when you think about it – was that there must be a role for morphine because there's a receptor. I remember very well, a very distinguished professor of pharmacology turning round to me and saying 'well, you know, there's a receptor for carbon monoxide, is this an endogenous mediator?' and I said 'of course not'. Well according to Snyder, it is now.¹⁵ But I didn't have that argument at hand at the time. Because something affects physiological events, can you necessarily say intuitively 'yes, there's got to be an endogenous factor mediating that'. When Lars Terenius came to work with us in the labs for six months in 1974, I think, or late 1973, he was still very dubious about what his results meant. He was working exactly in parallel with us, he had the idea at about the same time, he was the first person to use opioid receptor binding to look for an endogenous substance and, before that, he was the only other person to have gone into print.¹⁶

Many people I am sure had similar ideas, the only other person to go into print in addition to Terenius that I am aware of was Avram Goldstein. Avram theorized that if there was a morphine-like substance, although it might not be morphine it would be similar to morphine, and therefore should be recognized by morphine antisera. He did the experiment by mashing up brains and couldn't get any reaction to morphine antisera and I think he actually published a paper, I can't remember where the paper is now, but he certainly went into print saying that there can't be an endogenous morphine-like factor, because we got a negative response.¹⁷ These things always have interesting run-ons, don't they? Several years later Sidney Spector published his data on morphine immunoreactivity in the central nervous system.¹⁸ Then in the last few years Goldstein has published his studies on the existence of morphine in the central nervous system, and has come to the conclusion that there are very small amounts of morphine that occur naturally in the brain.¹⁹ It raises a lovely question, because there are only vanishingly small amounts. They are there however. Goldstein has proved it, I think, quite unequivocally, but it hasn't excited anybody.

I don't know of any groups, even Spector's, that are working on this any longer and it raises the question of even if you do find something like that, what significance does it have? My feelings are that it's a bit like cocaine, you know, there is a story, I don't know if it's true or not, that there's more cocaine in

¹⁵ Verma A, Hirsch D J, Glatt C E, Ronnett G V, Snyder S H. (1993) Carbon monoxide: a putative neural messenger. *Science* 259: 381–384.

¹⁶ Terenius L. (1973) Characteristics of the 'receptor' for narcotic analgesics in synaptic plasma membrane fraction from rat brain. *Acta Pharmacology and Toxicology Copenhagen* 33: 377–384. Terenius L, Wahlstrom A. (1975) Search for an endogenous ligand for the opiate receptor. *Acta Physiologica Scandinavica* 94: 74–81. For a retrospective view and a discussion of opiate receptors and addiction, see Terenius L. (1992) Opiate receptors – the historical breakthrough in drug research. In Wonnacott S, Lunt G G. (eds), *Neurochemistry of Drug Dependence, Biochemical Society Symposium* 59: 13–25.

¹⁷ Schultz R, Cartwright C, Goldstein A. (1974) Reversibility of morphine tolerance and dependence in guinea pig brain and myenteric plexus. *Nature* 251: 329–331.

¹⁸ Gintzler A R, Levy A, Spector S. (1976) Antibodies as a means of isolating and characterizing biologically active substances: presence of a non-peptide, morphine-like compound in the central nervous system. *Proceedings of the National Academy of Sciences USA* 73: 2132–2136.

¹⁹ Goldstein A, Barrett R W, James I F, Lowney L I, Weitz C J, Knipmeyer L L, Rapoport H. (1985) Morphine and other opiates from beef brain and adrenal. *Proceedings of the National Academy of Sciences USA* 82: 5203–5207.

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circulation on the backs of dollar bills than was ever being smoked or inhaled or whatever. You can actually apply cocaine tests to virtually any dollar bill in the United States now and you will detect cocaine.

I was talking about the differences in academic life 25 years ago and I think one issue I always return to is what would have happened if I had been left alone just to work quietly in my lab. That was what I was doing before we moved down to Foresterhill where we set up the Institute for Research on Addictive Drugs, I was just working on the idea and quietly extracting guinea-pig and rabbit brains when I could get hold of them, and getting the odd response but nothing terribly positive, although determined to go on with it. We then moved on and set up a focused drug discovery programme to do with addiction, and looking for the putative endogenous substance was only a minor part of that programme.

The major part of our programme was to look at the whole problem of addiction. It's not that Kosterlitz did not believe in the concept, Hans and I were enough in tune to know that we both believed that there must be endogenous-like ligands, it made sense. Hans's attitude was it would probably be far too difficult to look for it and really it might not solve anything anyway, but he humoured me in the sense that he said, 'okay, you can do that bit of research', because he knew I wouldn't go down to Foresterhill and join the unit if he didn't say that and I wouldn't write up a joint grant application. These things are kind of balanced, but it was almost, you know, a question of 'tolerating Hughes', the well-known eccentric, which I admit I used to be in those days, so that we can get on with the major business which is combating addiction. And I guess out of that arose some interesting incidents which I have talked about before. The first was that I got positive results quite early on, once I began to focus on that problem and that problem alone. If I'd been working on my own in academic labs of pharmacology, I would have quietly gone on beavering away and I wouldn't have said anything until I was absolutely certain and at least had a paper partly written or whatever. Hans went to a meeting of the INRC at Cocoyoc in Mexico, I think it was very early in 1974. He was in Washington on the Committee of Problems of Drug Dependence then, he went on to Cocoyoc and he couldn't contain himself, very much to my annoyance. He came back from that INRC meeting and said 'we've been invited to a meeting they're setting up in Boston, a Neuroscience Research Programme meeting on opioid receptors and endogenous ligands' and I said 'what?'. He said 'yes, I told them about your work' and I was incandescent with fury, I really was. In those days I did have a bit of a temper as well and I really told Hans what I thought of him. It was one of the few times we really did fall out, because I thought he had made a very bad mistake. I've always had the highest admiration for Americans and American science, having worked in the States for a number of years myself, but I know, as do most of us, how competitive American science is. It was very difficult then, and probably still is very difficult, for a British scientist, given the much poorer resources that we have in this country, to compete with large well-funded research teams. You [Tansey] were talking about the question of funding, of course once money began to flow from the National Institute on Drug Abuse (NIDA) there were some very well-funded research teams, with very focused aims.

Rees: Do you think that that had a material effect on subsequent events?

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Hughes: I can only speak from a personal point of view. Yes, it would have taken longer to identify the enkephalins, there's no doubt about that, because I would have worked at a slower and more measured pace. I think there would have been a lot more dotting of the 'i's' and crossing of the 't's' as well. Given the very competitive circumstances, once one knew one was competing, you either had to grit your teeth and go for it, or not. Lars Terenius was quite unequivocal. He said 'I'm not going to compete, I'm stopping now' and he would have nothing to do with it, nothing to do with it whatever.

Rees: What argument did he put forward to you about that?

Hughes: He never really explained completely. I sensed that there were two reasons. One, Lars is quite a reserved person, a bit like me, he likes to work cautiously and wait until all the evidence is in, and two, I think he very much doubted whether one could compete effectively against the Americans. He knew how the Americans operated. And both Hans and I suggested we should all join forces, and he wouldn't have any of it. We said we would share, we had shared all the information with him anyway, and once we realized he was working along the same lines, then we said look we'll continue to pool and you could do this and we could do that and we could probably move very fast, but no, he wanted nothing to do with it at all.

I guess at that point also the recognition dawned that we would need lots of collaborators on this particular project. What started out as a man and a boy, or a man and a girl because my technician, Helen, was an indefatigable supporter in those days, had to turn into really a team effort. And just going back to your point of how this altered things. I had already written the paper to *Brain Research*, with myself as the sole author, because I had done the work and developed the concept, Hans was given due credit for discussions and so on, but it was my work quite clearly and Hans accepted that and there was no argument within the labs. But immediately the paper was published Hans was inundated with telephone calls from his colleagues and friends saying 'why isn't your name on that paper?' I think neither of us had actually thought about it. We had published together and independently before that. There was no jealousy or rivalry there, it was just that this is the way that particular paper turned out, but the response of people who read that paper made us both stand back and think. And we went out for a beer, several beers in fact, and discussed it with absolutely no acrimony at all, except Hans was clearly worried about peoples' response, saying 'what's wrong, why isn't your name on it?'. That concerned him more than anything else. There and then, in the pub, we decided that all future papers from the lab, and I know in today's politically correct climate this would probably be considered wrong, would bear both our names. Now within Parke Davis, who fund my research, you're simply not allowed to do that.

I don't put my name on all papers coming from my Research Institute, just because I'm the Director and I wouldn't dream of doing it, but that was what we decided then. But it was not a decision to get more publications. It was a decision to say this is joint research and this is the imprimatur of the leadership, to which one had greater or lesser intellectual input. Obviously there are some papers where

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you have lesser intellectual input and others where you have more. Rather than argue the toss and say 'oh gosh, it's only five per cent on this one or so on', forget the arguments, just put the names down. I think that's what most sensible research groups would agree to do. But that changed things. As I say, once one knew there was a race on, it took a bit of the fun out of it. In fact, the years from 1974 to the end of 1975 were very stressful for me. As a young lecturer in the University, I had just got a senior lectureship and knowing that I was stepping outside the normal academic route to professorships or whatever, it was quite a gamble to go and set up the Research Unit at Aberdeen. Although I had some promises that I could step back into the Department of Pharmacology, I knew full well that it might not be an easy thing to do at the end of the day. That was a dangerous enough step to take. I suppose these days people say 'gosh, you were lucky to have a job that even offered five years', but things were different in those days, because there was security within the university system then. But the other decision was to embark on the enkephalin project, and this gave me many sleepless nights, to the exclusion of my personal research on anything else. This was also very dangerous, because the whole nature of looking for endogenous molecules, particularly when one's involved in a race, means you don't publish very much. There's only one result that actually means anything and that's the structure at the end of the day, I'm sure Howard will agree with that. Howard always used to moan about nonquantitative biologists when we got together and say 'come on give us the numbers boy, it's only the sequence that counts'.

Rees: It's not as bad as what he used to say about clinicians [laughter].

Hughes: Oh well, he's absolutely right there of course [laughter]. Well, you asked me about the beginning, they were some of the main impacts. It wasn't so pleasant at the time. Having said that though, being part of the opioid research community, which as Dr Tansey said, was a relatively small community, was pleasant. Meetings of the International Narcotics Research Club never usually exceeded more than 250 or so and I guess there was a core of 100 people worldwide. That makes it a very tightly organized and related community and one of the nice things about doing science, I think for most of us who have stayed in science and been involved in various projects, the greatest pleasure is those relationships. There's no doubt about that. The cut and thrust of scientific meetings, plus the social aspects of it. That is the scientist's life.

Rees: Well, thank you very much Professor Hughes. That's fascinating and I think we'll move straight on to hear from Professor Howard Morris of Imperial College.

Professor Howard Morris:²⁰ I should say something of my background as John was just joking about my views of pharmacologists, but my excuse is that my background is obviously a little more rigorous than a pharmacologist's background would be in the sense that I had a training in classical chemistry. In fact my first

²⁰ Professor Howard Morris FRS, Imperial College Lecturer, Department of Biochemistry from 1975 to 1978, Reader in Protein Chemistry from 1978 to 1980. Professor of Biological Chemistry, Imperial College, University of London since 1980.

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degree was mathematics, and I came into the field of mass spectrometry, training first of all for a PhD as a protein chemist and then swiftly moving on after about a year into my PhD research, to look at the then newly emerging technique of mass spectrometry for the structural elucidation of chemical and biologically interesting molecules.

Just a word about what mass spectrometry is for those of you who don't know too much about it. It's basically a technique that is able to analyse substances by first of all ionizing them and, if you like, pumping internal energy into the molecule. The molecule then breaks apart into lots of different fragments and the job of the mass spectroscopist is to try and interpret the mass spectrum produced, that is the spectrum of all the masses of the little fragments which the molecule has broken down into, back into what the original structure must have been. It's empirical methodology, there are no golden rules for ways in which molecules fragment and that's one of the things that makes it a quite interesting and exciting science to go into.

In relation to the enkephalin project and meeting John, I'd moved from Leeds where I did my PhD work to Cambridge in 1970, first of all to the University Chemical Laboratory, and then to the MRC Laboratories in Mill Hill.²¹ I think I'd given a seminar there at some stage or other which I fancy Leslie Iversen²² had attended, because I was working in my lab early in 1975 and I got a call from Leslie who told me that I really ought to attend one of his seminars, because he had a young interesting chap by the name of Hughes who had an exciting substance of unknown structure which I ought to be interested in as well. I think that was February 1975 and I went along to John's seminar to hear about, I think you were calling it substance X in those days?

Hughes: Naloxone reversible activity.

Morris: Okay. I listened to what was known about it at that stage in terms of isolation and purification and characterization and John mentioned that they didn't know a great deal about what the molecule was. It had a few amino acids in the structure, but a very unusual UV fluorescence spectrum which was reminiscent of the amino acid tryptophan, but didn't have the same λ_{\max} as tryptophan and therefore wasn't tryptophan itself. At the end of John's seminar, I don't know whether he remembers, but I asked him, taking my cue from Leslie, 'had he thought of using mass spectrometry to try to determine the structure of the molecule?' Because this was a technique that could be applied to unusual and unknown structures as well as to newer novel structures, John's reply was 'yes he had thought of that and it didn't work'. So he had tested it and it didn't work and he was very abrupt with me. He had used a mass spectroscopist, presumably in Aberdeen. So, tail between the legs, I left the seminar as soon as it finished, not wishing to press myself upon the problem.

A curious turn of events took place a while later, because I was switching laboratories also during 1975 from Cambridge to Imperial and was giving a seminar at Imperial in July that year. The subject of my seminar was the way in which mass spectrometry had been used to discover the new amino acid γ -

²¹ The National Institute for Medical Research.

²² Iversen was then the Director of the MRC Neurochemical Pharmacology Unit in Cambridge.

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carboxyglutamic acid. The theme of the story was that this was a discovery which could not have easily been made by classical protein chemistry techniques, and indeed was not made by classical protein chemistry techniques, not only because almost by definition you can't make discoveries of that type by classical methods, because they use reference compounds, and this turned out to be a new amino acid, but also because in the process of doing classical methodology you can often convert what is a natural substance into something else. That indeed was the case with γ -carboxyglutamic acid, which was easily decarboxylated into ordinary glutamic acid during classical protein chemistry and would therefore be missed.

The subject of my seminar was how mass spectrometry led to its discovery. At the end of that talk I was approached by a wild-looking bearded red-haired gentleman, who came down to the front of the audience and introduced himself as Barry Morgan,²³ again another guy whom I had never met before and I didn't know. He said he was a colleague of John Hughes and he thought the methods I'd been talking about were interesting and wouldn't I like to study John's compounds and I said, 'well, you may not know it, but I have already been rejected for the position'. What happened after that, I'm not too sure, but presumably he had discussions with you, John, in the weeks following and I then got a call from John round about mid-summer or so to try and set up a collaboration which I think started at the beginning of August. Barry Morgan, I remember, brought the sample down on that first visit, and the procedure he used was to make a volatile derivative.

One of the disadvantages of mass spectrometry is that in those days you had to make a volatile derivative of whatever you were studying, because the molecule had to be in the gas phase before analysis. So I took about two-thirds of the material and derivatized it with reactions called acetylations and permethylations and after a few hours the sample was then ready for analysis by mass spectrometry. It was a very, very exciting moment, of course, getting the information. I should perhaps on a philosophical point, point out that the strength of the technique is that you can visualize things that you wouldn't easily be able to visualize by other methods. For example, one had to have a totally open mind as to what this material could have been. In fact, I refused to accept any information – John already had some partial sequence information at that stage. We didn't accept that because it can cloud your judgement when interpreting the spectra later. All we knew was that it was probably a molecule of about a 1000 Daltons from John's gel data with the unusual feature of the tryptophan amino acid. So it was very exciting when the spectrum developed. I should add that in those days I was pretty proficient in interpreting spectra. I'd done virtually complete sequences of several proteins using this new technology, so I'd sequenced thousands of residues of unknown structures and I'd got myself to the stage where as I'm counting up the mass spectrum I could be signing the sequence and it would take me usually, say, 15 or 20 minutes, to sequence a peptide of say ten residues in length. So I started counting the spectrum and I was saying look it looks like a tyrosine, a glycine, and Barry Morgan was saying 'yes, yes', he was getting so excited, and I got to the phenylalanine and then the spectrum was quite strange. I could possibly assign

²³ Barry Morgan has worked at Reckitt & Colman. The organizer was unable to locate him to invite him to this meeting.

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other amino acids in the spectrum, but there were signals that were not immediately explicable.

The philosophical point I was making is that as a structure elucidation person you have to be extremely careful, of course, about the assignments you make and one thing which perhaps doesn't come across when you look at the answer, is that you have to realize there was no way of knowing this was just an ordinary peptide. In fact, we thought the reverse was true, that if it was a peptide, then it was modified in some way. So I couldn't, unfortunately for Barry, give him an absolute complete assignment at that time. I said that I needed to study it further to assign some of the signals we couldn't assign immediately and I then did a deuteration experiment, that is labelling with deuteromethylide to distinguish between the methyl groups we'd put on ourselves and those that might have been there naturally. It was about a week or slightly more of reflection before finally the penny dropped and I could assign every peak and spectrum to, not what was expected to be a long and single molecule, but rather a mixture of two molecules which were very, very similar except in one position, so the signals were the same for the bulk of the sequence and only the last residue was different; interpreted as Tyr-Gly-Gly-Phe-Met and Tyr-Gly-Gly-Phe-Leu.

