DRUGS AFFECTING 5-HT SYSTEMS

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary, University of London, on 20 November 2012

Edited by C Overy and E M Tansey

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WHAT IS A WITNESS SEMINAR?

The Witness Seminar is a specialized form of oral history, where several individuals associated with a particular set of circumstances or events are invited to meet together to discuss, debate, and agree or disagree about their memories. The meeting is recorded, transcribed and edited for publication.

This format was first devised and used by the Wellcome Trust's History of Twentieth Century Medicine Group in 1993 to address issues associated with the discovery of monoclonal antibodies. We developed this approach after holding a conventional seminar, given by a medical historian, on the discovery of interferon. Many members of the invited audience were scientists or others involved in that work, and the detailed and revealing discussion session afterwards alerted us to the importance of recording 'communal' eyewitness testimonies. We learned that the Institute for Contemporary British History held meetings to examine modern political, diplomatic and economic history, which they called Witness Seminars, and this seemed a suitable title for us to use also.

The unexpected success of our first Witness Seminar, as assessed by the willingness of the participants to attend, speak frankly, agree and disagree, and also by many requests for its transcript, encouraged us to develop the Witness Seminar model into a full programme, and since then more than 50 meetings have been held and published on a wide array of biomedical topics.[1] These seminars have proved an ideal way to bring together clinicians, scientists, and others interested in contemporary medical history to share their memories. We are not seeking a consensus, but are providing the opportunity to hear an array of voices, many little known, of individuals who were 'there at the time' and thus able to question, ratify or disagree with others' accounts – a form of open peer-review. The material records of the meeting also create archival sources for present and future use.

The History of Twentieth Century Medicine Group became a part of the Wellcome Trust's Centre for the History of Medicine at UCL in October 2000 until September 2010. It has been part of the School of History, Queen Mary, University of London, since October 2010, as the History of Modern Biomedicine Research Group, which the Wellcome Trust funds principally

[1] See pages 203–208 for a full list of Witness Seminars held, details of the published volumes and other related publications.

under a Strategic Award entitled 'The Makers of Modern Biomedicine'. The Witness Seminar format continues to be a major part of that programme, although now the subjects are largely focused on areas of strategic importance to the Wellcome Trust, including the neurosciences, clinical genetics, and medical technology.[2]

Once an appropriate topic has been agreed, usually after discussion with a specialist adviser, suitable participants are identified and invited. As the organization of the seminar progresses and the participants' list is compiled, a flexible outline plan for the meeting is devised, with assistance from the meeting's designated chairman/moderator. Each participant is sent an attendance list and a copy of this programme before the meeting. Seminars last for about four hours; occasionally full-day meetings have been held. After each meeting the raw transcript is sent to every participant, each of whom is asked to check his or her own contribution and to provide brief biographical details for an appendix. The editors incorporate participants' minor corrections and turn the transcript into readable text, with footnotes, appendices and a bibliography. Extensive research and liaison with the participants is conducted to produce the final script, which is then sent to every contributor for approval and to assign copyright to the Wellcome Trust. Copies of the original, and edited, transcripts and additional correspondence generated by the editorial process are all deposited with the records of each meeting in the Wellcome Library, London (archival reference GC/253) and are available for study.

For all our volumes, we hope that, even if the precise details of the more technical sections are not clear to the non-specialist, the sense and significance of the events will be understandable to all readers. Our aim is that the volumes inform those with a general interest in the history of modern medicine and medical science; provide historians with new insights, fresh material for study, and further themes for research; and emphasize to the participants that their own working lives are of proper and necessary concern to historians.

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[2] See our Group's website at http://www.history.qmul.ac.uk/research/modbiomed (visited 13 August 2013).

ACKNOWLEDGEMENTS

The topic of 'Drugs affecting 5-HT systems' was suggested as a Witness Seminar by Professor Paul Andrews and Professor Gareth Sanger and we are grateful for their assistance over several months in planning the meeting. Our thanks also go to Professor Rod Flower for his excellent chairing of the occasion, and to Dr Patrick Humphrey for providing images and documents to illustrate the volume.

As with all our meetings, we depend a great deal on Wellcome Trust staff to ensure their smooth running: the Audiovisual Department, Catering, Reception, Security and Wellcome Images. We are also grateful to Mr Akio Morishima for the design and production of this volume; the indexer Ms Liza Furnival; Mrs Lois Reynolds and Ms Fiona Plowman for proof reading; Mrs Deborah Gee for transcribing the seminar; Mr Adam Wilkinson for assisting in the organization of the meeting and also Ms Emma Jones and Mr Alan Yabsley for help with running the seminar. Finally, we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

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ILLUSTRATIONS AND CREDITS*

* Unless otherwise stated, all photographs were taken by David Sayer, Wellcome Trust, and reproduced courtesy of the Wellcome Library, London.

ABBREVIATIONS

5-H1AA	5-Hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine
5-HTP	5-Hydroxytryptophan
BDNF	Brain-derived neurotrophic factor
BPS	British Pharmacological Society
cAMP	Cyclic adenosine monophosphate / cyclic AMP
CNS	Central Nervous System
COPD	Chronic obstructive pulmonary disease
DHE	Dihydroergotamine
EEG	Electroencephalography
FDA	Food and Drug Administration, US
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
GPCR	G protein-coupled receptor
GSK	GlaxoSmithKline
hERG	Human Ether-à-go-go-Related Gene
HGS	Human Genome Sciences
HPLC	High-performance liquid chromatography
HTS	High throughput screening
IBS	Irritable bowel syndrome
IP	Intellectual property
IUPHAR	International Union of Basic and Clinical Pharmacology
LSD	Lysergic Acid Diethylamide
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor

MDMA	3,4-Methylenedioxymethamphetamine (ecstasy)
MRC	Medical Research Council
NCE	New chemical entities
NIH	National Institutes of Health
NMDA	N-methyl D-aspartate
NPY	Neuropeptide Y
OCD	Obsessive compulsive disorder
PBG	Phenylbiguanide
PDG	Phenyldiguanide
PET	Positron emission tomography
PK	Pharmacokinetics
PPI	Proton pump inhibitor
PTSD	Post-traumatic stress disorder
SMW	Small molecular weight
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization

ANCILLARY GUIDES

There are several reliable websites giving further details on drugs and pharmacological techniques mentioned in the text. See for example:

The DrugBank database
www.drugbank.ca/ (visited 16 September 2013)

Medicines Information from NICE
www.evidence.nhs.uk/about-evidence-services/content-and-sources/medicines-information (visited 16 September 2013)

The PubChem project
http://pubchem.ncbi.nlm.nih.gov/ (visited 18 September 2013)

The IUPHAR / BPS Guide to Pharmacology
www.guidetopharmacology.org/ (visited 21 October 2013)

Glossary of Terms and Symbols Used in Pharmacology (Boston University School of Medicine: Pharmacology and Experimental Therapeutics)
www.bumc.bu.edu/busm-pm/academics/resources/glossary (visited 21 October 2013)

INTRODUCTION

It was in the very early hours of a February morning in 1977 that I first looked down the microscope and saw yellow fluorescence, characteristic of 5-hydroxytryptamine (5-HT) in frozen sections of *Octopus* brain. After struggling for two years with the capricious fluorescence histochemical technique to locate catecholamines and 5-HT, I finally had a successful result, and the PhD that had seemed a remote possibility for many months finally began to look feasible.[1]

Given the enormously important topic of this volume – the discovery and development of drugs affecting 5-HT systems – this small excursion into *Octopus* neurochemistry might seem irrelevant. However, cephalopod molluscs have played important roles in the history of 5-HT. More than 30 000 pairs of posterior salivary glands of *Octopus vulgaris* were used by Vittorio Erspamer, for the first extraction and identification of enteramine, which was later shown to be identical to serotonin discovered by John Gaddum, and chemically characterized as 5-hydroxytryptamine.[2] Other molluscs have provided some of the most sensitive bioassays for 5-HT, as Gaddum and Paasonen described in 1955,[3] and several participants in this Witness Seminar recollected either using such bioassays or investigating invertebrate pharmacology at the beginning of their careers. Many reflected, however, that invertebrate receptors seemed to be very different from those found in mammals; they had, as David Wallis put it, 'a parallel pharmacology'.[4] One Witness, Merton Sandler, remembered attending a lecture by Vittorio Erspamer in London in the early 1950s, and being intrigued enough to start work on the degradative enzyme monoamine oxidase, a field which became highly significant for the development of a whole class of therapeutic drugs: the monoamine oxidase inhibitors.[5]

Chairing Erspamer's lecture had been Sir Henry Dale, who shared the Nobel Prize in 1936 for the discovery of chemical neurotransmission. One of the many young scientists he inspired was John Gaddum, who followed in his footsteps to the Wellcome Physiological Research Laboratories, and then to the National Institute for Medical Research in Hampstead in 1927. There he

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[1] See, for example, Tansey (1980).

[2] Erspamer (1948); Erspamer and Asero (1952).

[3] Gaddum and Paasonen (1955).

[4] See, for example, comments by Wallis, pages 9 and 78; and by Humphrey, page 79.

[5] Sandler, page 10.

joined Dale's lab, and became immersed in work that would demonstrate the neurotransmitter function of acetylcholine (for which Dale coined the word 'cholinergic' in 1934). Gaddum also began investigations into a wide range of physiologically active, naturally occurring chemicals, including Substance P and what was later recognized to be 5-HT. In the late 1950s, he was also one of the first to make a direct link between the brain and 5-HT from his work on the interactions of 5-HT and LSD, at a time when newly discovered psychoactive drugs such as chlorpromazine stimulated such work.[6] In 1957 Gaddum's work with Picarelli demonstrated two different 5-HT receptors: the D receptor on smooth muscle, and the M receptor on nerves. The resulting publication was a seminal paper cited by several participants as a major influence on their later work on 5-HT receptors and drug development.[7]

There was however a substantial delay between that publication and the work discussed at this Witness Seminar. Science is largely a social activity, and meeting like-minded, sometimes unlike-minded, people is an important part of the creative process. Widespread interest in 5-HT was slow in developing. Strange as it may seem nowadays, even neuroscience was not the dominant discipline it has since become. For example, my own exciting histochemical discoveries (well, I was excited) were first transmitted to the Sheffield branch of the Brain Research Association (now the British Neuroscience Association), which then comprised a couple of zoologists and biochemists, a few more physiologists and psychologists and a stray psychiatrist who was the only clinician to attend. For those intrigued by the actions of 5-HT, it took some time to create a critical mass. In 1957, for example, when Gaddum and Picarelli's work was published, an international bibliography of psychopharmacology lists only 17 publications on serotonin.[8]

Pat Humphrey, who started working on 5-HT receptors in the early 1970s, recalled giving a communication to the British Pharmacological Society (BPS) in 1976 that 'went down like a lead balloon', there was so little interest.[9] Two years later he had discovered 'kindred spirits' in Birmingham, Philip Bradley

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[6] Gaddum and Hameed (1954); Gaddum (1957). See also the Witness Seminar on drugs in psychiatric practice (Tansey, Christie and Reynolds (eds) (1998)).

[7] Gaddum and Picarelli (1957). See also the Witness Seminar on platinum compounds (Christie and Tansey (eds) (2007)).

[8] Caldwell (1958).

[9] Humphrey, page 41.

and also Richard Green, who was feeling somewhat isolated himself.[10] A major turning point was a 1984 meeting of the BPS in Birmingham, when several individuals with similar interests finally met each other, discussed results, ideas and future projects. The subsequent formation of the Serotonin Club in 1987 created an important international organization that anyone interested in 5-HT research could attend. That same year, when the International Congress of Pharmacology (later IUPHAR) met in Sydney, Australia, a 5-HT satellite meeting on Heron Island, Queensland addressed the vexed questions of how many 5-HT receptors there might be, and how to standardize and define their terminology. From that meeting, an international nomenclature committee was established, four members of which contributed to this Witness Seminar. That committee produced the definitive paper on 5-HT receptor classification in 1994 (one of the earliest attempts to sort out the classification of complex receptor systems), which has continued to inform the field ever since.[11] Further increasingly sophisticated analyses and understanding of 5-HT receptors, the development of precisely (and not so precisely) targeted drugs for these receptors, and their clinical management and utility, provided much of the engaging and frank discussion in this volume.