I was naturally very very excited at that stage and I must admit to not telling John the answer instantaneously, because I had to do one more experiment to confirm that assignment. As I said, this thing could have been anything under the sun, it could have been cyclic or whatever, and I wanted to do one more experiment and so John made up a new preparation of the material. The experiment involved a cyanogen bromide digest that should have shifted the methionine signal down to a homoserine while having no effect on any other signal in the spectrum, if the interpretation was correct. And sure enough we did that experiment, just one signal changing the spectrum, so it was certainly the solution to the structural problem and that's when I reported it to John.

After that, I understand that Barry then synthesized the materials and I think there's an amusing anecdote there John, isn't there? Because I got a telephone call from Barry Morgan saying, 'are you sure about this structure Howard?', and I said, 'why, what's the problem?'. He had apparently synthesized one of the structures and not got biological activity in your assay, is that right John? It was the leucine enkephalin?

Hughes: It wasn't that. No, I remember what he'd done. He'd actually synthesized a slightly longer version of the peptide and knew that the sequence was wrong, but he said 'try it anyway' and it worked. That was the problem.

Morris: He wanted to be certain that the structure was correct. But there was no way that it could be wrong, because when he synthesized the two pentapeptides, mixing them together and looking at the mass spectrum again, they were identical. The only other interesting part of the story after the structure elucidation was that I didn't anticipate small peptides like that to be synthesized nonribosomally and therefore we started to look for possible precursor molecules in the literature. We didn't do a very efficient job of it, I have to say, for one reason or other, apart from anything else I was moving laboratories to Imperial. We did a little bit of library

work with the *Atlas of Protein Sequence and Structure*²⁴ and came across things like Tyr–Gly–Gly, which I think was the nearest I got, which is in silk fibroin.

The other fortuitous event was a seminar which Derek Smyth gave at Imperial College at the beginning of October about a month or two after I had done those structures. He was giving a talk on a totally nonrelated subject which was lipotropin and one of his slides was an enzymatic digestion point where he was artificially digesting the molecule, trying to mimic what might have been happening in nature; he had the sequence Lys–Arg–Tyr–Gly on this slide and I, of course, had been screening for Tyr–Gly–Gly–Phe–Met or Phe–Leu sequences. So I asked him at the end of his seminar what came after the Tyr–Gly in the β sequence, and of course he didn't know that, you don't carry that information around in your head all the time. But when the seminar chairman brought him round to see the mass spectrometer facility, the new one we had at Imperial College, he said 'Oh I've probably got that sequence on one of my slides somewhere'. So he pulled a slide out and I got a little magnifying glass out and almost fell through the floor when I saw the methionine-enkephalin sequence, Tyr–Gly–Gly–Phe–Met, and then onto 31 or so residues of sequence.

Rees: Is that how it was? Sorry to interrupt you Howard, but I have a sort of fantasy about those days that Derek had the amino acid sequence of β -lipotropin actually up on the screen and you spotted the sequence in there. That wasn't true? [Morris: No]. Well, Derek, put the record straight then.

Dr Derek Smyth:²⁵ Well, at that time my group were studying the biosynthesis of ACTH and lipotropin (LPH) and we'd isolated their constituent fragments formed by processing at paired basic residues. Among these peptides were residues 1–38, 41–58, 61–87 and 61–91 of lipotropin. The 41–58 peptide was already known as β -melanocyte stimulating hormone but the others hadn't been reported before, so I named them the N-fragment, the C'-fragment and the C-fragment of lipotropin.²⁶ When I gave the talk at Imperial College I described, in detail how I isolated and identified these fragments, including the 61–87 and 61–91 peptides (later named β -endorphin 1-27 and β -endorphin 1-31). We had actually isolated these peptides a year before enkephalin was sequenced, but named them after their biosynthetic origin since we didn't know what their activities were.

²⁴ Day M O. (ed.) (1972) *Atlas of Protein Sequence and Structure*, Volume 5. National Biomedical Research Foundation, Washington, D–307.

²⁵ Dr Derek Smyth, Head of the Laboratory of Peptide Chemistry at NIMR, Mill Hill from 1971 to 1992. Members of his group at the time included Alan F Bradbury and Chris R Snell. Dr Smyth provided a larger account of his discovery of β -endorphin and the relationship of that research with the studies of Hughes and Morris, Smyth to Tansey, 31 March 1996.

²⁶ Bradbury A F, Snell C R, Smyth D G. (1975) Biosynthesis of β -MSH and ACTH. In Walter R, Meinhofer J. (eds), *Chemistry, Structure and Biology*. Michigan: Ann Arbor Publishers Inc., 609–615. Bradbury A F, Snell C R, Smyth D G. (1976) Prohormones of β -melanotropin, corticotropin and lipotropin: structure and activation. In Porter R, Fitzsimons D W. (eds), *Polypeptide Hormones: Molecular and Cellular Aspects*. North Holland: Elsevier, Excerpta Medica, 61–65.

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In fact Jim Edwardson²⁷ had invited me to give the talk at Imperial because we were collaborating together in a search for their biological activities. As it happens, we had isolated these peptides from the pituitary, so we were looking for possible peripheral roles, such as inhibition of insulin release or an action on sodium transport in the kidney and it didn't occur to us that they might have central activity. It was the breakthrough made by John and Howard, showing that the enkephalin sequence has opiate properties (though not analgesic), which led us to discover that one of the peptides we'd isolated was in fact an extremely potent analgesic agent. As you know, we found that β -endorphin (the C-fragment of lipotropin) is about 100 times more potent than morphine and its action lasts for up to six hours.

It was a very exciting peptide; but we didn't know what its properties were before John and Howard described their work on the enkephalins, the starting pistol in the opiate field was certainly the identification of the enkephalin sequence. We were working in another field, looking at pro-hormone fragments in order to identify a pro-hormone to adrenocorticotrophic hormone (ACTH), and by serendipity our work *converged* on the field of opiate peptides. Of course, after this we went on to study our β -endorphin and its related peptides in great detail. So, at the lecture I gave at Imperial College, I described the isolation of two peptides that started with the sequence Tyr-Gly-Gly-Phe-Met and showed that trypsin cleaved a model peptide from lipotropin rapidly and specifically to release Tyr-Gly-Gly, pointing to function for the C-fragment. It was this, I think, that caused Howard to jump up in the middle of my lecture and point at the slide, saying but, but, but.....

Morris: No, that's not true.

Rees: This is all mythology, then, and it's very upsetting, because I've actually got a cartoon slide, showing Derek at the blackboard and Howard leaping up out of the audience. Would you like to put the record straight?

Morris: That's not true at all. I didn't stand up at all during the lecture, I asked you the question did you know what the sequence was at the end, but you didn't.

Smyth: My clear recollection is that Howard did exclaim during the middle of my talk!

Morris: No, that is not true. I found the sequence, if you recall, when you came down to the laboratory after the lecture. Do you recall pulling the slide out, and with the magnifying glass was the only time we could see the sequence at that stage? When you put large sequences on a slide to be projected you can't see them all at once. And that was the point at which I saw the met-enkephalin sequence, on the slide with the magnifying glass, do you recall that? And that is the point at which I realized the significance of the C-terminal molecule with respect to the

²⁷ J A Edwardson was then at Imperial College. He later became head of the MRC Neurochemical Unit in Newcastle.

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opioid activity and I couldn't tell you the detail of what our discovery was, but I said would you be kind enough to let us have some of your sample for John's assay. It didn't arrive, unfortunately.

Tansey: Could I just ask a question here about Barry Morgan, because we tried to find him for this meeting and we weren't able to. He was at Reckitt & Colman. How had he become involved in this story?

Hughes: That's quite an interesting one. Hans Kosterlitz was a consultant to Reckitt & Colman, as I was in later years, and he'd got to know Barry Morgan as a young and upcoming chemist interested in opioids, they were doing work on buprenorphine at the time. Barry was a peptide chemist and believed in peptides and once he knew that we were looking for a peptide, he suggested to Hans that he might join the team. So I went down to Hull²⁸ and had a chat with him and he said he would be able to help in various ways, we were having problems with the slaughterhouse in Aberdeen at the time, it was being closed down because it was so unhygienic, not due to me [laughter]. It was a pretty awful place and I was facing losing my supply of pig brain and Barry offered to try to secure a supply, and to use the facilities at Reckitts to do a mass production. I was still really not even doing a pilot plant, it was still a lab bench extraction of all the brains, it was very hard and arduous work and took a lot of time to grind up all the brains and extract them. And he said 'well you know we can do this in a week'. 'If you come down to Hull, we'll get half a ton of brain and we'll use the big stirring things that they have in pharmaceutical companies, you know the 500 gallon vats, and we can get 500 litres of acetone and mash it up'. These were quantities that I had never dealt with, but quite normal in industrial processes.

So that's what we did. And of course it was an absolute disaster. What happened was that we had a very successful extraction and I ended up with a five-litre flask of material which I took back to Aberdeen and started to put through my chromatographic procedures. I put it on one rather primitive HPLC column that I was running at the time, which was fairly effective in isolating the enkephalins as we were calling them then, from the rest of the material. But before I did this I always did an assay of the crude extract. So I did a bioassay just to know how much I was starting with, which is standard practice, of course, and the response I got was just totally atypical. Normally, if you take an extract of enkephalins or most of the opioid peptides in the bioassay, you get a nice quick inhibition of the muscle twitch, then when you wash out, it comes back fairly quickly, except for dinorphin and β -endorphin that tend to be a bit longer. But this activity was obviously quite different, because it just wouldn't wash out, but if you put in naloxone it did come back, but again the response was different. This is where some of the advantages of dynamic pharmacology emerge. In a binding assay you can say it competes with naloxone, but you can't say how fast it competes with naloxone. In vas deferens or the guinea-pig ileum you can, and it was quite clear that naloxone would reverse this material, but it was doing it ever so slowly. Then when you washed naloxone out of the bath, the inhibition would come back again, so that the inference was clear – there was some very long-lived, long-acting

²⁸ Hull was where the main research labs of Reckitt & Colman were based.

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material present that we hadn't seen before and I got very excited at first and said to Hans 'we've got something else you know'. We were thinking of other products that Goldstein and his group had been isolating in California and thought it might be related to these. I then had a dreadful thought and I called up Barry and I said 'you know the apparatus that we were using, what else had it been used for?' I said 'it wasn't a Brasso production run or something like that was it?' Because they made Brasso. It wasn't Brasso, it was actually buprenorphine they'd been making.

Eventually we calculated that we'd used about 1500 litres of solvent during our whole pilot plant run and that 1500 litres had managed to scour off from this huge extraction vessel exactly five micrograms of buprenorphine. And it took weeks to work out and clarify the problem. That's one of the reasons why I would never allow any true opioids into my lab. It was kept an absolutely opioid-free zone. But you know Barry was, is, I presume he's still alive, no-one seems to know where he is, he went out to work for Sterling Health about ten years ago, emigrated to the States, and Sterling Health is no more and I am not quite sure where Barry is. He was a very engaging person, a very talented peptide chemist, and we worked very closely together on the extraction and on the synthesis.

The synthesis story had another interesting outcome, because although Barry was the first person to synthesize met- and leu-enkephalin, we had shared information fairly freely, not only with Reckitts but also with another defunct pharmaceutical company, the Wellcome Foundation, and we'd tried to do the kind of collaboration with the biochemists at Langley Park that we'd set up at Hull.²⁹ Various problems got in the way, mainly because there wasn't a decent slaughterhouse nearby and so on, but we'd shared information and continued to share information. I remember one meeting I had at Langley Park. Sir John Vane was there.³⁰ It was one of John Vane's famous lunches, where you have a table that's about twenty-feet long and you sit round in the old house there and all the department heads come across and some of the young scientists, you know good food and good wine, and then exchange information. I was asked during the course of that particular lunch 'well, you've got partial sequence data', because I'd been working with Linda Fothergill in the Department of Biochemistry. That was one of the reasons I was rather curt with Howard, which I have apologized for since then, and we are good friends nevertheless, despite that, and at least I did show some sense in the end didn't I? But Linda and I had been working very closely together since the beginning of 1975 and I had done the mass spectroscopy analysis in association with the Department of Chemistry in Aberdeen, and it had been a total disaster as Howard surmized, because we didn't know what we were doing, which had sensitized me somewhat. But we were beginning to get sequence data from samples I was giving to Linda, and by the time that Howard approached me we had partial Tyr-Gly-Phe data.

As Howard said, the rest was kind of shrouded in ignorance and what Howard also said, about not having preconceived ideas, was a very good point as well. Because I have to admit to having had preconceived ideas at the beginning, and so did Hans. Hans was thoroughly convinced that this must be an unusual structure and it must be a secondary amine, because morphine is a secondary amine, and

²⁹ Langley Park was the headquarters building at the Wellcome Foundation's research site at Beckenham, Kent.

³⁰ Sir John Robert Vane FRS, Group Research and Development Director, Wellcome Foundation from 1973 to 1985. Nobel Prize for Physiology or Medicine 1982.

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coming from the amine field, from the catecholamine field myself, my thoughts were that it was likely to be an amine of some sort, a tryptophan derivative, hence the excitement at the tryptophan spectrum. Fortunately however, we were open minded enough that we recognized early on that it was indeed a peptide. But we were still looking for something unusual and I guess, this really can get in the way of research. Everyone has preconceived ideas – we had a preconceived idea that there was an endogenous opioid substance. I think some people think scientists do start with a blank book. Maybe Howard does, maybe he has to clear his mind like that. The analytical person maybe is different in that respect, certainly analytical chemists, because I work alongside them still, and they do. I can understand that, but I think if you want a fertile line of scientific investigation that's going to turn up new concepts or new ideas, you really do have to have a concept in view first of all. It doesn't come ready made into the brain. I think most scientists do have an idea of what they are trying to achieve before they start. I mean there are some, I guess the Einsteins and the Morrisises of this world where it does come, in full flood [laughter]. Preconception is dangerous, but it's also powerful.

Rees: Well, thank you very much indeed. You've heard our two main witnesses and now it's open to others to say what you wish, please.

Professor Leslie Iversen:³¹ Can I just start by remembering two particular moments when I was fortunate enough to be present. One was in 1974, May, at the Neuroscience Research Programme, which is an offshoot of MIT. It was sometimes referred to as 'the invisible university of the brain.' This was an international group of neuroscientists who met regularly and held occasional workshops. I was fortunate enough to be a fellow of that programme at that time and so I was able to go to the workshop that Sol Snyder had arranged, to which both John Hughes and Hans Kosterlitz were invited and I think most of the eminent gurus of the North American opioid world were present. It was a fairly small group, I think about 24, 25 people John? Something of that sort?

Hughes: Slightly more, about 40. There were students invited as well, of course.

Iversen: And Sol Snyder was very, very hyper at the time, and the Americans were extremely competitive. I mean he had had the big success of the opioid receptor binding assay just a year before and that certainly reinforced in everyone's mind the idea that the endogenous ligand must be there. But it was really John Hughes who had the only data that anyone was aware of and these had already been reported if not in print at least at meetings. There was a determined effort by Avram Goldstein and Sol Snyder to extract the maximum amount of information from John Hughes and he was really given a very, very thorough grilling when he came to give his talk on the endogenous ligand. Sol Snyder and Gavril Pasternak were certainly hot on the trail at that time. They hadn't discovered the receptor, and I think I entirely agree with John's opening remark that the receptor as a

³¹ Professor Leslie Iversen FRS, Director of MRC Neurochemical Pharmacology Unit, Cambridge from 1971 to 1982. Director Merck, Sharp & Dohme Neuroscience Research Centre from 1982 to 1995. Visiting Professor of Pharmacology, University of Oxford, 1995 – .

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pharmacological construct had already been discovered years ago in Britain. However, in the binding assay they had a very simple way of screening for endogenous ligands and they were using that to good effect. So they were certainly hot on the trail and Avram was saying 'was that one molar acid John, that you were using? What was the temperature of the extraction?' And Sol Snyder was trying to get it all down on his dictating machine at the same time.

Rees: Leslie, were they not using a bioassay at all?

Iversen: No, nobody there was using a bioassay. I felt that John was really put on the spot, and I think you have indicated earlier that you didn't really want to go to that meeting and talk about the detail at that time. But you came through it okay. The second moment I recall is the arranged marriage that I tried to get together in Cambridge for Howard and John. Having been to the May 1974 meeting, I'd been following the field closely and we'd invited John to the MRC Neurochemical Pharmacology Unit in February 1975 to give a tea-club paper. I knew that Howard Morris had already been extremely successful in the structural analysis of biologically active peptides and I thought that this was something he would be interested in, and sure enough it all looked to be going very well until they actually spoke to each other [laughter]. I think Howard has downplayed it somewhat, because Howard is not a man to hide his light under a bush, and when John Hughes said 'we're not interested in that, we've already tried it', Howard said, I think something to the effect, 'you're missing a big opportunity here, because if you give me a fraction of a micromol, I can give you the answer by next weekend' [laughter].

Dr Angela Coutts:³² I worked with Hans Kosterlitz from 1969 to 1977, so I sort of predated John Hughes a little bit. I just want to put into context what the situation was in those early days. In the 1960s and early 1970s, Hans Kosterlitz was in the receipt of grants and monies from drug companies to look at a number of analogues of morphine and was doing many structure-activity relationships, and this probably explains why he maybe had a preconceived idea of the structure. Some of us were doing PhDs at that time and we were looking at the physiology of the gut and mechanisms of release for acetylcholine, but it was emphasized that our bread and butter work was to look at the assays of these new compounds. I think that this probably explains why Professor Kosterlitz wasn't too eager to devote all his time into looking for the new enkephalins where it was not so certain what the outcome was going to be. As regards the lack of bioassay in the States, I think it was when Avram Goldstein came over in 1973, when the INRC meeting was held in Aberdeen that he actually came up to the lab and I showed him how to make a myenteric-plexus preparation for the first time. So he had by then recognized the importance of bioassay.

³² Dr Angela Coutts was Angela Waterfield, now back working in the Department of Biological Sciences, Institute of Medical Sciences, at the University of Aberdeen, on the effects of cannabinoids on peripheral nerve-muscle preparations. See Coutts A, Ross R. (1996) Research directions. Back to the future. *TRP3* 8: 20–22.

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Tansey: What kind of assay technique was Lars Terenius using?

Hughes: Binding.

Tansey: And when he came to Aberdeen, did he learn the bioassay technique?

Hughes: He came specifically to learn the bioassay technique. One point about the binding assay is not that we didn't use it. I set up the binding assay quite early on after Pert and Snyder's publication³³ and one of the problems is that when you set up the opioid binding assay, or any binding assay for that matter, you take an extract of brain, run it through a chromatography column and start to analyse what you get, there are peaks of activity all over the place. All over the place. It really is extremely difficult to interpret, and you don't know what is real and what is unreal. We have done experiments over recent years, because we are still looking at other opioid substances in the brain and we always do a parallel assay. I was trained as a classical pharmacologist, and parallel assay is one of the mainstays of pharmacological analysis, and there are always some inconsistencies when you take tissue extracts. But the main point is that it is extremely difficult to analyse these binding assays of natural extracts, extremely difficult.

Tansey: Why do you think the Americans put so much faith in those techniques?

Hughes: Because it's easy and convenient. But basically you are trading convenience for accuracy. I'm not sure that it is cheaper, I mean one mouse would keep me going for 24 hours. You could do an awful lot of assays on that. *Vas deferens* is an amazingly robust preparation.

Coutts: I was just going to add that the binding doesn't tell you whether you are dealing with an agonist or an antagonist. You just know that something binds the receptor. You will discover what it is if you use a bioassay.

Rees: To go back to the funding question what was the main resource for what you were actually doing John?

Hughes: I had a personal MRC grant, at that time and Hans [Kosterlitz] had several grants. Then we also applied for the NIDA grant, which effectively established the Unit for Research on Addictive Drugs. I took my MRC grant with me when we moved out of the department into Marischal College, but the main funding was coming from the NIDA grant. I can't remember how much it was, but it was an enormous sum of money in those days and it supported 12 or 13 people. All the money was pooled. Again, there were things that don't happen these days. When you had any consultancy money, it all went in the same pot for the research and travel fund of the whole lab.

³³ Op. cit. note 9 above.

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Tansey: What kinds of agreements were there with Reckitt & Colman and the Wellcome Foundation?

Hughes: The only agreement was that we would share information with them. There wasn't any agreement to patent the material. In fact the enkephalin was patented. I actually hold the patent on enkephalin through the American Government. I was approached after publication and told that we really ought to patent it. I saw no particular reason for patenting the peptide structure, but the Americans insisted on it and in due process we did get a patent, which presumably is no longer viable. It was for the process of isolating and determining the structure of the pentapeptides.

Morris: I thought it was dropped some years ago.

Hughes: No, I've got the patent.

Rees: You made an interesting point about how the climate for research in this country has changed very significantly from the 1970s. Point number one is the issue about competition in research and the fact that all academic institutions in the main are subjected to research assessment exercises, on which future funding is partially, although not wholly, dependent. It raises the issue, for the scientific community at large, is this a desirable phenomenon. Does it now stop people exchanging ideas and information? I have my suspicions about it, but I'd be very interested in other views about this. Let's put a direct question to you Howard. Does the fact that the climate has changed, does it specifically influence you, do you think, in your exchange of information?

Morris: I suppose it does to some extent. Our biggest problem in a place like Imperial College at present is trying to get what appears to be a reducing pool of money from the research councils to support research. I have a sneaking suspicion that a great proportion is going into Europe, which is supposed to be new money, or so we were told at the time. I have many European colleagues who find it incredibly easy to get money in places like the southern countries in Europe, Southern Italy and Spain. I met a few of them at a meeting I was speaking at last week, where they get grants for instrumentation which we wouldn't have the audacity to apply for, because the instrument is so expensive and we know it would take the whole of one round of funding of a committee such as the Cell Board or similar of the MRC. So the pot is reducing all the time and I think there is a great deal of evidence for that.

We knew when we were doing this [enkephalin] research that you would be funded from Research Councils on grant applications rated a beta-plus and certainly an alpha-minus. Nowadays you are damn lucky if you are funded on an alpha-plus grant application. That's one of our major problems at present, getting the funding. The other one, in the universities at least, is the increased administrative load that has come about because of the concept of things like

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academic auditing, things that we used to take for granted years ago. We have to do a lot more paper work. That's disappointing as well from the point of view of the pure researcher.

Rees: You haven't directly answered my question. Do you think that if your department at Imperial College, or your division, wants to get a five in the National Research Assessment Exercise, does that actually prevent you from discussing your results with, let's use a hypothetical example, say somebody at King's or Aberdeen?

Morris: In my own case, it certainly wouldn't influence me from that point of view. I have always been very, very keen on interdisciplinary research and collaborative research, so that wouldn't inhibit me personally, but maybe it would some people.

Smyth: I can speak from personal experience that the EC are very favourable about awarding 'twinning grants', in which a laboratory of established reputation is linked with another group, generally from a developing area, to work together on a common theme. Maybe this fits in with what Howard mentioned. But now this system is no longer favoured and 'network granting' is preferred, where you have up to seven people from different laboratories all participating in a focused research project. I guess we are going more in the direction that the Americans went a few years ago.

Morris: The problem in my own experience is with one such project where we were invited to be collaborators on an EEC grant. There are, in fact, about seven or so partners. But the major problem is that the installation is in the South of Italy. It's all to do with the concept of introducing high technology and so on into these southern countries. So we have to travel to an installation in the South of Italy, a very sophisticated piece of equipment. We arrive there – I'll just tell you one little anecdote – having been told 'yes, the instrument's coming' and I knew the manufacturers, I knew it was ready for transport to the lab months earlier. I arrive to discover the instrument isn't there at all. The EEC money is sitting in a budget in Rome somewhere, probably making interest for somebody. The instrument was installed only about six months later, with no air-conditioning in the room. This is sophisticated instrumentation which has to be held at a steady temperature, the electronics cannot be allowed to go up to 30°C, whereas the lab was going up to 38–40°C routinely. The instrument collapsed about five times, sensitivities nose-dived by a factor of about 50. This was an ultra high-sensitivity instrument. It was the wrong place for an instrument like that.

We don't seem to be able to do anything about it. We have to accept the fact that the money is going down there and not up here anymore.

Dr Virginia Berridge:³⁴ I'd like to ask a question partly relating to that and also to the 1970s. I wonder if you could say something a bit more about the NIDA

³⁴ Dr Virginia Berridge is Reader in History, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine.

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funding of research and what the significance of that was in relation to both American drug policy and also to potential commercial applications.

Hughes: I'm not sure about commercial applications. In terms of drug policy that has changed several times over the last two decades. To get away from the politics behind it, I think the Americans are extremely good at focusing on an issue and then applying maximum force to try to solve the perceived problem, and clearly drug abuse was, and is, a major problem in the western world. It threatens to tear the fabric of our society apart. The American response to this was that more research was needed. I, frankly, was always dubious about that in the sense that I have never been a great supporter of focus-directed research and certainly the way that it's gone in this country, don't agree.

The idea that you can manage science is a nonsense I think. What you can do is to apply funds and I think this is Howard's point. If you apply funds to an area, you don't know what the spin-off is going to be. It probably won't be the spin-off you expected, but that doesn't matter, as long as there is a good spin-off. There have been enormous spin-offs from the NIDA-funded programmes, excellent centres of rehabilitation have been set up, there's been a lot of work on comparing the various methods of drug therapy, methadone maintenance, for example, and other maintenance programmes. I'm looking at community care programmes, I'm looking at returning a recidivist to the community after going through various stages, right down to looking at the molecular mechanisms of drug dependence at the finest level.

One of the focuses now in the States, is on cocaine, with the emphasis on possibly manipulating the transporter pharmacologically as a way of dealing with dependence, and all that is to the good. It adds to medical knowledge, medical practice and treatment. Whether it has achieved its aim, I'm not sure. Drug abuse is such a difficult and complex socio-economic problem, I'm not sure scientists will ever be able to come fully to grips with that. All that we can do is try to give a range of possible alternatives so that governments and the responsible agencies can try and make of it what they will. Science is not going to solve drug addiction. All it can do is provide tools that could aid social policies. That's my view of NIDA.

Professor Hannah Steinberg:³⁵ I should like to say something about the psychological element in drug abuse that has long been and is increasingly studied. It is easier, for example, to re-addict rats to opiates in the environment in which they were first addicted, so that even in the rat one can demonstrate place preference. People in this country are doing interesting work on the psychosocial aspects of drug abuse, showing that you can manipulate and change it by appropriate environmental changes, as well as by drugs. But what I really wanted to ask comes back to Professor Rees's important point about competition and communication in research. There has always been, as we heard earlier this afternoon, when one is doing something interesting, exciting, topical and new, the question of how much one should communicate, when and to whom? This problem existed 25 years ago, as I hope you will agree.

³⁵ Professor Hannah Steinberg is Visiting Research Professor, School of Psychology, Middlesex University since 1992. She was Professor of Psychopharmacology at University College London, the first such position in Western Europe, from 1970 to 1992.

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Rees: Thank you for that very important comment. I agree with you that it was there. My question, and I saw you nodding when I was speaking, was, has the climate in this country shifted so far to a situation where you become anxious about doing this because it may jeopardize your future; actually in truth not just the future of the research project but your job. I don't really know the answers to that question, because I, for various reasons, have not been actively involved in scientific research at the sharp end in the last few years, so I am not certain.

Steinberg: I do think it has become more difficult; the stakes have become higher and this is an enormous pity. In my view science should be open and what matters is to advance the subject rather than the person who's doing the work, but that is an ideal which I know cannot often be reached. At the same time, at present when there is so much emphasis on competition, it is crucial to have meetings like this where one can explore these problems and determine, for example, how much more quickly one could have progressed if one had said more or had said less.

Morris: I'll add just two reflections on what you've just said with regard to the enkephalins. I think the collaborators themselves were interacting very well in terms of feeding information backwards and forwards, if we wanted to know it. I'm in a very special situation as the structural elucidation person, because I don't want to be encumbered with some ideas which would mislead the interpretation. So in that sense, I don't want to know certain pieces of information. Not only that, you would not prematurely communicate structural information, because it may be totally wrong and your biological colleagues would then be going off at tangents, and wasting time and energy. So it's important in my own particular speciality to know what I am talking about precisely, before I open my mouth.

Steinberg: I agree, though sometimes you cannot actually know or you cannot decide when you know precisely. Biology can be quite difficult.

Morris: Biology, yes. I'm much more on the physical science side of things which is different.

Dr Irene Green:³⁶ I'd like to make two comments. One is about research and how it's conducted now, because I'm at the sharp end and the second comment would be to get back to opioids and where I began to work on opioid peptides and insulin secretion. I'm a senior research fellow in biochemistry at Sussex and I earn my living on soft money and have done so for the last 25 years. I am currently not working on opioids, but on nitric oxide and cytokines. We were very fortunate to have a sort of landmark publication on the induction of nitric oxide synthase by cytokines and the consequent effects on insulin secretion. When we were doing that work we were very concerned about the competition and this was work which we published in 1990. Since then, what I find, is that the competitive nature of research means that, in order to really advance very far, you have to collaborate

³⁶ Dr Irene Green is at the School of Biological Sciences, University of Sussex.

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between major groups. Now worldwide, instead of there being individual research groups within countries and so on, there are now kinds of conglomerates of groups. I now collaborate more and write more joint papers, which is a difficulty for me and for my colleagues because when a grant is being reviewed this work could be done in various labs. I feel that the funding may not be given to anybody, because we all fall between various stools with some of the projects. Certainly research funding and the competition are altering my behaviour.

If I can get back to opioids, I became involved in working on opioids and insulin secretion in about 1979 which was triggered by work being carried out by David Pyke, Bill Stubbs and David Leslie³⁷ at King's College in London, Dulwich. They had written a paper where they were studying type two diabetics and they had a hypothesis that I was able to do something towards testing which was to say whether or not opioids could have any effect on insulin secretion. I did some experiments in our *in vitro* system with a long-acting enkephalin-dam from Sandoz which was the product they were using. Having found that this substance had an acute stimulatory effect on insulin secretion, I then found myself in Sweden and by a convoluted way in Terenius's office. I was visiting the Biomedicum in Uppsala and my friend, Professor Helestrom, took me to talk to Terenius about having made a preliminary and totally unpublished observation. I was able to talk to him and say, 'if you're reading a paper in the opioid field and you're going to believe the results, how do I need to do the experiments, what compounds do I need to use, what compounds do I need to avoid and so on'. So we discussed how to go about it and I was then able to publish a paper on the direct effects of some opioid peptides and morphine sulphate on insulin secretion. We went on to study this mechanistically and also to look at obesity, but that was my initial involvement in working in opioids.

Tansey: Could I just go back to this question of communication and open communication. There's clearly a difference in 1974 when you went, Professor Hughes, to Boston feeling uneasy at having been put in that position, by Hans Kosterlitz, having spoken openly about your work two months earlier and you said you had a disagreement about this. Could you elaborate a little? Was Hans Kosterlitz being naive? Was he not aware of the pressures you were under? Was it a different generational attitude about the conduct of science?

Hughes: He certainly wasn't naive. I think he just became carried away in the heat of the discussion at that particular meeting and I think that the discussion had turned to 'are there endogenous opioids?' And someone maybe said 'no there aren't.' He really couldn't contain himself, so the damage had been done. I was put in the invidious position, having realized that it was a *fait accompli* that I had got to go, and you can't just go and say nothing. So to make the best of a bad job I went, I gave them the most up-to-date information that I had. Leslie is quite right, and by the way Les Iversen played a number of seminal parts in this story, it's quite interesting how Les pops up here and there and he did a lot of distinguished work on opioid peptides himself with his group, but Les is right they were trying to pump me. My answer to that was, because I'd read the articles of the

³⁷ Leslie R D, Pyke D A, Stubbs W A. (1979) Sensitivity to enkephalin as a cause of non-insulin dependent diabetes. *Lancet* 1: 341–343.

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Neurosciences Research Programme (NRP) and the NRP was a discussion meeting which was not concerned with methodology but with concepts, and I said, 'Look this meeting is supposed to be about concepts not methodology, so please don't ask me those questions'. Goldstein looked at me, a very forbidding man Goldstein, I don't think he was used to a 28-year-old, or however old I was at that time, speaking back to him and saying no I'm not going to answer your question. I jolly well wasn't going to give them that kind of information. I wasn't that naive either. No Hans wasn't naive, but he became carried away and also I really don't think he had appreciated at that time where it all would lead. We were all focused on our own particular area and I will repeat at that time, Hans wasn't really very interested in what I was doing with that particular bit of work. I mean, we would discuss it, but he really wasn't fired up about it. He was more interested in the work we were doing on partial agonists and trying to characterize new receptors and so on. I think his attitude was a realistic one in the sense that if there's something there you may be right, but it's going to be awfully difficult to do anything about it.

Rees: When you submitted the structural paper to *Nature*, did they publish it very quickly?

Hughes: Oh yes, because I know Leslie Iversen was one of the referees. I think it was accepted within two weeks, it must have been a very rapid turn around.

Iversen: I don't think the editor of *Nature* needed much persuasion to see that this was an important paper.

Professor Miles Weatherall:³⁸ Going back to the point when Hans Kosterlitz persuaded you, or obliged you, to go to the meeting. If you had won, or if he'd said 'oh, of course, a mistake, we won't go' you would, I imagine, quite soon after that have been writing up various parts of your work and submitting them and they would have gone to referees.

Hughes: Oh, I was already writing the *Brain Research* paper at that time. I was well into the second draft of the paper when I went to Boston. In fact, I may well have got the final draft.

Weatherall: So the papers would have been going to referees quite possibly in the States to some of them quite quickly, quite soon afterwards. Did it really make much difference to how soon the word got round about what you were doing? Did it not possibly get round much more accurately when people could read what you had said rather than what they thought they had picked up at a conference?

³⁸ Professor Miles Weatherall was Professor of Pharmacology at the London Hospital Medical College, University of London, from 1958 to 1966, now Professor Emeritus; Head of Therapeutics Research Division and a director at the Wellcome Research Laboratories, Beckenham, near London, from 1967 to 1975.

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Hughes: Maybe, Professor Weatherall. Maybe. That *Brain Research* paper didn't get published – I think it was submitted in March 1974 it might have been April 1974, and it wasn't published until May 1975, it was deliberately held up. There wasn't any competitive reason for it being delayed. One of the referees, I know, liked it – I think that was Les [Iversen] again.

Iversen: I wasn't involved in all your work [laughter].