Meetings of the BPS, the Serotonin Club and IUPHAR were, and still are, regularly attended by industrial, academic and clinical researchers. Many of the Witness Seminar participants commented on the collaborations, the potentials and the tensions engendered by this mix, and the shifting priorities within universities and industrial labs from the 1970s through to the first decade of the twenty-first century (a theme that has arisen in several previous Witness Seminars).[12] Whilst industrial organizations were frequently praised for promoting research in their own labs and for providing travel funds, studentships and project grants to academics,[13] the downside of commercial expectations, especially from marketing departments, was also acknowledged.[14] Scientists working in industry were not immune from similar pressures as Wes Miner graphically illustrates with his account of a particularly tense meeting

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[10] Humphrey, page 43; Green, page 45.

[11] Hoyer *et al.* (1994)

[12] See, for example, the Witness Seminars on clinical pharmacology (Reynolds and Tansey (eds) (2008 a and b)) and platinum compounds (Christie and Tansey (eds) (2007)).

[13] See comments by Bakhle, page 88, and Green, page 90.

[14] See, for example, Curzon, pages 129–31.

with Beechams' management.[15] However a major, and repeatedly accredited, debt to the pharmaceutical industry was the free distribution of experimental compounds. This facilitated a wide range of innovative research, especially in understanding basic physiological control mechanisms in health and disease, much of which might not have been conducted in a solely industrial lab (for example, in the development of the 5-HT_3 receptor antagonists).[16] As Mike Tyers emphasizes, these exchanges were not only between academe and industry, but also between industry and industry.[17]

The work described by the participants at this meeting has contributed to the development of some of the most frequently prescribed, and most profitable, medicinal compounds in the world. Migraine, emesis, psychiatric and GI disorders, amongst others, all have therapeutic, and in some cases prophylactic, treatments based on their effectiveness on 5-HT systems. There was nothing inevitable about their development. The stories told here emphasize the importance of serendipity, collaboration and communication across many disciplines and several institutional locations; and they illustrate some of the false starts, disappointments and frustrations as well as the satisfactions and rewards of such research, for researchers, companies and ultimately for patients.

E M Tansey
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[15] Miner, pages 59–60.

[16] Miner, page 88; see also the Witness Seminar on platinum compounds (Christie and Tansey (eds) (2007)).

[17] Tyers, page 83.

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DRUGS AFFECTING 5-HT SYSTEMS

Participants*

Professor Paul Andrews
Dr Jeffrey Aronson
Dr Y S (Mick) Bakhle
Dr Tom Blackburn
Professor David Clarke
Professor Phillip Cowen
Professor Helen Cox
Professor Gerald Curzon (pm only)
Dr Colin Dourish
Professor Rod Flower (Chair)
Professor Richard Green
Professor Daniel Hoyer
Dr Patrick Humphrey
Dr Jackie Hunter (pm only)
Professor Alberto Kaumann
Professor Charles Marsden
Mr Wesley Miner
Professor Gavin Reynolds
Professor Merton Sandler
Professor Gareth Sanger
Dr Mike Tyers
Professor Tilli Tansey
Professor David Wallis

Apologies include: Dr Alec Coppen, Dr Gunther Engel, Dr Wasyl Feniuk, Dr John Fozard, Dr Graeme Martin, Dr Derek Middlemiss, Professor Robert Naylor, Professor Trevor Sharp

* Biographical notes on the participants are located at the end of the volume

Figure 1: Professor Rod Flower and Professor Tilli Tansey.

Professor Tilli Tansey: Can I begin by welcoming everybody to this full-day meeting on Drugs Affecting 5-HT Systems.[1] The purpose of this meeting is to find out what really happened. These Witness Seminars are meetings where we ask clinicians and scientists to tell us how ideas developed, how projects developed, who were the drivers, what the brakes were; to go behind the scientific papers. This meeting came out of an earlier meeting we had on platinum compounds[2] which ended up talking about 5-HT receptor antagonists and it seems that looking at drugs affecting 5-HT systems was going to be a very profitable, rich area for us to work on. Paul Andrews and Gareth Sanger, who worked with me on this meeting, and I have been talking for some time about doing a meeting on 5-HT and a Strategic Award grant from the Wellcome Trust has enabled us to develop and continue our programme and, indeed, this is one of the first meetings under that new Strategic Award. Our purpose today is to record all the discussions, all the debates, disagreements, if there are any, differences of opinion; this is the stuff of history. It will be transcribed and edited for publication. Everything is made freely available on the web to download. But let me stress that nothing will be published without your permission. You will have plenty of opportunity to amend the record, to add footnotes and you will be asked to assign copyright to the Wellcome Trust. So nothing will be published without your express permission.

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[1] For consistency the term '5-HT' has been used throughout and in most cases, the term 'serotonin' has been changed to 5-HT.

[2] Christie and Tansey (eds) (2007).

As we were planning this meeting and we'd set it up, I received a letter from David Wallis asking if I would consider a meeting on 5-HT because he was writing a book on the history of 5-HT.[3] This was a very useful confluence of ideas and different perspectives, so David has also been involved with Gareth and Paul and me in setting up the meeting. A key part of any meeting is selecting the chairman and I'm delighted that we've persuaded Rod Flower to chair this Witness Seminar. Rod is an old hand; he's already chaired two of these meetings for us. So without further ado I'll hand over to Rod Flower.

Professor Rod Flower: Thanks very much Tilli and good morning everyone. Actually the discovery that defibrinated or clotted blood contained a vasoconstrictor substance was made over a century ago but it remained in the literature as an isolated observation for many years.

John Gaddum, in an early edition of his pharmacology textbook, called it *Spätgift* and elsewhere refers to the substance(s) as vasotonins.[4] He evidently thought there was more than one. He also pointed out, in what I thought was a very prescient comment at the time, that this factor could be removed from the blood during a passage through the lungs. In 1948 this substance was isolated in a pure form from serum by a group at the Cleveland Clinic and was given the name 'serotonin' because it was a serum-derived substance that had an effect on vascular tone.

Meanwhile Vittorio Erspamer in Italy had identified a substance from enterochromaffin cells that contracted the intestine and which he called 'enteramine'.[5] It wasn't until 1952 that it was realized that serotonin and enteramine, as well as many other substances with similar names such as vasoconstrictine, vasotonin, thromocytin and thromobotin, were identical and it was renamed 5-HT – although we still adhere to the old nomenclature sometimes.[6]

Gaddum and Picarelli did the pioneering experiments on 5-HT receptors suggesting that there were two types, which they termed D and M.[7] Later, of course, this notion was overthrown by the radio ligand binding data. We now

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[3] Wallis (in preparation).

[4] Gaddum (1948), page 250. For biographical details of Gaddum see page 147.

[5] See, for example, Erspamer (1948); Erspamer and Ghiretti (1951). For biographical details of Erspamer see pages 145–6.

[6] Erspamer and Asero (1952).

[7] Gaddum and Picarelli (1957).

know we have at least 14 5-HT receptors and one additional receptor in the mouse. Most of these are G-protein coupled receptors but there is one ligand-gated ion channel.

These discoveries initiated a very fertile era of drug discovery across a wide range of diseases. There are drugs that affect mood, nausea and vomiting and, of course, migraine. Indeed, I think there are currently about 11 drugs for treating migraine on the market.[8]

So how we got from those early observations of vasoactive factors in clotted blood to the current situation where we have some 14 receptors and a clutch of highly successful drugs, is what we're here to find out about (Table 1). Let's go back to the beginning of the story. As I've said there were a variety of substances reported in the literature in the 1940s and 1950s. Can anyone remember back that far and remember the sorts of discussions that went on? I noticed that Gaddum's pharmacology book, which I referred to, was published in 1948. I think it was his third edition. So Mick did you read that book when you were at Oxford?

Before the 1970s Metabolism, distribution, synthesis Techniques of investigation Binding sites Receptor classification
The 'heady days' Scientific communication 1984 Serotonin Receptors Symposium, Birmingham 1987 The Serotonin Club 5-HT receptors and their classification
From theoretical pharmacology to practical use Funding Industry and academe – tensions and collaborations Specific drugs
Impact

Table 1: Outline Programme for 'Drugs affecting 5-HT Systems' Witness Seminar

[8] The 11 drugs include both therapeutic and prophylaxis, see the *British National Formulary.*

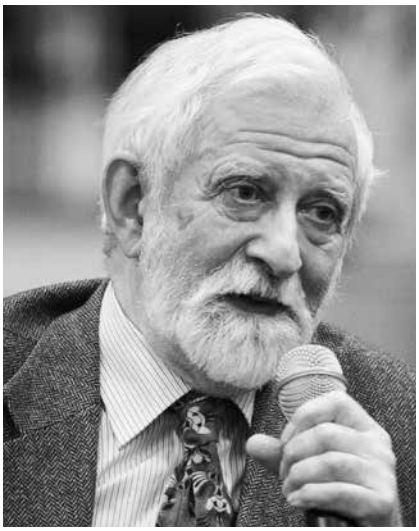

Figure 2: Dr Mick Bakhle.

Dr Mick Bakhle: I have to admit I don't think I ever read Gaddum's *Pharmacology.* But my contact with 5-HT was at the end of the 1960s, 1968–70, something like that, at the Royal College of Surgeons, as a part of the work we were doing on metabolism of vasoactive materials, endogenous vasoactive substances, in the pulmonary circulation. It came after some work John Vane had done *in vivo* and Val Alabaster and I took that on a stage further to look at what happened in a perfused lung.[9] 5-HT was one of the things that was cleared very effectively by a single passage through the pulmonary circulation, which was, perhaps, why I always thought you got right-sided cardiac lesions in the carcinoid syndrome and not left-sided lesions, because all the 5-HT had gone.[10] It had been secreted into the intestinal circulation, come up the venous side, and essentially been cleared on passage through the pulmonary circulation. So, maybe arterial blood was relatively free of 5-HT whereas the venous blood had been fairly thick with 5-HT. Anyway, that's what we did and it seemed very clear from our work that there was an uptake system in the lung, which was very like the uptake system already shown by Les Iversen for catecholamines.[11] There was also a

[9] Thomas and Vane (1967); Alabaster and Bakhle (1970). For Sir John Vane see page 135, note 353 and biographical details on pages 157–8.

[10] Professor Merton Sandler added: 'See Goble, Hay and Sandler (1955) and Gobel *et al.* (1956) for the first formulation of this concept in the scientific literature.' Note on draft transcript, 12 February 2013.

[11] Iversen (1967); see also biographical details on pages 150–1.

monoamine oxidase (MAO) activity because none of that 5-HT which went into the lung through the pulmonary circulation was retained; it all came out again as metabolite, in this case 5-HIAA (5Hydroxyindoleacetic acid). So it was a very rapid, and I thought very interesting, physiological clearance mechanism because, in a sense, you couldn't overfill the lung with 5-HT because it was continuously cleared. So this was a continuous mechanism for clearing 5-HT from venous blood,[12] apart from the platelets, which were doing it all the time. Later on, of course, we found out that the clearance was taking place in the endothelial cells. The only important thing, I think, about the pulmonary circulation is that it is one of the two circulations that take the entire cardiac output. So this was a highly effective clearance mechanism. The only other comment I'd like to make on this point is that about ten years after we did this work, a PhD student (Marie-Anne Pilot) came to us from the London Hospital Medical School, where she was studying the secretion of acid in the isolated blood-perfused stomach of a dog, and said: 'We can't do it. It won't work.' Then we found out that it was already known that the isolated dog stomach, perfused with blood, won't secrete acid, but if you then cross-perfuse that isolated stomach with blood from another dog, it *will* secrete acid. And this all turned out to be due to the fact that there was a lung in circuit, so that you had the dog's own pulmonary circulation still in the circuit but it was then pump perfused through the stomach and the stomach then secreted acid very well.[13] The failure to secrete acid was methysergide-sensitive, which I thought was a very nice way to show that this lung clearance was relevant. That was my early exposure to 5-HT.

Professor Richard Green: John Vane had actually published a method for bioassay in about 1957.[14] I'm not very convinced about the lung story in that normally, if platelets are harvested intact and not damaged (as so easily can be done by taking the blood), you will find essentially no 5-HT at all because platelets are not full of 5-HT and they take it up very avidly. Going back, Reginald Stacey, at Tommy's [St Thomas' Hospital, London], was one of the very first people together with Mike Rand to actually show that platelets contain

[12] Professor Merton Sandler wrote: 'There was even speculation about the possible role of this in the pathogenesis of migraine, Sandler (1972).' Note on draft transcript, 12 February 2013.