Hughes: Sorry, Les, it wasn't you in that case. I think one of the referees quite liked it – he didn't say very much, but another one of the referees who I discovered later was the Professor of Pharmacology at Loyola University, Karczmar,³⁹ told me later that he was quite proud that he had refereed it and he didn't realize the impact he had on it. I had a 14-page critique of my paper sent back to me by *Brain Research* and this critique started with the words 'this is a very interesting paper, but teleologically it does not seem sound that the body could produce an endogenous morphine-like substance.' Now that was a fixed attitude if you like and the points the referee made were on the whole valid, but they required an enormous amount of extra work to rebut them or to answer his points, because the paper wasn't going to be published otherwise that was quite clear. In my mind I know that the paper that finally was published was a far better paper than I originally submitted, there's no doubt about that, but it represented almost an extra six months of work. The odd result was that both the *Brain Research* paper and the *Nature* paper were published in the same year, which was rather strange and it got the chronology all wrong. I don't know, I have mixed thoughts about this. It was meant to be a scientific critique. He very freely admitted to me that he was the referee when I met him at a later date, so he wasn't trying to steal anything, he wasn't in the field anyway, not as a competitor.

Rees: You raised a very interesting issue which I was discussing with Stephen Lock the other day. About the trend for asking people who submit their papers to suggest whom they might like to referee them. Stephen, you might like to talk about this issue, because I think it's quite an interesting point.

Dr Stephen Lock:⁴⁰ Yes, several journals have been experimenting with getting authors to nominate one of the two referees who should consider a paper. This works surprisingly well and in my experience certainly doesn't guarantee bland or favourable reviews. What Dr Hughes has just been describing is well recognized in peer review: that is, that referees can understand 'normal' science (to us Thomas Kuhn's classification), but are usually quite incapable of assessing 'paradigm shifts' (or 'revolutionary' science).

³⁹ Professor Alexander G Karczmar, Department of Pharmacology, Loyola University Medical Center, Maywood, Illinois.

⁴⁰ Dr Stephen Lock is a member of the Steering Committee of the History of Twentieth Century Medicine Group, Wellcome Institute for the History of Medicine and was editor of the *British Medical Journal* from 1975 to 1991.

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I'm also interested to know whether you ever considered forming a new journal, so that you wouldn't have to go through the rigmarole of doing all the work the referee asked for. Derek de Solla-Price showed that new knowledge takes at least 36 months from concept to publication, but that his 'invisible college', or peer group knows about the findings on the old boy net at about 18 months.⁴¹ So there's a temptation not to meet the referee's wishes, which would mean that the invisible college had known about the work for much longer before the revised version was eventually published, but to start a new journal instead – which at its start, at any rate, can offer quick publication. After all, new disciplines are split off from old ones every ten years or so, and these naturally need new journals for the subspecialist writers – readers – so why not put this new work into a new journal?

Finally, in view of the scramble for publication over the past decades, I'd be interested to know about another aspect: your decision process over publishing this work. Were you publishing important chunks every time, or were you salami-ing it?

Hughes: One of the nicest things anyone ever said to me after that *Brain Research* paper was published was 'John we repeated your methodology, and it worked exactly as you said.' That was one of the nicest things anyone has ever said. We weren't salami slicing – the whole methodology was described and if someone followed the techniques and used the materials that we used, they could do it. I know many people did repeat those experiments and were quite impressed by the fact that they worked. Because quite often you do read a paper and you think that sounds interesting, you try to repeat the results, it's happened to all of us, and you jolly well can't do it for some reason and that's terribly frustrating. That's why you should be writing papers, because it's an educational exercise, you're expounding your know-how to the scientific community. You are also establishing a marker and saying 'I've done this piece of work', which is the other point I was saying here, that the 16-month delay or whatever it was didn't prove critical in the end. It could have done though, because I must admit I was quite paranoid through the whole of 1974 that either Snyder or Goldstein or someone else was going to publish a paper establishing them, and anyone with a casual reading of the bibliography, could not have told otherwise.

Tansey: I think one thing that has changed is the way in which many of the journals nowadays include just below the title, the acceptance date and submitted date. It's interesting if you look at that *Brain Research* paper. It says when it was accepted, which was 14 December, but there's no way you can tell that it was submitted eight or nine months earlier, where now I think a lot of journals, including *Brain Research*, do in fact do that which, of course, helps the historian establish the chronology. It's extremely difficult otherwise.

Steinberg: I agree with this; some journals now put 'final version accepted.'

⁴¹ De Solla-Price D J. (1963) *Little Science, Big Science*. New York: Columbia University Press.

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Morris: I know that John and Hans and everybody was very neurotic in that 1975 year about getting the structure very urgently because of Sol [Snyder] and so on. I got a letter, funnily enough, I think in February of 1976, from his mass spectroscopist, who presumably had been trying to get Sol the structure as well. It was an interesting letter because it said that they couldn't understand the origin of the some of the signals in the mass spectrum, so in fact they were probably a bit further behind than we knew at the time in 1975.

Rees: Can we can go back to the authorship question for a minute? Stephen, you heard what John said about the fact that when he published without Hans Kosterlitz's name on the paper, people expressed dismay at this. This is something now that has completely changed, hasn't it? Would you like to comment on that?

Lock: I think that this is because the number of authors has gone up so high and we have fraud cases on both sides of the Atlantic, in virtually all countries, where there's been this gift of honorary authorship. I think if you go back to this question of authorship historically, it probably dates back to the turn of the century where the Prussian state parliament produced the first Declaration of Helsinki, an ethical code for working in subjects. The final point of this code was that the professor or the head of the department ought to sign off the work as being his responsibility. Certainly he took responsibility for the ethical aspects of clinical work. I suspect it was then that heads of department started putting their names on papers, I'm not sure, but I'd love to do a study on this.

Dr David Tyrrell:⁴² I've been listening to these stories of the 1970s and hearing echoes of things that happened to me and I would like to make one point which hasn't been made yet. This concerns the great power and dynamism of American science and how one has to think out your position in relation to it. For instance, at the Common Cold Unit we decided that we were not going to join any US bandwagons on typing the next 200 rhinoviruses. But there's been a story going around that there was bitter rivalry between groups on the two sides of the Atlantic on things like discovering new viruses. For us, it was more subtle and more complex than that and in some ways a lot more fun. My experience was that our relationships were such that we *did* communicate things before they were published (and on more than one occasion we very nearly had the ideas apparently stolen because we tried to be open about it). Equally we experienced a great deal of generosity on their part with reagents and results and I suppose it's a bit like falling in love – you have to take a chance of being hurt in the process. In fact, the analogy goes a bit further, because there was unquestionably competition between the groups in Washington and ourselves in the South of England, but at the same time we were, and still are, very good friends. I suppose you even have something like it in a family, sibling rivalry. You know your brother and you compete, but you are also his mate. I'd like to think that if things are really working well, you get the benefit of both. You get the benefit of the competition, but also the cross-fertilization and support of other people. Sorry for the long speech, but I wanted

⁴² Dr David Tyrrell FRS (1925–) was at the MRC Common Cold Unit at Salisbury from 1957 and Director from 1982 until his retirement in 1990.

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to explain my feelings (which may be wrong), that in your particular area it actually worked out beneficially in the end, although it was a bit untidy round the edges.

Hughes: Oh, yes, I am sure you are right David. Sol Snyder, Hans Kosterlitz and I remained firm friends. We never fell out. Sol fell out with a lot of people, but they were Americans, they weren't Europeans. There was far more jealousy between the Americans, I should say, than there ever was between the British and the Americans and you are right, competition is healthy and good. The only point that I was really making earlier on is perhaps from a sense of inferiority, knowing how good their labs are. What I have to accept, of course, is that the funding that allowed us to go forward was American funding. You are right, it's not one-sided, there are pluses and minuses.

Rees: I think you make a very important point, that it is very easy for those of us privileged enough to undertake research to whinge about the fact that there are never enough resources, never enough this, never enough that, and I suppose if you took an alternative point of view, you could say that perhaps there was complacency in some academic units; perhaps people were not doing all they could do. So I think it's always easy to see it from a negative point of view. I put that in, perhaps, just to make a balance to the situation that we all find ourselves in.

Does anyone wish to say anything else before we close the meeting?

Steinberg: I wondered if in two sentences or so, people could sum up the kind of status of these problems, and where it's all going.

Hughes: The opioids you mean? The opioid peptides along with the tachykinin and substance P type molecules were archetypal in that they established that peptides were very important messengers along with the hypothalamic releasing factors. Twenty years on from all of those discoveries, we are still very far from understanding their role in the nervous system and the brain, despite cloning of the receptors and identification of second messenger systems. There are still many unanswered questions and I guess the development of a tachykinin neurokinin-1 antagonist will probably be the proof of the pudding. As yet, through all this scientific work, there has been no real therapeutic spin-off. Les [Iversen] and I have worked in this field for a number of years and both of us have tried very hard to develop drugs in this area. It is extremely difficult. It won't be the opioid field I have to say that will probably yield the first drug. Maybe, the kappa receptor work might yield something yet, but I guess the neurokinin-1 antagonist will be the proof of the pudding. It's quite extraordinary, all this work and still no therapeutic pay-off. It takes a long time. I hope that answers your question.

Steinberg: My colleagues and I work on physical exercise and mental health;⁴³ as you know physical exercise is supposed to release endorphins into the blood

⁴³ Steinberg H, Sykes E A. (1985) Introduction to symposium on endorphins and behavioural processes: review of literature on endorphins and exercise. *Pharmacology, Biochemistry and Behavior* 23: 857–862. See also Steinberg H, Sykes E A, Le Boutillier N. (1995) Exercise addiction: indirect

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stream. Professor Rees has done some very distinguished work on this.⁴⁴ Many people ring me up, including the media, wanting to know what the real role of endorphins is in all this? Usually, I am rather cautious about it and I wondered whether maybe you could give me some updated assurances?

Hughes: Endorphins are good for you!

Rees: I am absolutely certain from my own personal experience of exercise that it's good for you and it's all in there with the endorphins.

Perhaps on that note, I could end and thank our two witnesses for giving us an absolutely fascinating account of a very, very interesting piece of medical history. To Tilli, for giving us a brilliant introduction to the field, thank you very much indeed, and all of you for participating in what I think has been a really fascinating afternoon.

Tansey: And may I add my thanks to the Chairman for her hard work, and to the Wellcome Trust for their financial support of this meeting.

measures of endorphins? In Annett J, Crisp B, Steinberg H. (eds), *Exercise Addiction: Motivation for Participation in Sport and Exercise*. British Psychological Society Occasional Publication, Annual Conference Satellite Workshop, Sport and Exercise. Psychology section of the British Psychological Society, 6–14.

⁴⁴ Howlett T A, Tomlin S, Ngahfoong L, Rees L H, Bullen B A, Skrinar G S, McArthur J W. (1984) Release of beta-endorphin and met-enkephalin during exercise in normal women: response to training. *British Medical Journal* **288**: 1950–1952.

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The Committee on Safety of Drugs

The transcript of a Witness Seminar held at the Wellcome Institute
for the History of Medicine, London, on 12 March 1996

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The Committee on Safety of Drugs

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Dr Stephen Lock:¹ Today, to discuss the Committee on Safety of Drugs, we have invited a group of very distinguished participants to debate the relevant issues. We want to encourage comments and reminiscences from as many people as possible, and after a short background presentation, we are going to start with Willie Turner, who was there before it all happened. Unfortunately, one of the principal witnesses of these events, Bill Inman, is not fit enough to come to London. So we travelled to Winchester and video-recorded an interview. I will then ask Professor Owen Wade, who became the second Chairman of the Subcommittee on Adverse Reactions, to speak.

Dr Tilli Tansey:² As is well known, regulatory control of drugs in Britain developed in a somewhat piecemeal fashion during the first 60 years of the twentieth century. The first significant piece of legislation was passed in 1925. This was the Therapeutic Substances Act (TSA), which regulated the manufacture, standardization and supply of just four classes of substances: antitoxins and sera, vaccines, posterior pituitary preparations and arsenicals of the Salvarsan type. Over the following decades developments in pharmacological therapeutics were reflected as the TSA was updated, and the recognition and manufacture of penicillin in the early 1940s led to the passing of Penicillin Acts that regulated its production, standardization and supply. These were not the only relevant pieces of legislation – some medicines were controlled by the Pharmacy and Poisons Act, and others by the Dangerous Drugs Act. But there was no cohesive framework of appropriate legislation, and it was perfectly possible for any manufacturer or supplier to claim as medicinal and to offer for sale any substance.

In America, things progressed rather differently. In 1906 a Pure Food and Drugs Act had been passed to eliminate adulteration and misbranding of substances, but in 1937 the weaknesses of this legislation were exposed when an elixir of sulphanilamide dissolved in diethylene glycol caused the deaths of 76 people in the first year. The only offence the makers, Massengill, could be prosecuted for was adulteration, and the owner was fined \$150 for each death.³ The lesson was rapidly learned: the US Congress acted quickly to legislate that no

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³ American Medical Association Chemical Laboratory. (1937) Elixir of Sulfanilamide-Massengill: chemical, pharmacologic, pathologic and necropsy reports; preliminary toxicity reports on diethylene glycol and sulfanilamide. *Journal of the American Medical Association* **109**: 1531–1539; Geiling E M K, Cannon Paul R. (1938) Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning: A clinical and experimental correlation: Final report. *Journal of the American Medical Association* **111**: 919–926.

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new drug could be marketed without licence from the Food and Drug Administration.

That lesson was not learned in the UK, although during the 1950s a number of significant events occurred – there were two pieces of consolidating legislation, intended to tidy up some of the diverse acts then on the Statute Book – these were the Dangerous Drugs Act 1951 and the Therapeutic Substances Act 1956. In the summer of 1959 the Poisons Board, concerned at the development of over-the-counter drugs that affected the central nervous system, but were not regulated by either of those Acts, warned of ‘the probability of hazard’ to the health of the public from ‘widespread use of ... [potent medicines] for self-medication’. Their report demanded specific legislation administered by the Ministries. A few months later, in November 1959, the Interim Report of the Interdepartmental Committee on Drug Addiction, chaired by Sir Russell Brain, recommended ‘that drugs having an effect on the central nervous system and liable to produce physical or psychiatric deterioration should be confined to supply on prescription, subject to the advice of an independent expert body.’

In that same month, November 1959, a further interdepartmental body, a Working Party to consider medicines legislation was established. We’re very grateful to Dr Roy Goulding, who is with us today, for drawing our attention to this body, of which he was a member. The Working Party sat from November 1959 until 1963, the 11 members were all civil servants, seven men from the Ministries of Health, three from the Home Office and a parliamentary counsel. Their brief was:

‘to review the legislative provisions which relate to the control of medicinal substances and to recommend what changes should be made to rationalise and simplify the law with a view to ultimate amendment and consolidation.’

The draft report of that Working Party was produced in April 1962 and it made a number of recommendations: they recognized the urgency of extending legislation to protect the public, and proposed that there should be an independent expert body to advise the responsible Ministers on the appropriate form and extent of necessary control, and they commented that ‘it is a serious defect of the present law that new medicines can be offered for sale or supply with insufficient evidence for their safety’.

That interim report was produced in April 1962, and thus chronologically followed, but was largely independent of, the withdrawal of thalidomide in December 1961 by its manufacturers.

The tragedy of thalidomide, of gross malformations appearing in children of mothers who had taken thalidomide as a sedative and anti-emetic preparation during pregnancy, stimulated the appointment, in June 1962, of the so-called Cohen Committee. This was set up by Enoch Powell, the Secretary of State for Health, and was formally a Subcommittee of the Standing Medical Advisory Committees for England and for Wales, and for Scotland. As that pedigree suggests, it was an expert committee of medically and pharmaceutically qualified men. It was chaired by Lord Cohen of Birkenhead, and its secretary was E L Mayston, who had also served as Secretary of the Interdepartmental Working Party, and was thus a formal link with that earlier body.

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The final report of the Cohen Committee appeared in March 1963, and its recommendations included the establishment of an independent advisory board, and in June 1963 the Committee on Safety of Drugs (CSD) was established as an interim measure until comprehensive legislation could be enacted. This was chaired by Sir Derrick Dunlop⁴, and in accordance with naming conventions is frequently referred to as the Dunlop Committee. Very soon three Subcommittees were also established: one on toxicity, one on adverse reactions and a third on clinical trials and therapeutic efficacy. It had no statutory powers, and when appointed sought and obtained agreements from all pharmaceutical companies selling drugs in the UK that no new drug would be marketed without its approval – a voluntary system that seemed to work well. As I'm sure we will hear from witnesses the Dunlop Committee's deliberations led ultimately to the safety of medicines legislation of 1968 and the establishment of the Medicines Commission.

We're delighted to have with us today several people who served on or who advised the Cohen Committee, the earlier Interdepartmental Working Party, and subsequent Safety Committees. We hope that they, and others, will examine the factors, social, political and medical, that influenced the creation and subsequent role of the CSD and its successor body, the Committee on Safety of Medicines (CSM), and discuss also general and specific issues related to the regulation of medicines in this country.

Lock: Perhaps we could go straight on to Willie Turner, who was there at the time.

Mr Wilfred Turner:⁵ First of all I would like to say how grateful I am for this opportunity of coming back after 30 years since the Committee on Safety of Drugs. I have been in a lot of places throughout the world since then, but I still regard that period that I served with the Committee as being one of the most exciting parts of my career and although I met a great many people throughout the world, I don't think I've met such a group of interesting, positive, personalities as those I met when I was Secretary of the Committee on Safety of Drugs and I am delighted that quite a few of them are here today. My experience of the control of medicines was for a very limited period. It was from 1963 until July 1966, when I left the Home Civil Service to join the Diplomatic Service. This, however, was a vital period in the establishment of comprehensive control of the safety of medicines in the UK, as Dr Tansey has said. I came on the scene immediately after the report of the Cohen Committee. That was the seminal action leading to the present comprehensive system operated by the Medicines Control Agency.

⁴ Sir Derrick Dunlop (1902–1980) held the Chair of Therapeutics at Edinburgh from 1936 until his retirement in 1962. He was appointed **Chairman of the Ministry of Health's Committee on Safety of Drugs from June 1963 to 1969 and Chairman of the Medicines Commission from 1969 to 1971**. He served as Chairman of the British Pharmacopoeia Commission from 1948 to 1958.

⁵ Mr Wilfred Turner CMG CVO was at the Ministry of Health from 1960 to 1966 and served as **Secretary to the Committee on Safety of Drugs from 1963 to 1966**. He then joined HM Diplomatic Service and served in a number of countries in Asia and Africa. He was British High Commissioner to Botswana from 1977 to 1981. After his retirement, he was Director and Chief Executive of The Southern Africa Association from 1983 to 1988 and a Director of a subsidiary company of British Rail from 1987 to 1990.

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The thalidomide disaster brought home to the public and hence politicians the thorough inadequacy of the control of medicines in the UK. Inevitably, the reaction was the setting up of a committee and, either by wisdom or good fortune, the Minister of Health appointed the late Lord Cohen of Birkenhead to chair the Committee. Even looking back from this distance, one can't fail to be impressed by the perceptiveness and the practicability of the recommendations of the final report which was submitted in March 1963. As you have been told, the main features were that there should be comprehensive legislation on the control of drugs, but in the meantime the Committee on Safety of Drugs should be established to review the safety of new drugs, to monitor adverse reactions to existing drugs and to keep medical practitioners informed. Submissions by manufacturers should be voluntary and the Committee would have the responsibility of advising the Minister if a drug did not receive the approval of the Committee.

There was a minority report of the Cohen Committee. This was by the two pharmacists on the Committee and they argued that the voluntary system would have far too many loopholes and in their Minority Report they implied suspicion of both the industry and, indeed, the political motivations of the Minister, even though one of them was a Conservative Member of Parliament.⁶ I don't know that Enoch Powell took well to that.⁷ In the Report the majority recorded the view that the publicity that a drug had not been approved would be a sufficient sanction and this, in fact, proved to be correct.

The Ministry of Health moved quickly on the Final Report and the Minister announced the setting up of the Committee on Safety of Drugs with Professor Sir Derrick Dunlop as Chairman. I was appointed Secretary with a concurrent responsibility for other aspects of drug policy, including drafting the Bill, which ultimately became the Medicines Act of 1968. And, for instance, I was responsible for the Therapeutic Substances Act. This was a rather bizarre dual function, because it was made clear to me that as Secretary of the Committee my responsibility was entirely to the independent committee, while I remained responsible to the Minister on all other matters concerned with drugs. On occasions, therefore, I found myself corresponding with myself on something which the Committee wanted and to which other parts of the Ministry didn't want to accede.

Typically, having set up the Committee, the Ministry of Health was reluctant to give it resources to do the job. The secretariat at the outset was entirely part-time, reflecting my own dual functions and on the administrative side it consisted of me, a higher executive officer – not very senior – and a clerk, and I shared typing facilities with two other Principals. That's how we started. Shortly after I was appointed the Ministry appointed Dr Dennis Cahal⁸, formerly a medical director in

⁶ Joint Subcommittee of the Standing Medical Advisory Committees. (1963) Note of Dissent by Mr J Grosset and Sir Hugh Linstead. *Safety of Drugs: Final Report*. London: HMSO. The Cohen Committee sat from August 1962 until March 1963 and was chaired by Lord Cohen of Birkenhead, with Professor S Alstead, A B Davies, Professor Sir Charles Dodds, J B Grosset, Sir Hugh Linstead, Professor E J Wayne and Professor G M Wilson, with E L Mayston as Secretary.

⁷ The Rt Hon Enoch Powell MP was Minister of Health from July 1960 to October 1963. He became a member of the Cabinet in July 1962.

⁸ Dr Dennis Abraham Cahal (1921–1983) was Senior Principal Medical Officer at the Department of Health and Social Security from 1963 to 1981 and **Medical Assessor to the Committee on Safety of Drugs from 1963 to 1970**. He was visiting Professor of Pharmacology and Therapeutics at St Mary's Hospital Medical School from 1967 to 1969. Prior to joining the Ministry of Health, he had been

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industry as Medical Assessor. Thus the Committee started with three of us – Sir Derrick, Dennis and me – to set up the organization. It was extremely fortunate that we had a rapport which lasted the whole of my time with the Committee. I was also fortunate that the Chief Medical Officer, Sir George Godber⁹, was determined that the Committee would be a success and, typically, he told me that if I had any nonsense from the rest of the Ministry, he wanted to know about it!

Gradually, during 1963 the membership of the main Committee and the three Subcommittees recommended by the Cohen Report was built up. As the only administrative member of the Committee, I had the key function of interpreting ministerial attitudes and behaviour to the eminent members of the Committee and keeping the Ministry assured that the Committee was pursuing its terms of reference, which I might say were extremely simple, very short and admirably brief and succinct.

At first there was caution in the Committee among its members, at having a civil servant appointed by the Minister to an independent Committee, the work of which could have political implications. But with the help of Sir George Godber, I think that I managed to convince them that I was very much one of them; I would like to hear what members of the Committee present today think about that. As we recruited more medical staff, I had the job of introducing them to the arcane ways of the Civil Service and that was quite an important personnel management job.

Those first days were immensely satisfying. I think all of us would agree that Sir Derrick was a wonderful Chairman. He had his own very firm ideas on how the Committee and Subcommittees would run, but he was highly successful in establishing these ideas with fellow members, each of whom was pre-eminent in his own right. And with the occasionally doubtful acquiescence of the Committee, he established a number of principles which remained throughout my time with the Committee. Here are some of them – some fairly obvious in retrospect: relations with industry should be cooperative; the term ‘new drugs’ to be considered by the Committee should have the widest interpretation and should include reformulations and new uses, as well as new chemical compounds, but nit-picking should be avoided; the Committee should be concerned with efficacy only in relation to safety; the Committee should accept that safety was comparative (I remember Derrick saying, ‘show me a safe drug and I’ll show you a useless drug’); there should be a minimum of bureaucracy and nothing must be done to hold up consideration of potentially valuable new compounds. None of this must in any way undermine the primary responsibility of assessing new drugs with the fullest scientific rigour needed to protect patients. And when it came to reports of an adverse reaction, a report should be viewed with caution, avoiding the *post hoc ergo propter hoc* fallacy. Professor Wade will remember the number of times that that was pointed out.

head of the medical services of Allen and Hanburys from 1959 to 1962.

⁹ Sir George Godber joined the Ministry of Health in 1939, took part in its 1944 survey of hospitals and was ‘actively concerned’ with the introduction of the NHS. He was appointed Deputy to Sir John Charles, who was Chief Medical Officer, and succeeded him in 1960. His departmental remit was later extended to the Department of Health and Social Security, the Department of Education and Science, and the Home Office until his retirement in 1973. Anon. (1973) *Medical News: Change of CMO. British Medical Journal* 2: 724.

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Sir Derrick's view on these principles were influenced by the unfortunate reputation at that time of the US Food and Drug Administration (FDA). Industry complained of the long periods which the FDA took in considering new drugs; their excessive bureaucracy and the unreasonable demands for, what appeared to them, unnecessary detail. The clinicians were equally concerned that the FDA appeared to be depriving them of useful drugs. So to look at this monster at close hand, Sir Derrick and Dennis Cahal and I went to the United States for talks with the FDA and with major pharmaceutical manufacturers. Needless to say, the manufacturers repeated all the complaints we'd received on this side of the Atlantic. But we were somewhat surprised to find that their views were confirmed to a large extent by officials in the FDA themselves. Most of those we met were medical doctors and the more impressive of them were inhibited by the procedures which prevented them, as they saw it, from releasing valuable drugs without unnecessary delay. They blamed politicians for demanding 100 per cent safety in drugs when clearly this was unrealistic.

It was also obvious that some of the medical men thought their colleagues were of inferior calibre, who'd taken jobs with the FDA because of lack of success in clinical work or in industry. And the story of thalidomide inspired cynicism. We were told more than once by officials themselves that the United States avoided the scale of the disaster in the rest of the world because the officials responsible, particularly Frances Kelsey, found the submissions tedious and complicated, and kept putting the files to the bottom of the in tray. Whether that's true or not I don't know. Sir Derrick came back determined that the Committee on Safety of Drugs would avoid the mistakes of the FDA. But with the shadow of thalidomide hanging over us, the Committee were very conscious of the potential threat to its professional reputations. I think it is to the enormous credit of those early Committee members that this didn't inhibit them from making courageous decisions about releasing new compounds which were potential reducers of suffering. And this, of course, gave particular relevance to the responsibility of the Committee in monitoring adverse reactions to drugs already in use or released by the Committee. The Adverse Reactions Subcommittee therefore carried a particularly heavy responsibility, but in my view, as an observer, this didn't weigh them down. This group of six, with quiet confidence, took on the daunting task of avoiding another therapeutic disaster, with, at that stage, and I think Professor Wade would probably support this, very little material to work on. In due course, Dr (now Professor) Bill Inman did valiant work in building data for them.

It must be obvious that behind setting up the Committee and the Subcommittees there was a large amount of professional and administrative work – liaison with industry and with the professions, details such as protecting the confidentiality of commercially highly sensitive information (that was a very serious matter, as you can imagine), methods of recording adverse reactions, liaison with overseas bodies, and so on. The ease of relationship between the eminent members of the Committee and Subcommittees and the secretariat in the few months at the end of 1963 got everything ready for the start date of the first of January 1964.

Now the story of the yellow card, I think, is typical of the many administrative complexities which we faced. The Adverse Reactions Subcommittee needed a method by which doctors could report adverse reactions. A list of questions was prepared by the Medical Assessor from which I produced a draft

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card. We agreed that the card must be post-free for doctors, if we were going to get them to submit it to us and I tried to negotiate what, in those days, was an 'On Her Majesty's Service' frank, which appeared on all official correspondence. The Stationery Office wouldn't have it, so I then tried the idea of the post-paid business reply rate which businesses used. Now you must remember in those days the Committee had no budget of its own and the Ministry of Health Finance Department didn't like the idea of using money to pay the necessary fee for a business reply envelope. We had to work very hard indeed in persuading the Ministry to go to the Treasury and get the Treasury actually to allow that bit of money that we needed to pay the fee for the business reply envelope. So we got over that. Then there was the problem of distribution which in theory sounded easy, but we had to negotiate with several parts of the Ministry, those responsible for general practitioners, for hospitals, and the health committees, to get this yellow card out to the people who ought to be using it. There were difficulties and obstructions all the way.

Thus, this very simple form which is still used today, experienced a difficult gestation. It was interesting that other bodies overseas took an interest and I remember that I got a letter from Senator Hubert Humphrey¹⁰, who was Chairman of the United States Senate Committee on Drug Safety, and he asked me to let him know about this yellow card. I was amused to find, because he sent me a copy with a compliment slip, that my correspondence with him and the copy of the yellow card actually got written up in the US Congressional Record. And the reason for the card being yellow is also amusing, because it arises from my own colour blindness. Each Subcommittee wanted a colour-coding for their papers and as I kept the Secretaryship of the Adverse Reactions Subcommittee to myself I chose yellow as the house colour, because this was a colour which I could most easily identify. Greens, and pinks, which were the others, were quite beyond me. Hence, with the house colour of yellow, inevitably the card that we used was a yellow card and that's why it's known as the yellow card.

By January 1964, the Committees were up and going and invited the first submissions, and that first year proved that the outline design by the Cohen Committee was right. I don't think there was any new drug, even with a wide interpretation of the term, that escaped the scrutiny of the Committee. Industry was cooperative, many of them, I think, at the relief that they were not having an FDA-type organization imposed on them and even minor manufacturers were anxious to avoid the sanction of being pilloried with a reputation of non-cooperation in drug safety. During 1964 there were 600 submissions to the Committee; 386 were approved, 15 were not approved, 32 were withdrawn, usually after objections by the Committee, and 99 were referred back for further information. The majority of these new drugs were, of course, reformulations, but there were no fewer than 55 new compounds. Even reformulations produced a lot of paper. In the case of new compounds, a submission of a thousand pages was not unusual and it must be recorded, and I think this is very important, that the detailed work on these submissions was carried out by a professional staff which started with only two doctors and one pharmacist. By the end of the year there were three doctors and two pharmacists and this staff was supported by my minuscule administrative staff. The first year established a pattern of work, the

¹⁰Senator Hubert H Humphrey, Jr (1911–1978) was Vice-President of the United States from 1965 to 1968 and the Democratic nominee for the US Presidency in 1968.

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success of the Committee earned the confidence of industry, professions, and the concerned public. We even managed to persuade the Ministry to provide further resources, even if not lavishly.

By the end of 1965 there were six doctors and three pharmacists on the professional staff and I was granted a few more administrative staff to support the Committee. I can't conclude without referring to the vital contribution the Committee made to the development of the drugs legislation which we have today. My dual responsibility enabled me to draw on the experience of the Committee to devise a statutory scheme which contained as much as possible of the undoubted benefits and flexibility of the voluntary scheme. As well as carrying out their basic responsibilities, the members of the Committee and Subcommittees were very generous in giving advice to those of us involved in the detailed work of drafting the Medicines Bill. If the Medicines Act has any faults the Committee on Safety of Drugs bears no responsibility. It was all very hard work in those early days, but from my point of view it was enormously satisfying. There is no doubt that the Committee was a success in carrying out its terms of reference and I believe the major reason was the spirit of cooperation which infused everyone concerned, committee members, professional staff, and down to the most junior administrative staff. It was typical, I think, of the spirit that members of the Committee insisted that junior clerks, who worked in the back rooms, should attend meetings so that they could see what their work meant. In my view, it was a great team.

Lock: How did they come to nominate Dunlop?

Dr Roy Goulding:¹¹ He was about to retire from Edinburgh. He was thinking of going out to Africa and I think someone from the Ministry approached him. I don't know who approached him, but I know he changed his mind about it and took up this post.

Dr Ekke Kuenssberg:¹² My suspicion is that it was Sir George Godber. Derrick, of course, was a great man and he had made his contribution in the pharmacopoeia field very much so. I would just like to pinpoint something which is slightly different in my memory. The praise that has been given to the British model was perhaps not always the case. The FDA, the American FDA, did in fact do one thing which we didn't do and that was on the oral contraceptive pill. The Americans risked the oral contraceptive, releasing it to use. I think it was three years before it was allowed in Britain.¹³ Now, there are all kinds of reasons for this, but it is just an example of how the two bodies worked differently and had a different

¹¹ Dr Roy Goulding is Emeritus Consultant in Clinical Toxicology at Guy's Hospital, London. He was Senior Medical Officer at the Ministry of Health from 1957 to 1962 and Director of the Poisons Unit at Guy's Hospital from 1962.

¹² Dr Ekkehard V Kuenssberg (1913–) was in General Practice from 1939. He held many positions including President of the Royal College of General Practitioners from 1976 to 1979 and Chairman of the General Medical Services Committee of Scotland and UK from 1960 to 1968. He was a member of the Subcommittee on Adverse Reactions of the Committee on Safety of Drugs from 1964 to 1971.

¹³ Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration. (1969) *Second Report on the Oral Contraceptives*. Washington DC: US Government Printing Office.

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horizon in many ways. I'm not accusing the Safety of Drugs Committee of lowering its horizon but it just happened that way. We were much more reluctant to go ahead with the introduction of the oral contraceptive pill.

Lock: Bill Inman will be talking about the Pill later, and our discussion could focus on that afterwards. I would like to ask Professor David Finney, who was Professor of Statistics at Edinburgh, whether he knew Derrick Dunlop and knows anything about the machinations that went on – whether it was George Godber's idea.

Turner: I am sure that it was George Godber who thought of Derrick Dunlop, because George told me once that Lord Cohen was furious that he was not appointed. In fact, I was dragged before Lord Cohen and instructed by him on how I was going to behave as Secretary of the Committee on Safety of Drugs.

Goulding: I am speaking from memory, which is always treacherous at my age, and I think the moving spirit in nominating Dunlop was indeed George Godber, but he did a lot of canvassing in the department. I know he discussed it with Cohen. I was a civil servant at the time and advice was taken also from the independent advisers to the Ministry, who were canvassed as well and I think that when George floated the name of Dunlop it was approved of generally. There were one or two quibbles, but we won't go into those.