[13] Pilot (1979).

[14] Vane (1957).

5-HT.[15] I think they're the real mechanism for getting rid of excess. With David Grahame-Smith, we used to look at the carcinoid syndrome because it was one of his big interests,[16] and the only time you could find 5-HT in the plasma was really when the condition was so severe that the platelets were loaded up and they just couldn't take up any more.

Professor Merton Sandler: I love hearing all these pharmacologists speculate. [Laughter] But you know I came in from the clinical side and let me mention the name straight away of Michael Pare, with whom I worked for donkey's years.[17] Back then, Mike and I were in the army together pottering around and trying to do significant things with amino acids because we were bored out of our minds with military duties. So we built some chromatography equipment and came up with some semi-quantitative observations of interest. When I came out of the army in 1953, I went to work at the Brompton and teamed up with a couple of bright Antipodeans, Alan Goble and David Hay. They soon went to work down the road at the National Heart Hospital and promptly encountered one of the first cases of carcinoid syndrome to hit the headlines, which we investigated to the hilt![18] David Hay and Alan Goble astutely recognized this new syndrome, previously described in only two or three places in the literature. Carcinoid syndrome and its bizarre clinical presentation, of course, was what led me down the monoamine avenue, where I've remained ever since. I was still at the Brompton, so daily, 24-hour samples of urine and blood obtained by cardiac catheter from various sites used to come to me. We detected massive amounts of 5-HT and, of course, of urinary 5hydroxyindoleacetic acid, which is still the way you make the diagnosis clinically. So I became a bit of a carcinoid expert.[19] Fred Lembeck in Austria was actually the first to identify enteramine – which is what Erspamer first called 5-HT at that time – in small semi-malignant

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[15] Reginald Stacey (1905–1974) was at the time Reader in Pharmacology and Therapeutics at St Thomas' Hospital; he was Professor there from 1958 to 1970. Michael Rand (1927–2002) held the Chair of Pharmacology at the University of Melbourne from 1965 to 1992. See Rand and Reid (1951); Hardisty and Stacey (1955).

[16] Grahame-Smith (1968). David Grahame-Smith (1933–2011) was Rhodes Professor of Clinical Pharmacology at the University of Oxford from 1972 to 2000. See further biographical details on page 147.

[17] See page 20 and note 277.

[18] Goble, Hay and Sandler (1955); Gobel *et al.* (1956)

[19] Williams and Sandler (1963).

carcinoid tumours of the small intestine.[20] Little 'semi-benign' carcinoids in the gut that he had somehow picked up and good luck to him; Fred should be remembered as setting up this major signpost.[21]

Flower: Before we move on I want to try to capture as much as possible about those very early days when we didn't really understand 5-HT metabolism or removal. David, have you got a comment on that?

Professor David Wallis: Yes, I was going to say, there's a kind of parallel pharmacology with 5-HT in invertebrates; in fact someone just mentioned John Vane's sensitive assay, which I think was rat's stomach strip.[22] But before that, John Gaddum had used an invertebrate heart preparation in 1953 that was very highly sensitive to 5-HT[23] and, of course, the work by Erspamer to

Figure 3: Professor David Wallis.

[20] Lembeck (1953). Fred Lembeck (b. 1922) worked as an assistant in the Institute of Physiology in Graz. He later became the Director of the Institute for Experimental and Clinical Pharmacology at the University of Graz.

[21] Professor Merton Sandler wrote: 'It led directly to the direct quantification of the 5-hydroxyindole pathway by Udenfriend and his team at Bethesda.' Note on draft transcript, 12 February 2013. See Bowman, Caulfield and Udenfriend (1955); Bogdanski *et al.* (1956).

[22] Vane (1957).

[23] Gaddum and Paasonen (1955).

some extent concentrated on invertebrate mechanisms. And I think there was a kind of lag where the physiology and pharmacology of 5-HT in invertebrates took ages to catch up; the receptors were peculiar, they didn't seem to fit in with schemes from the mammalian classification. This parallel history finally did catch up but it's an interesting aspect of the story.[24]

Flower: Has anyone else got any comments on the very early days?

Sandler: Erspamer came to London to give a special University of London lecture and he was obviously thought to be important at that time because they put Sir Henry Dale in the chair of that meeting! When Erspamer spoke nobody could understand a word of what he said. From my point of view it was a bit of a damp squib; monoamine oxidase had never really impinged on my consciousness at the time but still I came away from that lecture thinking: 'We must measure monoamine oxidase.' Indeed I teamed up with Alan Davison at Queen Square and we were the first to identify human monoamine oxidase using the Warburg apparatus, which dated from the Middle Ages of biochemistry![25] Erspamer was a nice man who rarely travelled and hardly ever moved in scientific circles. We gathered that this was one of the few times that he'd ever been to England – or anywhere in Europe for that matter – because he couldn't speak anything but what sounded like broken Italian!

Flower: David, were you at the lecture as well?

Wallis: No, just that the early discovery by Maurice Rapport was very quickly followed by the synthesis by Abbott Laboratories and Upjohn, and they distributed samples of 5-HT worldwide as far as I can see.[26] So a lot of the early observations depended on this largesse; I think John Gaddum got his 5-HT from one of those two firms[27] and one of the earliest electrophysiological observations of actions in the mammalian nervous system was by A S Paintal.

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[24] Professor Paul Andrews wrote: '5-HT is also found in plants. Stinging nettle contains 5-HT as well as ACh and histamine (Collier and Chesher (1956)). There is a nice experiment (Brittain and Collier (1957)) showing that contraction of a range of smooth muscle tissues *in vitro* was reduced by dock leaf extract.' Note on draft transcript, 7 January 2013.

[25] Davison and Sandler (1956).

[26] Maurice Rapport (1919–2011) was working at the Cleveland Clinic, see pages 12–13. For further biographical information see page 154.

[27] See page 12 and note 35.

He got his 5-HT from one of the two drugs firms as well.[28] I think these firms did quite a lot to promote investigating actions by people who previously had not got access to the pure material.

Flower: I'd like to say that when drug companies do this sort of altruistic thing it makes a huge difference to the field. The same thing happened with the prostaglandins: if it hadn't been for Upjohn distributing free samples of standardized materials the field would never have got anywhere.