Professor David Finney:¹⁴ At the time of the establishment of the Dunlop Committee I was not in Edinburgh at all; I was in Aberdeen. I came into this in the wake of the thalidomide story. I was spending a sabbatical year at Harvard, and the late Professor Dave Rutstein, of the Harvard Department of Preventative Medicine, encouraged me, in the light of what was happening over thalidomide, to embark on a study of what statistical science might do to help prevent this kind of disaster in the future. I was totally ignorant of the medical side of things. I was a fairly experienced statistician, whose applied work had been largely in connection with agricultural research. So I started from scratch, but with the tutelage of a number of good American colleagues. I also paid a visit to

¹⁴ Professor David Finney FRS (1917–) was Reader, later Professor of Statistics at the University of Aberdeen from 1954 to 1966 and Professor of Statistics at the University of Edinburgh from 1966 to 1984. He also was Director of the Unit of Statistics, Agricultural and Food Research Council (formerly the Agricultural Research Council) from 1954 to 1984 and a **member of the Subcommittee on Adverse Reactions of the Committee on Safety of Drugs (later Medicines) from 1963 until 1981.**

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Washington, to meet Frances Kelsey¹⁵ and heard something of her story. The outcome of that was that I wrote what would probably now be regarded as a rather naive paper on how a national drug safety organization might be set up.¹⁶

With Dave Rutstein's encouragement, I gave quite a bit of publicity to this through various channels, including the World Health Organization, and when I came home again in 1963 I received a letter from Derrick Dunlop, a name I had never heard before, inviting me to join his Adverse Reactions Subcommittee. I say I had never heard of Derrick Dunlop, that doesn't imply any disrespect, because I learned enough of him later to regard him with very great respect. I therefore joined the Adverse Reaction Subcommittee from the start, and I will echo what Willie Turner has just been saying about the enthusiasm that manifested itself. All of us, certainly on that Subcommittee and I think the same was true of the other Subcommittees, had a tremendous spirit of getting on with the new job. There were no guidelines laid down on how we should proceed. I think I made my own small contribution in trying to keep the statistical aspects on line, but they were very far from perfect and we did work together exceedingly hard and with great satisfaction, feeling that we were doing a worthwhile job and so we proceeded. I am afraid, despite what Willie Turner has said, I regard by comparison the changeover from the CSD to the CSM as deplorable.¹⁷

Dr Derek Bangham:¹⁸ When the thalidomide problem came to light, the MRC set up a committee with a theoretical remit to advise the Government on what test on animals should be done on a new drug to show if it was 'safe'. This Committee on Safety Testing for New Drugs was chaired by Sir Charles Harington, then Director of the National Institute for Medical Research, and was composed of various eminent academic physicians and scientists. As Secretary, my job was to draft a list of the proposed animal safety tests, starting from scratch. This task was utterly unrealistic, as the MRC soon realized, especially as the ABPI ran a separate committee with the same aims; the members drawn from the pharmaceutical industry knew far more about drug testing than the distinguished academics appointed by the MRC. I was involved because the Division of Biological Standards at the NIMR was the only Government laboratory then involved in the

¹⁵ Dr Frances Kelsey was Medical Officer at the Food and Drug Administration in Washington, DC. She handled the application from Richardson-Merrell for Kevadon, their trade name for thalidomide as licensee, from 1960. Knightley P, Evans H, Potter E, Wallace M. (1979) *Suffer the Children: The Story of Thalidomide*. London: Andre Deutsch for Times Newspapers Ltd, see 73–81; Kelsey F O. (1963) in *Interagency Coordination in Drug Research and Regulation. Part I, Review of Cooperative Drug Policies among Food and Drug Administration, National Institutes of Health, Veteran's Administration, and other Agencies*. Washington DC: US Government Printing Office.

¹⁶ Finney D J. (1965) The design and logic of a monitor of drug use. *Journal of Chronic Diseases* 18: 77–98.

¹⁷ Professor Finney's notes prepared for the meeting said: 'the deplorable replacement of CSD by the Committee on Safety of Medicines (CSM). Clarification of statutory duties and legal requirements may indeed have been desirable, but the change brought increased bureaucratic obstruction to all efforts to develop improved methodology in the primary task of attention to drug safety. Instead came increased allocation of limited resources to the machinery of drug licensing and consequential reduction in the feeling among members of subcommittees that they were volunteers participating in an operation of great practical importance.'

¹⁸ Dr Derek Bangham was Head of the Division of Biological Standards at the NIMR from 1961 to 1972. He was later Head of the Hormones Division of the National Institute for Biological Standards and Control (NIBSC), from 1972 to 1987.

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control and laboratory testing of 'biological' drugs administered parenterally covered by the TSA. The MRC Committee was disbanded after about a year, without producing any final report.

Dr Josephine Weatherall:¹⁹ I wanted to take up a slight point about Dr Kelsey who is not only a colleague but a personal friend of mine. I asked her one day whether it was really true that she put the file 'at the bottom'. She said, 'Yes, because I didn't like the look of the substance and I wanted further information from the manufacturers, and the file went down while I waited for this.' So there was a very good reason for 'putting it at the bottom'.

Turner: I wasn't implying any criticism of Dr Kelsey. I was reporting what, in fact, her colleagues at the FDA were saying.

Mr Stephen Hall:²⁰ I'd like to make some comments about the thalidomide disaster. If you challenged any of the companies whether they really believed that it could not happen again, I never found any who would agree. They were always prepared to accept that we might be faced with something in the future that was perhaps even worse. This belief, of course, was immensely beneficial to the secretariat in persuading some companies to provide the necessary data. It was a sort of insurance policy, and we pointed out on many occasions that if companies chose to market a product, depending on what it was, they were perfectly entitled so to do. But they would then ask the question, 'What would happen if we did?' I used to reply that the Ministry would notify all the medical and other professions in the field that, as a company, you are prepared to market this product without submitting any evidence to this Committee. I used it several times and I always found that companies were ready to comply with our requirements. It was very important.

I am sure that the thalidomide disaster helped immeasurably in getting this voluntary scheme to work, although I accept what others have said about having serious reservations, on a point of principle, in operating legislation by voluntary control. I can see their point. Regarding the actual incidents. The Cohen Committee at the time had recently pronounced on thalidomide and had got some sort of accolade. However, two weeks before thalidomide was withdrawn, at one of the regular meetings, Chris Alstead came to me privately afterwards, saying he had heard some very disturbing results from Liverpool and Glasgow about adverse effects from the administration of thalidomide. He said these adverse effects were irreversible, which of course is very serious. His words to me were 'I think we will have to have another look at this'. As it happened, there wasn't time. But the point I want to make is that the Committee weren't sitting in ignorance. They had already received comments from doctors and others that there was something

¹⁹ Dr Josephine Weatherall was Medical Officer at the General Register Office, later the Office of Population, Censuses and Surveys, from 1965 to 1982. See Weatherall J A C. (1965) Oral contraceptives and thromboembolic episodes (letter). *Lancet* ii: 1344; Tomkinson J, Turnbull A, Robson G, Cloake E, Adelstein A M, Weatherall J. (1979) Report on confidential enquiries into maternal deaths in England and Wales, 1973-1975. *Reports on Health and Social Subjects* 14: 1-166.

²⁰ Mr Stephen F Hall was then **Pharmacist in the Pharmaceutical Section of the Ministry of Health.**

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unusual, something wrong, about this drug. There were adverse effects which were irreversible.

Sometimes it's thought that thalidomide could happen again. The thalidomide tragedy did help the secretariat immensely, and I have difficulty in thinking of more than one or two companies who were really difficult about the provision of data and they really weren't major companies. Most of them were only too willing to cooperate. Some of them thought it would be an awfully good idea if they could come along and meet the Committee and have a general discussion, they'd make notes and go away, and do what the Committee wanted and all would be fine. We had to point out to them that you can't do things that way.

Goulding: There is just one little ironic twist. The Medical Adviser to Distillers, the company which put thalidomide on the market, had been my predecessor at the Ministry of Health under the Therapeutic Substances Act. This was Dr Kennedy.²¹ And he telephoned me there and told me, long before we had the trouble, that this splendid new drug was coming on the market, that mothers could take it and children wouldn't come to any harm from it. It was absolutely innocuous, you see. And that turned out to be thalidomide. Just to take up one other point, that the fuss against thalidomide started with the peripheral neuropathy and I remember this, because I had two patients in the ward with it, and it was causing us a lot of trouble. One final point – it's all very well to say we should have tested it more thoroughly, but we had no means at all for testing for teratogenicity at that time and it took a long while to get any such procedure.²²

Lock: That brings Bill Inman in, who was the first Medical Assessor of the Witts Subcommittee on Adverse Reactions, one of the of the key figures in the early days of regulating new drugs in the United Kingdom. I went down to his home near Southampton, because he is in a wheelchair, and interviewed him there.

Professor Bill Inman:²³ I suppose the first indication of trouble was 1956 when Dr Heinrich Mückter of Chemie Grünenthal invented thalidomide. It was marketed

²¹ Dr Walter Kennedy was a senior medical officer at the Ministry of Health until he went to Distillers as its chief medical adviser in 1956. Distillers was invited by the Ministry of Supply to make penicillin at Speke, Liverpool, as the Government's agent, in 1942. During a visit to Chemie Grünenthal in June 1956, Dr Kennedy was shown thalidomide and wrote a glowing report on it. Knightley P, Evans H, Potter E, Wallace M. (1979) *Suffer the Children: The Story of Thalidomide*. London: Andre Deutsch for the Times Newspapers Ltd, see 40–41, 141. Distillers sold its biochemicals subsidiary to Eli Lilly from January 1963, which traded as Dista Products Ltd. Anon. (1962) *British Medical Journal* 2: 1135; Anon. (1962) *Company News. Chemist and Druggist* 178: 459.

²² Derek Bangham has pointed out in a later letter: 'I take every opportunity to point out, in discussions about thalidomide, that 20 years later German chemists published experiments to show that "thalidomide" consisted of a mixture of two chiral isomers, one was a useful sedative, the other was a potent teratogen (the S(-)-enantiomer).' Blaschke G, Kraft H P, Fickentscher K, Kohler F. (1979) Chromatographic separation of racemic thalidomide and teratogenic activity of its enantiomers [author's tr., German]. *Arzneimittel-Forschung* 29(10): 1640–1642. Derek Bangham to Dr Tili Tansey, 22 October 1996.

²³ Professor William H W Inman, qualified at Cambridge, acted as medical adviser to Imperial Chemical Industries, and joined the Ministry of Health's Committee on Safety of Drugs in 1964 as

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in this country in the following year as Distaval and in Germany as Contergan and two or three years passed really before Bill McBride in Australia spotted an association between thalidomide and congenital abnormalities.²⁴ In the same year Dr Widukind Lenz said he'd seen 52 babies in Germany with these limb problems.²⁵ At the time I was working at ICI in their medical department and I discussed this at meetings in the Association of Medical Advisers in the Pharmaceutical Industry (AMAPI) and so it was known that I was interested in setting up some sort of scheme to monitor new drugs. Out of the blue a letter came from Sir Derrick Dunlop at the end of 1963, inviting me to show an interest in the new Committee which he was forming.

Lock: The Committee had been set up by then?

Inman: It had already been established. As far as adverse reactions were concerned the total number of yellow cards was the contents of one shoe box, literally, when I joined, and I would in fact have been in right at the beginning had I not been late starting – I was ill. I had been working for ICI for about five years by that time. My career was very much dictated by the fact that I had had polio as a medical student and it seemed that it was dermatology, psychiatry or something like laboratory work, which didn't appeal to me. And I had an ICI background, as it had been in the family since the early 1920s. My father was a founder member of the company.

Lock: So you got to the Committee in 1964, and what happened then?

Inman: Eventually arriving in 1964, by which time yellow cards were just beginning to trickle in and there were various bits of publicity to encourage that. Sir Derrick Dunlop himself wrote a letter to all doctors, circulated it with yellow cards, and they started to come in. I can't remember the exact rate but it was a thousand a month easily, maybe more than that. Derrick Dunlop was the Chairman of the main Committee and he operated three Subcommittees. The first was a Subcommittee on Toxicity – the Chairman of that was Professor Frazer;²⁶ the second was the Clinical Trials Subcommittee, which was chaired by Bob Hunter;²⁷ and the third was Adverse Reactions with Leslie Witts.²⁸ I think it was

Senior Medical Officer, later Principal Medical Officer, to develop its voluntary reporting system, and was Medical Assessor of Adverse Reactions.

²⁴ McBride W G. (1961) Thalidomide and congenital abnormalities. *Lancet* ii: 1358.

²⁵ Lenz W. (1962) Thalidomide and congenital abnormalities. *Lancet* i: 45, 271–272.

²⁶ Alastair C Frazer (1909–1969) was Professor of Medical Biochemistry and Pharmacology at Birmingham University from 1943 until he resigned in 1967 to become the first Director General of the British Nutrition Foundation. He was a member of the Committee on Safety of Drugs and Chairman of the Subcommittee on Toxicity from 1963 to 1969. His appointment as Dunlop's successor was announced on the day of his sudden death. Anon. (1969) Professor A C Frazer (obit.). *British Medical Journal* 2: 767. His deputy, Professor Eric F Scowen, took over as Chairman of the Subcommittee and later as Chairman of the CSD in October 1969.

²⁷ Professor Robert B Hunter, later Lord Hunter of Newington (1915–1994) was Professor of Materia Medica, Pharmacology and Therapeutics from 1948 to 1968 at St Andrews University, Dundee University after 1966; a member of the Committee on Safety of Drugs and Chairman of the Subcommittee on Clinical Trials and Therapeutic Efficacy from 1963 to 1968. From 1968 to 1981

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really the Subcommittees that the attention was focused on when things went wrong as with the Pill and with asthma deaths and so on. We got most of the press attention.

Lock: Leslie Witts was the distinguished professor at Oxford?

Inman: He was a specialist in blood dyscrasias and I think that was felt to be one of the target areas we might get involved in. I liked him very much indeed. He was very quiet, very considerate, a perfect gent, in fact. I was very fond of him.

Lock: And who else was working there?

Inman: At the moment I can recall, it's now nearly 30 years, Ekke Kuenssberg, a GP in Edinburgh, Owen Wade who at that time was in Belfast, Bill Mushin in Cardiff – an anaesthetist and Michael Linnett.²⁹ And Roy Goulding put in an occasional appearance from the National Poisons Information Service.

Lock: How exactly did you work?

Inman: The keystone of the whole operation was the yellow card, which was a very simple business reply card, folded double and glued round the edge for security and confidentiality, and these were issued periodically to doctors who were encouraged to report any suspected reaction to a new drug and any serious reaction to any drug, however old or new it was. And it was an entirely voluntary system. They didn't get paid for it and on the whole, I think, they responded very well, but of course the yellow cards really grossly underestimated the probable numbers of events which were occurring.

The first drug that struck us as dangerous was benziodarone, used in heart disease, and it quite obviously caused jaundice. The company was persuaded to remove that voluntarily without any pressure. It was kept under wraps. There wasn't much publicity. We didn't seek publicity. Another good example is Dytransin which was the trade name for ibufenac which is still on the market. Exactly the same thing. Two waves of jaundice occurred, once when they issued it to hospitals and again when they issued it to general practitioners. Boots had no difficulty taking that one off the market straightaway.

Lock: When the drug was taken off the market, did you issue warnings to GPs?

he was Vice-Chancellor and Principal of Birmingham University.

²⁸ Professor Leslie J Witts (1898–1982) was Nuffield Professor of Clinical Medicine at Oxford from 1938 to 1965 as well as a Fellow of Magdalen College. From 1963 to 1968 he a **member of the Committee on Safety of Drugs and Chairman of the Subcommittee on Adverse Reactions**.

²⁹ Dr Michael Linnett (1926–1996) was in General Practice from 1957; served the Royal College of General Practitioners as a member of its council from 1970 and Chairman from 1976 to 1979; and acted as Apothecary to the Prince and Princess of Wales from 1983 to 1990. He succeeded Dr Ekke Kuenssberg as the general practitioner on the Safety of Drugs Committee.

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Inman: Several times. We issued the Adverse Reactions Series, which pharmaceutical companies called the Yellow Peril. The first was on monoamine oxidase inhibitors. We put up one on chloramphenicol which wiped out aplastic anaemia virtually, except for the odd patients who'd used the stuff on holiday in France or Spain if they got a cold and came back to die in England.³⁰

Lock: And then there was the Pill.

Inman: The Pill first impacted about 1965 when there were odd anecdotes in various journals. I think the first was from a man called Jordan in the West Country.³¹ He described three cases, probably pulmonary embolism, and by the beginning of 1966, the estimated incidence was what you'd expect from the Registrar General's figures if we had 100 per cent reporting. Clearly, we didn't believe that we were getting 100 per cent reporting. So we had a *prima facie* case that the Pill might be causing thrombosis. With some difficulty I organized a national study, picking out all deaths within the childbearing age group that would occur in 1966. I had to wait for them to occur and follow them up. By that time I had recruited a team of field workers – we called them Derrick's Dolls – they were personable, mostly young, doctors who visited the general practitioners to get the information at first hand, which the doctors appreciated. We got the cause of death from death certificates, and I used the same team to follow up the yellow card reports. So these girls went out and collected I think about three or four hundred cases and at the beginning of 1967 there looked like at least a six-fold, maybe an eight-fold, excess of Pill users. We took living controls, at the same practices, and this was a major first for the Committee.

Lock: When was this published?

Inman: It was eventually published in 1968. But quite a lot happened before that. Way back in 1965, before we had even shown that there was a statistically valid case against the Pill, I had already spotted a difference between mestranol and ethinyloestradiol which I thought was possibly chemical. I didn't do very much about it until considerably later. Late in 1966 Leslie Witts and I went to the MRC to try to encourage them to set up parallel studies, because one set isn't enough, and we did it with great difficulty. They were persuaded to do a study looking at hospital admissions, not deaths. And we persuaded the College of General Practitioners to do the same thing and they did a study, a small one, mainly on superficial venous thrombosis in general practice.

Lock: What was the difficulty? You said you had some difficulty.

Inman: Well, they didn't really seem to be very interested.

³⁰ Committee on Safety of Drugs. (1964) *Monoamine Oxidase Inhibitors*, Adverse Reactions Series No. 1; *idem*. (1967) *Chloramphenicol*, Adverse Reactions Series No. 4, HMSO.

³¹ Jordan W M. (1961) Pulmonary embolism (letter). *Lancet* ii: 1146–1147.

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Lock: The MRC wasn't interested?

Inman: Not at first, no. We had to make two visits to them altogether. But once I got some data to show them they were a little bit more impressed.³² This basically was Richard Doll and Martin Vessey, whom I hadn't met at that time. So we got together and these three different studies were supposed to be published early in 1967 as an MRC Report. But the Royal College of General Practitioners had in the meantime jumped the gun.³³ In order to be in first, they published their little series so we were forced, I think, to publish the MRC Report prematurely. This was May 1967.³⁴ Anyhow to cut a long story short the Vessey and Doll paper and our paper, by Martin Vessey and I, were published on the same day, in the same edition of the *British Medical Journal*, and things then quietened down a bit after the initial media response.³⁵

I went back to the yellow cards. I had about three or four thousand of them by that time, and they used to go home in a suitcase every night and were arranged in piles according to first the dose, the chemical, the age of the women, how many children they'd had, and suddenly the penny dropped that where the two hormones were equally distributed in the market, and I got that data from the Intercontinental Medical Statistics Ltd, there was a 52:48 per cent split. There was a huge relative excess, of the larger doses, irrespective of what chemical it was. And at that stage I hadn't looked at progesterone and I advised the authorities not to publish anything until we'd had time to do that. But Mr Crossman³⁶ wanted

³² Derek Bangham later wrote 'the MRC was stirred into action, formulating safety trials on the pill, at least in part by the Report of the First WHO Working Group on the Pill. I was a member of that group (a Government scientist involved with control of biologicals and much sensitised to the varied validity of radioimmunoassays of hormones – due to our collaborative studies on international standards). On return to the NIMR I wrote a letter to Medawar, then Director of the NIMR, contrasting the mass of data available from the USA with the paucity of Pill studies in the UK. I am fairly sure that Medawar, with his strong support for contraception, would have stimulated/reproached/admonished the MRC to get on with it.' Bangham to Dr Tilli Tansey, 22 October 1996. His letter to Medawar adds, 'The overwhelming influence of the USA figures sharply reveals the lack of well planned studies which might have been obtained in this country had there been interest and backing on anything more than an amateurish scale. The problems outstanding are real and need tackling with the best collaboration that the MRC can offer. Although it should not be necessary, let me stress again that the meeting was a purely scientific one, to discuss scientific problems among scientists.' Bangham to Sir Peter Medawar, 17 December 1965. We thank Dr Bangham for permission to quote from this letter.

³³ Royal College of General Practitioners. (1967) Oral contraception and thromboembolic disease. *Journal of the Royal College of General Practitioners* 13: 267–279.

³⁴ MRC Subcommittee. (1967) Risk of thromboembolic disease in women taking oral contraceptives: A preliminary communication to the MRC by a Subcommittee. *British Medical Journal* 2: 355–359. The Subcommittee members were: Lord Platt (chairman), Professor W Melville Arnott, Professor H J B Atkins, Sir Charles Dodds, Dr R Doll, Professor A S Duncan, Sir George Godber, Mr M J R Healy, Sir Austin Bradford Hill, Sir Harold Himsworth, Professor F T S Prunty and Professor L J Witts. Report prepared by Dr R Doll (chair), Dr D L Crombie, Professor A S Duncan, Sir Austin Bradford Hill, Dr W H W Inman and Dr M P Vessey.

³⁵ Inman W H W, Vessey M P. (1968) Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age: A report to the Committee on Safety of Drugs. *British Medical Journal* 2: 193–199; Vessey M P, Doll Richard. (1968) Investigation of relation between use of oral contraceptives and thromboembolic disease. *British Medical Journal* 2: 199–205.

³⁶ The Rt Hon Richard Crossman (1907–1974) was Secretary of State for Social Services, i/c Department of Health and Social Security from 1968 to 1970.

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something to say in Parliament and just before Christmas in 1969, ‘something’ as you’d say in America ‘hit the fan’ and the Committee was heavily criticized.³⁷

Lock: Can you tell us just a bit more about this. Because there was a leak, wasn’t there, to Chapman Pincher of the *Daily Express*?

Inman: Yes. I predicted that if we held a conference with members of industry, because they are legally obliged to inform their masters in America, then the FDA would have the story within 24 hours. I also predicted that there would then be an automatic leak to the *Washington Post* through Mr Morton Mintz.³⁸ I think they used him as a sort of safety valve, really to take the heat out of some of these things. But I was wrong because Chapman Pincher had it a day earlier.³⁹ And the doctors hadn’t been informed. The Committee was then forced to issue an urgent Yellow Peril, which is a piece of A5 paper typed on an ordinary typewriter, and tried to fob that off as one of the leaflets in their Adverse Reactions Series.⁴⁰ This fooled nobody and the doctors were even more insulted after receiving this pathetic little bit of paper. The end of the story really was I got the nickname of ‘father of the minipill’ in respectable circles and ‘Bill the Pill’ in the eyes of the industry, who weren’t too pleased about this. It’s alleged that a lot of women came off the Pill. George Godber, and I never knew whether he was fooling or not, claimed nine months later that I had caused a slight eruption in the population. I said ‘Well, you know, I am a man that can still move around, I’m probably the father of a lot more than I bargained for’.

Lock: So this almost brings us to the end of the Committee on Safety of Drugs? Then we get the Medicines Act?

Inman: The main paper on oestrogen dose was published in 1970⁴¹ as soon after the Christmas furore as we could get it out, by which time I had been to Sweden and to Denmark and got all their data and these showed exactly the same thing. Then from September 1971, I think it was, the Medicines Act became operative and everything changed.

³⁷ Mr David Ennals answered questions in the House of Commons on Monday 15 December 1969. Anon. (1969) News and Notes. *British Medical Journal* 2: 817. See Eric Scowen’s letters (1969) Oral contraceptives containing oestrogens. *British Medical Journal* 2: 744; *idem*. How it happened. *British Medical Journal* 2: 805.

³⁸ Morton Mintz, a journalist on the *Washington Post*, had been writing on oral contraceptives since 1962. See *idem*. (1969) *The Pill: A Report*. Fawcett Publications Inc.

³⁹ After the confidential briefing of the pharmaceutical companies by the CSD on Wednesday 10 December 1969, the information had leaked within two hours and an article appeared in the *Daily Express* on Thursday 11 December, and was publicized by David Frost on a television programme. Anon. (1969) News and Notes. *British Medical Journal* 2: 817.

⁴⁰ Committee on Safety of Drugs. (1969) *Oral contraceptives containing oestrogens*. Adverse Reactions Series No. 9, HMSO.

⁴¹ Inman W H W, Vessey M P, Westerholm Barbro, Englund A. (1970) Thromboembolic disease and the steroidal content of oral contraceptives: A report to the Committee on Safety of Drugs. *British Medical Journal* 2: 203–209.

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Lock: What do you think the main lessons we learnt from this period?

Inman: I think I learnt three things. First of all, the value of independence; secondly, the need for transparency, the ability to communicate freely with the people outside; and thirdly the need for more information about the efficacy of drugs. If I take the last one first, I think that was a serious defect in the Act, probably initiated by pressure from the industry, but many countries now insist that a new drug has to have a margin of superiority or to be very considerably safer than existing drugs. In other words, you have got to have the complete equation – relative safety and relative efficacy, and the Medicines Act really prohibits these considerations. As far as the independence is concerned, I always felt that it was a great mistake to expect doctors and other scientists working in the department to be loyal to a scientifically independent committee on the one hand and to the Minister of the day on the other hand. There may be a perfectly good reasons why ministerial decisions apparently clash with the scientific decisions and if they were separate these problems wouldn't arise. I think the doctors now working at the Department find themselves more as medical advocates rather than being free to communicate scientifically.

Lock: Let's now turn to Owen Wade, who was a member of that first Committee on Safety of Drugs.

Professor Owen Wade:⁴² The first meeting of the Committee on Safety of Drugs was in the afternoon of 6 June 1963. We didn't realize that we were creating history. The CSD was the first of many similar drug regulatory bodies which now exist in many countries around the world. The Food and Drugs Administration, the FDA, is older but has a different provenance. For me it was the beginning of 21 years of service to quasi-autonomous non-governmental organizations, QUANGOs, concerned with drug safety in this country. That first meeting was in Alexander Fleming House, a hideous, uncomfortable and poorly ventilated building at the Elephant and Castle lodged between a railway and a busy road junction. At that meeting the Chief Medical Officer, Sir George Godber, said that the CSD should have a short life, less than three years, as the Minister intended to establish a statutory body under new legislation which was to be put to Parliament. In the event the Dunlop Committee lasted for seven years.

After that initial meeting we met regularly on the top floor of Queen Anne's Mansions, now long destroyed. Twice each month I travelled from Belfast on the sleeper from Stanraer to Euston. Derrick Dunlop was an austere man and the meetings under his chairmanship were not remarkable for enthralling discussion. They were short and formal. I felt very junior to the other members of the main Committee and usually kept pretty quiet.

⁴² Professor Owen Wade was Whitla Professor of Therapeutics and Pharmacology at Queen's University, Belfast from 1957 to 1971, then Professor of Therapeutics and Clinical Pharmacology at Birmingham from 1971 to 1986. He was **Deputy Chairman of the Adverse Reactions Committee, Committee on Safety of Drugs from 1963 to 1968 and Chairman of Committee on the Review of Medicines from 1978 to 1984**. See his autobiography, *When I Dropped the Knife*. Bishop Auckland: Pentland Press, 1996.

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Fortunately the main work of the CSD was handled by its three subcommittees. The Subcommittee on Toxicity, chaired by Professor Alastair Frazer of Birmingham University; examined the data on animal toxicity tests, undertaken by pharmaceutical firms during the development of a new drug. These were done before deciding if it was justifiable to administer the drug to patients, and to carry out clinical trials of its effectiveness. The Subcommittee on Clinical Trials was chaired by Professor Hunter of Dundee. Its duty was to examine the subsequent clinical trials that pharmaceutical firms carried out, to ensure that they had been appropriate and adequate, and whether it was reasonable to allow the drug to be marketed.

The Subcommittee on Adverse Reactions to Drugs was chaired by Professor Leslie Witts of Oxford. I was the deputy Chairman. Later I became Chairman. I was delighted that Professor Witts had particularly asked that I should sit on his Subcommittee and meetings under his chairmanship were excellent. We met less as a subcommittee to a governmental drug regulatory body and more as a research group, for Witts was a thoughtful and scholarly man who encouraged members to think and discuss matters in depth. We faced substantial and novel problems, which no one had had to handle before.

The Dunlop Committee had no statutory powers, although when first appointed it sought, and obtained, agreement from all the pharmaceutical firms marketing drugs in the UK, that no new drug or drug preparation would be marketed without its approval. The agreement was strictly honoured; which was a tribute to the standing of the Committee and the competence of its officers, as well as to the probity of the pharmaceutical firms.

The Dunlop Committee worked well because everyone wanted it to work well. The Ministry of Health was anxious to calm public fears aroused by the thalidomide tragedy, and it seconded efficient administrative officers to us. The pharmaceutical industry cooperated because we lightened them of the tremendous responsibility of deciding whether a new drug should be marketed or, in some cases whether drugs which had had reports of adverse reactions should be removed from the market.

The CSD was supposed to become officially effective from the first of January 1964, but at our first Subcommittee meeting in July 1963 we asked the secretariat to prepare a letter to be sent to all doctors in the United Kingdom. This was a warning about serious adverse reactions which had been reported from patients who had been given monoamine oxidase inhibitors, MAOIs, used in the treatment of depressive illness. The draft of that warning was circulated with the papers for our next Subcommittee meeting in August; it was couched in formal civil service officialese and I knew its tone would be repellent to doctors. So I prepared my own version which I tried out on my secretary, Miss McConnell, and then sent a copy to Witts.

At that time internal documents in my Department were typed on some rather cheap yellow paper and, therefore, it was on this paper that my suggested version was typed. When we met, Witts read out both versions and it was mine that was immediately accepted by the other members and it was thus sent to all doctors in February 1964. My colleagues had been rather taken by the yellow paper, and so the circular went out on the now characteristic bright yellow paper in bright yellow envelopes. These have been used for warnings about adverse reactions

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to drugs ever since. This was the first official warning about adverse drug reactions ever issued by any drug regulatory body. It was sent to all doctors in the United Kingdom by the Ministry of Health. But it went by extraordinary slow and devious routes; to hospital doctors via Regional Health Authorities and to general practitioners via the General Service Committees with which they held their contracts of service.

There was an unexpected reaction to that warning from Dr William Sargent,⁴³ a very distinguished psychiatrist at St Thomas's Hospital, London. He believed so greatly in the value of monoamine oxidase inhibitor (MAOI) drugs that he would not accept that they caused any serious adverse reactions and he castigated the Committee on Safety of Drugs in no uncertain terms. We were to find that this was not an uncommon response to reports that we issued about adverse reactions to drugs. There were always doctors who thought our warnings meant that the drugs were banned from use (which was not true), and that patients for whom the drug was of special value would be denied the treatment they needed (which was not true either).

Lock: Can we just go back a little? How did you come to be invited onto the Committee?

Wade: I went to Belfast as Professor of Therapeutics and Pharmacology in 1957 and began to appreciate that adverse reactions to drugs were becoming a serious problem. I was invited to attend a meeting in 1960 at the MRC Headquarters in London to discuss a multicentre clinical trial of prophylactic therapy for chronic bronchitis. I also made an appointment to see the Secretary of the Council, Sir Harold Himsworth, which I remember well for a peculiar reason. Himsworth knew me well because he had been my Professor of Medicine at UCH when I was a medical student. He looked me up and down when I went into his room and noticed that I had a small slide rule in my breast pocket. At an earlier meeting, we had been discussing the number of patients needed in the clinical trials for statistically significant results to be achieved. Himsworth remarked, rather severely I thought, that he was surprised that the time had come when professors of clinical medicine had to carry slide rules! Thirty-five years later the fact that I ever used a slide rule is taken as evidence that I am of the pre-computer age and practically Neanderthal man!

I spoke to Himsworth of my concern that the side-effects of the synthetic drugs then available were becoming an increasing problem. I suggested that the MRC plan a multicentre study to prepare a compendium or atlas (because so many of the side-effects were rashes) of these reactions. He seemed to regard me as a young, enthusiastic (but inexperienced) professor with fire in my belly for my discipline, and seeing the problem out of perspective, although he was polite and attentive. Perhaps a year later he would have responded differently. Certainly neither of us, nor anyone else, foresaw the consequences which were to manifest themselves in 1961 of giving thalidomide to pregnant women. I think because I

⁴³ Dr William Sargent (1907–1988) was Physician in Charge of the Department of Psychological Medicine at St Thomas's from 1948 to 1972 and worked at the Maudsley between 1932 and 1948. He describes the benefits of the MAOIs in his autobiography, *The Unquiet Mind: The Autobiography of a Physician in Psychological Medicine*. London: Heinemann, 1967, 203–205.

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was one of the few people to have been concerned about adverse drug reactions (before the thalidomide disaster) that I was asked to be a member of the Committee of Safety of Drugs (CSD). That was the Dunlop Committee, so called because of its Chairman, Sir Derrick Dunlop.

Two Committee decisions in the early days were, to my mind, less than satisfactory. The first was in 1964 when Boots marketed an analgesic (ibufenac) similar to ibuprofen. Very soon we received 70 to 80 reports of jaundice in patients receiving the drug, and when Boots learned about this they withdrew the drug. Unfortunately, this achievement by the Adverse Reactions Subcommittee got little publicity, because it was thought that a company which had been tremendously cooperative might be harmed by publicity. But I think it should have had a great deal of publicity, which would have shown doctors the value of reporting adverse drug reactions and our reporting system would have got off the ground much quicker than it did.

The second decision of which I am critical, was also related to the main Committee's appreciation of the enormous cooperation we received from the pharmaceutical firms. The Committee agreed to handle the submissions to market new drugs or new preparations of drugs as rapidly as possible. To achieve this it was decided to give the two Subcommittees most concerned with these submissions, Frazer's and Hunter's, a higher priority for staff than the Adverse Reactions Subcommittee. Our work suffered as a consequence. We needed more staff to help Dr Inman, the medical officer who serviced us. He had a daunting task not only in identifying and characterizing the adverse reactions that might be caused by a drug but also in measuring the prevalence of those reactions in relation to the use and value of the drug and weighing up the ill-effects that the drug caused against the benefits that patients derived from its use.

We expected our main source of reports to be doctors working in hospitals, and were surprised that most reports came from general practitioners. On reflection, this is not surprising as 80 to 90 per cent of the drugs prescribed by doctors in this country are prescribed outside hospitals.

It became clear to me later, from colleagues in the Royal Victoria Hospital and the Belfast City Hospital that there were three reasons why hospital staff did not send in reports even when an adverse drug reaction was the cause of a patient's admission to hospital. The day-to-day care of patients and drug prescribing was usually the responsibility of junior doctors who did not necessarily realize that it was their duty to look for, and report, adverse reactions to drugs. Secondly, although they had been asked to report '*suspected adverse reactions*', many physicians felt they should only report a reaction they were certain had been caused by a drug. And certainty is hard to achieve, when a patient may be receiving several drugs at the same time. Thirdly, some doctors were worried, as Sargant had been, that drugs they valued greatly, could be taken off the market if they reported adverse reactions to it.

Sir Christopher Booth:⁴⁴ I think the other part of that subject, of few acute reactions being reported from hospitals, is that hospital consultants see patients only for three weeks or so and they didn't have time to see the adverse reactions.

⁴⁴ Sir Christopher Booth, the first Convenor of the History of Twentieth Century Medicine Group, Wellcome Institute for the History of Medicine, from 1990 to 1996, is Harveian Librarian at the

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Tansey: Several people have expressed surprise at being appointed by Dunlop. What was your reaction?