Bakhle: The only further point I would make about the metabolism and the clearance in lung is that, to me, the big difference between the system that appears to be now in the endothelial cell and the other systems, for instance in nerves or indeed in the platelets, is that in nerves and in platelets the amine is taken up and stored in vesicles. It's preserved for whatever purpose; you could say for later release. Whereas in the endothelial cell, and therefore in the pulmonary circulation, it is a true clearance: it goes in, is metabolized and then is spat out again as metabolite. So it's just a clearance mechanism.[29] It isn't a storage mechanism and, as far as I know, nobody has suggested that the amines that might be taken up by the endothelium are then 'releasable', as they might be neurons or from platelets. So the lung endothelium operates in a different way from nerves or platelets – I used to call it 'physio-pharmacokinetic'; essentially that is what was happening in the lung and it wasn't in any sense a neuronal or a functional way of protecting 5-HT, or any other amine, for further release.

Professor Charles Marsden: Just to bring the Erspamer story a bit more up to date. I was invited to give a talk in June 2009 at the 100th anniversary of his birth. The event was held at Sapienza University of Rome and was organized by the Italian Society of Histochemistry.[30] His wife, Giulianna, who is also a scientist, was there and the event was of interest to me because my first links

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[28] Professor Paul Andrews wrote: 'Paintal and others (especially John Widdicombe and Ainsley Iggo) used phenyl bi/di guanide (PBG / PDG) to activate vagal afferents. Most of the relevant papers are in the *Journal of Physiology*. PBG turns out to be a 5-HT_3 receptor agonist and together with the more potent m-chloro PBG is still used today. The use of PDG seems to have originated with von Bezold at the end of the nineteenth century, and, of course, the von Bezold-Jarish reflex played an important role in identification of the 5-HT antagonist effect of metoclopramide identified by Fozard and which in turn made a major contribution to identification of selective 5-HT_3 receptor antagonists.' Note on draft transcript, 7 January 2013.

[29] See note 9.

[30] For Erspamer, see notes 5 and 6.

with 5-HT were with invertebrates and, of course, the majority of Erspamer's work was invertebrate based, particularly with the molluscs, which were the invertebrates that I began my career working on.[31]

Flower: Before we leave this, you mentioned a group at the Cleveland Clinic, Maurice Rapport, Arda Green and Irvine Page. Does anyone have any memories of them because obviously that was a very important step forward in the history of 5-HT?[32]

Sandler: I remember them very well. There were a lot of meetings at that time, some in England and some in the United States, that one was lucky as a very young worker, as a youth really, to get involved in. But Page was sort of a business man as I remember it. He had a decent team around him. I hope I'm not slandering him. He was alright; a nice enough man.

Green: Well, Maurice Rapport only died a couple of years ago and used to come to the Serotonin Club meetings.[33] A delightful gentleman. The interesting history is that, whilst he worked as a post doc under Page and they isolated the substance, it was Maurice Rapport alone who actually did the structural identity.[34] I think he ticked off Irvine Page quite seriously in publishing it and going and telling him that after submission. Again just to link what we were talking about Abbott and Upjohn: the very first substance was actually made at Columbia University. Maurice Rapport got them to do it and they then passed it on and asked these two companies to make it. I handed a letter over to the Royal Society Archives that Maurice Rapport gave me, in which John Gaddum thanks Maurice Rapport for a sample of a very few milligrams as I remember, and which Gaddum still managed to put into his bioassay system. He later got 25mg, which I suspect he then got because Abbott and Upjohn were making this freely available.[35] But as a memory of Maurice Rapport, he did say to me that he'd tried to keep up with this interesting new substance that he'd been

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[31] For example, Marsden and Kerkut (1969, 1970).

[32] Irvine H Page (1901–1990), director of the Research Division in the Cleveland Clinic, worked with Maurice Rapport (1919–2011) and Arda A Green (1899–1958) to isolate and characterize 5-HT. Rapport, Green and Page (1948). For biographical information, see pages 147–8 and 153–4.

[33] See page 51 and note 165.

[34] Rapport (1949).

[35] This letter in fact thanks Maurice Rapport for the 25mg sample in 1951 not the earlier 0.65mg sample. It is reproduced in Green (2008), page 1586.

involved with for several years, but by the later 1950s, when I think papers were coming out at a rate of several hundred a year, he gave up feeling that he could in any way keep up with all the material being published.

Wallis: On the same topic: in that speech he gave to the Serotonin Club he gave an amusing anecdote of how the discovery process went on when he was trying to identify samples from fluids and blood and so on. They were all tested on the perfused rabbit ear vein, of which Arda Green was in charge, and Maurice was very much the junior partner in the set up. So it came about that during the course of the day, Arda would set up an ear preparation, test a number of things, but Maurice Rapport's sample had to be last. And it frequently happened that that was applied and the ear stopped responding and Arda Green said: 'The ear didn't like that; that's it for today.' [36] [Laughter]

Flower: Merton actually introduced the topic of monoamine oxidase so maybe this is a good point to move on a bit to the first studies into the synthesis and metabolism of 5-HT?[37]

Dr Patrick Humphrey: I just want to finish off what we were talking about. I didn't know Erspamer or Page or any of these men, but when I started working on 5-HT in 1972, it was their books that I was reading. And I always remember that Erspamer's books and articles were great fun; you could sit there for days reading them because there was so much data in there but it was very difficult to get much medically relevant specifics from it because it was just huge numbers of experiments that had been done on a multiplicity of animals and tissues and so on, but one was struck by the fact that molluscan hearts were incredibly sensitive, 10pM to -10nM. You had the feeling that 5-HT was really a potent neurotransmitter, just like adrenaline and noradrenaline, which I think was quite an exciting concept to people who were starting in the field, but you couldn't make much of it. And I think Irvine Page was maligned. I was going to ask when we were going to mention Page, because he wrote two reviews in *Physiological Reviews,* which for me was the eye opener because there he was starting to look at physiology and showing that 5-HT was not only a constrictor but it was also a vasodilator and, of course, we've already talked about the chronotropic effect, the multiplicity of physiological effects that he

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[36] See, for example, Rapport (1997).

[37] Professor Merton Sandler wrote: 'The situation in those early days came under careful scrutiny at a large meeting in the mid-1960s (Costa and Sandler (1968)).' Note on draft transcript, 12 February 2013.

Figure 4: Dr Patrick Humphrey.

studied and referred to, which certainly tweaked my interest.[38] So, Page was an important person, certainly for me, because he set me on the road to think seriously about 5-HT. I want to read something from a book I bought about 15 years ago and never even looked at – Irvine Page's last thoughts on 5-HT. As I was coming to this meeting, I thought I'd better look at it. I still haven't really read it, but I read the beginning and I read the end and there is a rather nice note here, well two things. He says: 'There are already ample reviews and excellent books, large and extensively documented', that tell you about what they saw; they are not really trying to analyse. 'What seems lacking is briefer and more intimate discussions by one or two authors, discussions that represent a single point of view to provide possibly unity to a field that is becoming chaotic.' And, of course, once we opened Pandora's box another decade or two later, it became even more chaotic. Finally, at the end of the book, he's summing up his thoughts and he makes the point that: 'Serotonin has added yet another facet to the equilibrated system which controls many bodily functions. In disease states, it and its derivatives will be detected and measured because of their abnormal amounts, but in normal circumstances it seems to take its part with other substances in an orderly fashion, scarcely displaying the multiplicity of actions that so delight the pharmacologist and the biochemist.'[39] I think he

[38] Page (1954, 1958).

[39] Page (1968), pages *S*1, 116.

was working on this in the 1950s and Erspamer was in that sort of period, even earlier. All this was written up, waiting to be explored. So I think they certainly played a massive role in my start in the field, and of many others, I'm sure.

Flower: You've brought up an important point: when did researchers begin to realize that 5-HT was important in the brain as well as in platelets and the gut, because this must have been a tipping point in the development of the field?

Professor Daniel Hoyer: The answer is very early on, in 1943, when LSD was found, except that we had no proof that it was going to be for 5-HT or primarily through 5-HT receptors (they were not known at the time), but this was actually what started the Sandoz efforts in the field because LSD had such a potent effect on people's behaviour.[40] They clearly knew that the effects were centrally mediated. Sandoz at the time started looking into compounds like these, the next in the series was psilocybin. Originally, when Hofmann synthesized LSD the first time in 1938, they didn't know what the compound was all about; it was rediscovered in 1943 (the famous bike trip);[41] we had a 50th anniversary for LSD/5-HT (a small closed meeting in Ticino, Switzerland) which was not supported very much by Sandoz. But this was the start of 5-HT research even before 5-HT was known. Several points can be made: 1) LSD had very potent effects in the brain; 2) it started the whole chemistry around ergot natural products again; the whole ergotamine chemistry developed and lots of Novartis chemistry was based on the indoles (the indole synthesis was then published in the early 1950s); and the indole ring is one of the major components in all these molecules (5-HT, LSD, ergolines, ergopeptides). By the time we found out that ergotamine and dihydroergotamine (DHE) were working in migraine, this is also primarily mediated by 5-HT receptors.[42] It took some time to make the link between ergotamine and migraine and internally we had some quite heated discussions, but eventually it was by reconciling the incredible number of receptors and their pharmacological signatures that got things going. We sorted out the mess that was created initially when people were describing all kinds of

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[40] Professor Daniel Hoyer wrote: 'Albert Hofmann investigated extracts of many mushrooms in/from Central and South America known to cause hallucinations.' Note on draft transcript, 16 January 2013.

[41] Albert Hofmann (1906–2008), was a Swiss research chemist at the Sandoz Laboratories in Basle. Having previously, inadvertently, experienced the effects of LSD, Hofmann carried out a self-experiment on 19 April 1943 to examine the effects by taking 0.25mg. He later had to be taken home on his bicycle accompanied by his lab assistant. 'Bicycle day' is detailed in his autobiography (Hofmann (1979)). For a general account of psychedelic drugs, see Snyder (1986), Chapter 7.

[42] See, for example, Hoyer, Schoeffter and Gray (1989).

Figure 5: Left to right: Professor David Clarke, Professor Daniel Hoyer, Professor Richard Green and Dr Tom Blackburn.

effects of 5-HT in the most varied tissues and sometimes 5-HT was extremely potent. John Vane's fundus preparation is probably the most sensitive one in vertebrates; 5-HT has an incredible affinity for this 5-HT_2 (5-HT_{2B} receptor as characterized much later), which was unexpected, as 5-HT_2 receptors were thought to have low affinity for 5-HT. But this is when things started moving; 5-HT compounds largely evolved from the old LSD/ergot derivatives chemistry (at least at Sandoz, Eli Lilly and a few other pharmaceutical companies).

Humphrey: But again in Erspamer's reviews and work, he described 5-HT levels in just about every organ going, so you knew there was lots of 5-HT in the brain, the gut and the heart, or rather platelets, and so on.[43]

Green: Adding to what Danny said, Gaddum, of course, used LSD in his preparation and suggested that since he'd found 5-HT in the brain, that it might have something to do with mood, based on the already existing human stuff on mood change.[44] The Americans Woolley and Shaw, as I remember, saw the structural similarity between 5-HT and LSD and said: 'You know, this probably

[43] See page 4, note 5.

[44] See Green (2008).

means there's something going on in the brain with 5-HT and mood.'[45] But I think the other major breakthrough was from B. B. Brodie's lab, which was an absolute powerhouse in the later 1950s when, having developed a fluorescent method for actually analyzing 5-HT, because bioassay can't do large numbers, they started putting every psychoactive drug they could think of into rats and measuring 5-HT concentrations.[46] Drugs like reserpine and MAO inhibitors, and by the late 1950s everyone got most interested in 5-HT in the brain.

Bakhle: Where does ergotamine fit into this? Obviously, they would clearly have seen central effects from ergot ingestion for centuries – St Anthony's Fire and all that sort of stuff.[47] The question I'm really asking is: when was ergot and LSD connected with 5-HT?

Green: If you really want to go back over a period, one of the interests of Henry Dale in about 1910 was the ergots, and in the Wellcome Labs, he and Patrick Laidlaw were looking at tryptamine and ergot compounds in about 1912.[48] I think that's why Gaddum wanted to look at LSD in the system because tryptamine is so structurally related, that's where he linked the two. That's clever pharmacology.