Wade: I too was surprised at the invitation. My only previous contact with Dunlop had been as an examiner with him in clinical medicine at Edinburgh the previous year. It had not been a pleasant occasion: at the examiners' meeting I had argued with Dunlop over the low mark he gave to a student that we had both examined. The student was bound to fail the whole exam because of that mark, despite having done reasonably well with all the other examiners. Dunlop had clearly resented my criticism and at the time I thought he would hold this against me. I know now, however, that authoritative people like Dunlop, used to overruling others, often respect – even over-respect, perhaps – those who stand up to them.

Booth: Of course, you held one of the very few chairs in therapeutics at that time.

Wade: I think also that Dunlop and the Ministry of Health wanted a member from Northern Ireland.

Lock: Dr Goulding, how did you come to be involved?

Goulding: I joined the (then) Ministry of Health in 1957 and one of my responsibilities was the Therapeutic Substances Act. This dealt with 'biological' products, such as antibiotics, vaccines and insulin which had to be standardized by biological techniques. Manufacturers had to be individually licensed and part of my job was to see that their methods of manufacture and potency testing met the stipulated requirements. But these constituted only a minority of medicines in the pharmacopoeia. The rest could be produced and marketed 'without let or hindrance', the only other restriction being that they could not be advertised to cure cancer, venereal disease, or Bright's disease. As I went my way I had increasing misgivings about this *laissez-faire* attitude.

Then I found myself, over 1958 to 1960, visiting the Scandinavian countries, where medicines were more controlled. Back in the UK, I 'minuted' the Chief Medical Officer (Sir George Godber) with a plea to have some regulated scheme in this country. Within the Civil Service, as you know, progress is made slowly but, after broad consultation, an 'interdepartmental working party' was set up to study the question, and to make recommendations. So far as I can recall, an administrator was chairman. As for the other members, they have gone from my memory, except for myself and a Parliamentary Legal Draughtsman. Meetings appear to have taken place throughout 1961, with a draft report eventually being prepared.

Before this could be advanced any further, the thalidomide disaster had burst upon us, with the drug being taken off the market at the end of 1961. Such was

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the public outcry that the governmental response had to be impressive. To trot out an interdepartmental working party and its proposals would have been far too timid. So a much more commanding body was set up under Lord (Henry) Cohen, the deliberations of which led, as you know, to what, at the outset, was the Committee on Safety of Drugs, with Sir Derrick Dunlop as chairman and without statutory backing. It worked extremely well, though, on a voluntary basis, largely because of the willing cooperation of the pharmaceutical industry, owing much to the personality of the Association of British Pharmaceutical Industry's President, Dr Denis Wheeler⁴⁵ of the Wellcome Foundation.

Very soon, the three subcommittees were constituted, one being devoted to adverse reactions, and of this I became Secretary, drawing up a provisional form of notification on which doctors could report suspected incidents of this kind. According to my memory, it just so happened that it was 'duplicated' on yellow paper, this colour becoming sanctified in the 'yellow cards' which came into use. It's been interesting to hear alternative versions of that history this afternoon.⁴⁶

I must confess to having become disappointed with their operation. With my idealism I thought that, in the UK, we were in an almost unique position for, having prescribing figures under the NHS, we would easily be able to calculate 'incidence'. What, being starry-eyed, I had overlooked, was that critical factor of validation – the biggest stumbling block of all.

There was another odd piece of legislation controlling medicines and that was the Pharmacy and Poisons Act. Under that, the Poisons Board, on which I served for over 30 years, was empowered to stipulate which items should be limited to sale on medical, or veterinary prescription – a responsibility that now falls on the Medicines Commission.

Turner: I seemed to remember that there was a great argument over how one would define medicines. Roughly as I can remember it was anything that was injected or introduced into a body orifice.

⁴⁵ Dr Denis Wheeler (1910–1977) was Managing Director of the Wellcome Foundation from 1948 to 1967 and Deputy Chairman from 1967 to 1970. He served as President of the Association of British Pharmaceutical Industries (ABPI) from 1962 to 1964. In August 1962, he announced the formation of an expert committee on drug toxicity under the chairmanship of Dr R S F Hennessey, of the Wellcome Foundation Ltd. Anon. (1962) *Medical News*. *British Medical Journal* 2: 426.

⁴⁶ Yet further alternatives on the origin of the Yellow Card were offered in later correspondence. 'While I remember the discussions around the Yellow Card, and Dr Turner's colour blindness being mentioned, there were some other contributory reasons to the origin of the yellow card. It was quite clear to me that the greater number of contributions to the reporting on yellow cards would at least initially be those from general practitioners. This made it essential that any reporting system must be acceptable to the vast number of GPs. The desk trays of GPs, however, were full of bureaucratic papers for all kinds of purposes, in white and all sorts of colour combinations: only yellow was not in use at that time. Furthermore, as the only GP on the Safety of Drugs Committee, I had a number of meetings with the General Medical Committee to settle the argument as to whether general practitioners would only report if paid.' Ekkehard V Kuenssberg to Dr Tilli Tansey, 27 November 1996. 'I cannot add authoritatively to the ideas about the original choice of colour. I thought it was chosen as a warning colour, as in football, and in view of our wartime experience of driving at night, I used to tell people that it was a good colour for seeing in the dark, which was where we were most of the time, working in the drug safety field.' Professor W H W Inman to Mrs Lois Reynolds, 9 January 1997.

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Tansey: There have frequently been problems with their definition. In the 1930s when stilboestrol was first isolated by E C Dodds, he went to Edward Mellanby, the Secretary of the MRC to ask for pressure to get it classified as a poison, because he was so worried about its possible misuse.

Wade: When the sulphanilamides were introduced I think they too came under the Poisons Act initially. Up until 1968 when the Medicines Act came into being the British drug regulatory legislation was really a cock-up, as Tilli Tansey has already pointed out. It worked because people wanted it to work. But at the same time, it was made up of different systems. There was the Therapeutic Substances Act, the Poisons Act, and some special act passed in 1917 about the treatment of VD, and the Dangerous Drugs Act.

Professor Miles Weatherall:⁴⁷ I think that it is relevant at this point, it goes back to a remark made some time ago by Derek Bangham, that one or two manufacturers came along saying ‘what sort of evidence, what sort of experiments would you like us to do?’ and the Committee very firmly saying ‘you’ve got to submit your evidence and decide for yourselves’. Now it hasn’t been said very clearly today that there was no way, and there still is no way of predicting the safety of drugs. About 1959 the FDA produced a series of guidelines, suggestions or proposals, and then the Association of the British Pharmaceutical Industry set up an Expert Committee on Drug Toxicity, composed of the most toxicologically minded persons in each of several major companies, Wellcome, Glaxo, and so on. It produced a series of recommendations about what sort of animal experiments should be done. The logic was obscure. For drugs which were to be given only once to a patient, the standard of safety was to feed it to animals for at least a week. On the other hand, if the drug was to be used repeatedly, perhaps for the whole of the patient’s life, the testing should go on for three or six months, presumably because that was as long as any firm was prepared to hold up release of a new agent.

The whole set of recommendations involved a very large number of animal experiments of very dubious value, but what else could one do? They had some sort of face value, proper tests had been done and if after the proper tests had been done some unfortunate patient got a disease which hadn’t been tested for because nobody knew there was a test for it, well that would have to be dealt with when it happened. But it may well be that this was not pursued very closely by anyone, because nobody wanted to touch it if they could help it.

Bangham: This is the ABPI Committee to which I referred to earlier as working in parallel with the MRC Committee, set up with the same aims. The MRC soon realized how absurd it was to try to define all the tests to show whether a drug was ‘safe’. I would like to describe an episode that occurred about 1962, which shows the lack of new drug surveillance at that time. Sir Alexander Haddow, then

⁴⁷ Professor Miles Weatherall was Professor of Pharmacology at the London Hospital Medical College, University of London, from 1958 to 1966, now Professor Emeritus; Head of Therapeutics Research Division and a director at the Wellcome Research Laboratories, Beckenham, near London, from 1967 to 1975. He served as a **Medicines Commissioner from 1979 to 1981**. See Hanley T, Udall V, Weatherall M. (1970) An industrial view of current practice in predicting drug toxicity. *British Medical Bulletin* 26: 203–207.

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Director of the Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, came to me at the NIMR, saying that he had been doing some research with the iron-dextran complex, then widely given (by injection) for the treatment of iron deficiency anaemia. I cannot remember what was the main aim of his research, but he had injected the product intramuscularly into several guinea-pigs and rats, and several of them had developed malignant muscle sarcomas. He came, absolutely puzzled, to ask who in the country was concerned with the safety testing of such a drug. At that time preparations of dextran were controlled under the TSA by the Division of Biological Standards – but the iron-dextran was not. (The product is still in clinical use and no such adverse reaction has been reported in man.)

Professor David Davies:⁴⁸ Can I just make a quick point with regard to which regulation regulated which drug? When the Prescription-Only Medicine Subcommittee was formed it was an extraordinary surprise that we had difficulty in getting the pharmacists to agree to classifying almost any drug as a prescription-only medicine because, it pointed out (something that none of us knew), that drugs as dangerous as digoxin, trinitrin, for example, had never been under any kind of control at all. The pharmacists argued that as there had been no trouble with these drugs throughout history, why should we now want to stop the pharmacists providing them without a doctor's prescription?

Sir William Asscher:⁴⁹ Ron Mann⁵⁰ drew my attention to a report whose recommendations were never enacted because of the outbreak of the First World War. It was the Select Committee Report on Patent Medicines of 1914.⁵¹ This Committee was set up after Sir Joseph Beecham claimed that his pills could cure syphilis and gonorrhoea. Parliament felt that such claims should not be allowed and its recommendations were meant to prevent it. The report turned out to be a forerunner of the Medicines Act of 1968. Ron Mann claims that the thalidomide disaster might never have happened if this earlier report had become the law of the land. The recommendations *inter alia* required that all medicines should be registered and that the qualifications for being on that register should be that of quality, safety and efficacy, precisely the same reference as detailed in the 1968 Act.

⁴⁸ Professor David M Davies was Director of the Northern Regional Clinical Pharmacology Unit; Consultant Physician to the Newcastle University Hospitals and Shotley Bridge General Hospital; and Senior Lecturer in Clinical Toxicology at the University of Newcastle upon Tyne between 1962 and 1986; and Foundation Professor of Clinical Pharmacology at the Chinese University of Hong Kong from 1986 to 1988. He served on the **Committee on Safety of Drugs and Committee on Safety of Medicines from 1968 to 1986**, and on the Prescription-Only Medicines Subcommittee of the Medicines Commission from 1970 to 1972. He founded the *Adverse Drug Reaction Bulletin* in 1966 and was editor until 1995. He is editor of the *Textbook of Adverse Drug Reactions*. Oxford: Oxford University Press, 2nd edn, 1981.

⁴⁹ Professor Sir William Asscher was Professor of Medicine at the University of Cardiff from 1976 to 1987 and Director of the Institute of Nephrology in Cardiff from 1970 to 1987. In 1988 he became Dean (later Principal) of St George's Hospital Medical School until his retirement in 1996. He was **Chairman of the Committee on the Review of Medicines of the Department of Health from 1985 to 1987 and Chairman of the Committee on Safety of Medicines from 1987 to 1993**.

⁵⁰ Ronald Mann is Director of the Drug Safety Research Unit at Southampton and author of *Modern Drug Use: An Enquiry on Historical Principles*. Lancaster: MTP Press Ltd, 1984.

⁵¹ House of Commons. (1914) *Report from the Select Committee on Patent Medicines* (414). London: HMSO. Ordered to be printed on 4 August 1914.

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My question to Mr Turner is whether those who drafted the Medicines Act were acquainted with this 1914 Select Committee Report?

Turner: I don't recall that. I know that we went very deeply into it, into the history of various controls to satisfy the Parliamentary Legal Draftsmen who were very fierce. In fact, they identified drugs control going back to some law of Henry VI, I think. The Parliamentary Draftsmen were very thorough in their researches.

Asscher: The other thing that I was obviously going to say, having been associated with the Committee in the modern era is *plus ça change* because with the release of bad news which Bill Inman was talking about on the Pill, we have only recently seen exactly the same problems again. The timing of this is never right in the minds of doctors and patients. If you withdraw a drug too early people will always say 'Why did we have to lose a good medicine?' If you leave it too late the comment will be, 'Why did so many patients have to suffer before this drug was eventually withdrawn by the CSM?' You can't win, and nothing seems to have changed over the years, at least in this regard.

I was interested to hear comments on the difficulty these days (it is virtually impossible) to inform doctors of adverse drug reactions before patients get to hear about it through leaks. Even today it is still the same problem, despite E-mail and all modern means of communication. Media interest is so intense that leaks are almost inevitable.

Finally I was saddened to hear that Professor Finney felt there is no spirit left in today's CSM, comparable to that prevailing in the pioneering days of the CSD. As its recently retired chairman, I can assure them that the spirit of the CSD is very much alive in the CSD today. Perhaps its present Chairman should invite Professor Finney to the next CSM Christmas Dinner for him to find out that nothing has changed.

Lock: Well, Bill, we'll let you come back in 25 years and say so.

Asscher: I can guarantee that under Mike Rawlins⁵² the Committee is still functioning, and there is a tremendous freedom of expression on that Committee and I regard it as the best postgraduate centre in the United Kingdom actually.

Lock: I wonder if Professor Finney would like to have a final coda. I think we have short-changed him a bit. Is there anything you would like to add? Points that haven't been raised?

Finney: I think it's only proper that I should reply to that. Certainly it was not my intention to give offence, but I obviously hurt someone's feelings. It's not my normal intention to hurt feelings, unless I do it deliberately. I want to avoid any

⁵² Professor Michael Rawlins (1941–) has been Ruth and Lionel Jacobson Professor of Clinical Pharmacology at the University of Newcastle upon Tyne since 1973 and Chairman of the Committee on Safety of Medicine since 1993. A member of the Committee since 1980, he served on the Committee of Toxicity from 1989 to 1992.

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suggestion that I think CSM worthless or lacking in spirit, although my original words may have given a wrong impression. My knowledge is, of course, restricted to adverse reactions. If, as Sir William says, things are better today, I am delighted. When we began our work in 1963, we were a group of people who did not know one another and who scarcely knew what they were intended to do. My impression was that we rapidly developed a strong team enthusiasm – an *esprit de corps* – that made our meetings spells of hard and rewarding work. To have missed a meeting would have been letting the side down.

After the change to CSM, there was much greater bureaucracy, civil servants telling us what we could and could not do and wanting everything formalized. I think that there was even a silly business of our being paid an attendance fee or of having to conform to Inland Revenue requirements on our expense claims lest the Treasury should inadvertently pay us for a sandwich that was properly a charge on an individual pocket. One consequence was that members became less conscientious about attendance at and participation in every meeting. Silly little things, but a definite change in the atmosphere of an activity that I had for years found fascinatingly challenging. One particular matter was the unexpected departure of Bill Inman, who was allowed to resign and disappear without a word of thanks or a minute of appreciation from the organization within which he had so long been effective.

But if things are very different today – of course I have no knowledge of this, it's now many years since I was myself connected in any direct sense with the body – I am delighted to hear that it is operating so successfully today. From a professional point of view, of course I am especially delighted that it has now improved its facilities both in computing and in having its own statistical staff, which was something I was very conscious of as lacking in the old CSD.⁵³ I think something that has just been referred to in passing was that I was also conscious with the CSD that we never got a proper feedback mechanism to the medical profession operating as well as we might.

The other thing that I felt was very sad in those days was that we missed the opportunity that undoubtedly existed in the early days of Britain playing a leading part in an international network. WHO does not have the best of names, I suspect, within the medical profession in Britain, but there was a time when they were receptive to new ideas. We had many successful and forward-looking discussions in Geneva and elsewhere with Hans Halbach⁵⁴ and other people in WHO, where

⁵³ These remarks were later amplified: 'In the Adverse Reactions Subcommittee, I and others were perpetually arguing for adequate computer facilities, always to be fobbed off with temporary expedients. In the mid-1970s, we thought we had begun to progress, and we had prepared a formal case for the Department to provide a suitable computer to be dedicated to CSM work. Almost at my last meeting, I ventured to ask about the progress of this proposal. A civil servant who attended as a representative of officialdom answered firmly that members of the subcommittee had no power to ask questions about this matter.' David Finney to Mrs L A Reynolds, 9 January 1997. Dr Kuenssberg also remarked on the paucity of computer support in a later letter: 'I would also like to comment on the expressions of the "good working" of the Safety of Drugs Committee. I remember that there was considerable unhappiness among the Committee members, the reason being that the Committee was certain that it required computing facilities to do its job properly. During my membership, however, we seemed to be prevented from obtaining this essential resource. I think it was during my last two years of membership that I certainly considered resignation because we as a Committee were making no progress with the computer question.' Ekkehard V Kuenssberg to Dr Tilli Tansey, 27 November 1996.

⁵⁴ Halbach H. (1964) Development of a WHO programme for drug safety. *Pharmakotherapie* 2 (1): 239–243.

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there was a possibility of a real advance on the world front in monitoring the dangers that were bound to arise from time to time with new drugs. But there was a certain obstructiveness, that I think again increased after the change from CSD to CSM, increased obstructiveness, the unwillingness of Britain to commit itself to doing anything positive within Europe.

Lock: Can I finish by thanking all our principal speakers who have travelled from far and wide, often at great inconvenience to themselves. I think we have had a splendid afternoon. Thank you all very much.

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