Hoyer: I think it was Pat who made the link and he should say something to this effect because, by the time we figured out that sumatriptan was working, by and large, on similar receptors to ergotamine and DHE,[49] then the link was made. It wasn't obvious at the beginning because we thought that ergotamine and DHE were working on a very specific combination of receptors in some vascular tissue (probably more adrenergic than 5-HT-like, as was the saphenous vein) and, at the time, we could never figure out the target because these compounds are working on adrenoreceptors (and dopamine receptors as well). It was a bit

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[45] Woolley and Shaw (1954).

[46] Bernard Brodie (1907–1989) was Head of the Laboratory for Clinical Pharmacology at the National Institutes of Health in Bethesda. See note 21 and Costa, Karczmar and Vesell (1989).

[47] Poisoning from the consumption of ergot (ergotism) is characterized by convulsions and burning gangrene in feet, hands and limbs from its vasoconstrictive properties; it is known as St Anthony's Fire after the Order of Antonite monks who established hospitals for sufferers of ergotism around 1100 AD. See, for example, the discussion in Tansey (2001).

[48] Henry Dale was at the Wellcome Physiological Research Laboratories at Herne Hill from 1904 to 1914. For Dale's scientific work on ergot and publications with Laidlaw, see various papers in Dale (1953).

[49] See Hoyer, Schoeffter and Gray (1989).

messy, but by the time we had sorted out the receptors things became clear, but I think some people (Pat) knew before that the link was there, although the target was called 5-HT_1-like at the time.[50]

Humphrey: Thank you very much Danny; it's very kind of you. I think this is another discussion; we could have a whole day on migraine,[51] but suffice to say that when I did start on the migraine project, 5-HT had already been infused into people and shown to abort an attack, which is clearly not a therapeutic strategy because of all its undesirable effects. We knew ergotamine worked and, again, preferably if it was given parenterally rather than orally. Strangely, my good friend James Lance in Australia, a brilliant clinician, had found that methysergide was also acutely active in some of his patients even though it was given normally prophylactically and was purported to be a 5-HT antagonist.[52] We worked out that it was probably an agonist when it was working acutely. And so, what was the common denominator between 5-HT, ergot and methysergide? Well, it turned out to be the 5-HT_{1B} receptor, but obviously it took us a while to get to that point, but we actually made another compound, sumatriptan, which mimicked the desirable effect (selective cranial vasoconstriction) and was an agonist for that receptor.[53] So ultimately it all came full circle and became very clear. To finish on that point: every one of those four compounds I mentioned, they're all indoles, so chemically they're highly related.

Professor Gareth Sanger: I just want to throw another molecule in, synthesized by the Delagrange company in 1964, and it's called metoclopramide.[54] It was made to improve on the anti-arrhythmic actions of procainamide, but was found to inhibit vomiting, antagonize at the dopamine D2 receptor and stimulate gastric motility; later research into the mechanisms of action of this drug then gave birth to 5-HT_4 receptors and greatly helped clarify the role of

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[50] Professor Daniel Hoyer wrote: 'i.e. sumatriptan was acting selectively on 5-HT_{1B}/5-HT_{1D} receptors as we reported in second messenger systems'. Note on draft transcript, 16 January 2013.

[51] A Witness Seminar 'Migraine: Diagnosis, Treatment and Understanding *c.*1960–2010' was held on 28 May 2013, and will be published in 2014.

[52] Curran and Lance (1964). James Lance was Professor of Neurology at the University of New South Wales from 1975 to 1992 and since then, Professor Emeritus. He has published widely on headaches and migraine. See page 100.

[53] See Humphrey, Ferrari and Olesen (eds) (2001).

[54] See, for example, Justin-Besancon and Laville (1964 a and b).

Figure 6: Professor Gareth Sanger.

the 5-HT_3 receptor in the mechanisms of severe vomiting. It was a molecule that was circulating around at the time in exactly the same manner in the others we've discovered – again, in the 1960s and 1970s.

Dr Tom Blackburn: While we're on the tryptamine story, at about the time that Pat Humphrey was referring to, we were seeing the development of histofluorescent assay technology developed by Falck and Hillarp in the early 1960s in Sweden that revolutionized the study of monoamines in the central nervous system (CNS).[55] They were able to identify serotoninergic pathways and cell bodies along with tryptaminergic pathways system that tryptamine-like drugs such as LSD were thought to act at. Perhaps Charles Marsden can talk more about this during his post-doctoral years at the Karolinska[56] and the tremendous amount of important histofluorescent/histological studies of the brain, mapping out these different 5-HT pathways from the raphe cell bodies, which created an enormous amount of interest in the role of the raphe serotoninergic system within psychiatry and neurology.[57]

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[55] See Falck *et al.* (1962); Carlsson, Falck and Hillarp (1962).

[56] Professor Charles Marsden wrote: 'I was not at the Karolinska but in Bergen, though I had important research connections at the Karolinska particularly with Urban Ungerstedt and the development of microdialysis.' Email to Ms Caroline Overy, 21 June 2013.

[57] See Murphy, Campbell and Costa (1978).

Sandler: In the early 1950s when Mike Pare and I came out of the army, I played about in a lab at the Brompton and he went to work at the Maudsley. In fact, the Maudsley talked about nothing else but 5-HT in the brain and monoamine oxidase, and monoamine oxidase had just about come in. Does anybody here remember Nate Kline? [58] He was a big operator – he had his photograph on the front of *Fortune Magazine* as one of the ten best-known men in America; not ten best-known psychiatrists, best-known men in America. He was a grand phoney actually. [Laughter] Well, a showman at any rate! I had the good fortune of going every year to a meeting in the Caribbean that he organized through the generosity of one of his patients. And there was a nucleus of people that you would all be familiar with, like Arvid Carlsson.[59] 5-HT was all the rage at that time and so were monoamine oxidase inhibitors (MAOI). Nate Kline had really stumbled over the action of iproniazid in particular in depressive illness.[60] And also Gaddum had been publicizing the fact that LSD was a 5-HT antagonist.[61] We decided to try to test this hypothesis *in vivo* – in man – and we got six or eight volunteers, registrars at the Maudsley, and we gave them LSD, a rather dangerous thing to do. But we knew no better in those days. We gave them LSD and we also gave them 5-hydroxytryptophan (5-HTP) to try to modify the LSD reaction. The thing that upset us was the fact that one of the registrar volunteers, after receiving LSD, became psychotic, clinically schizophrenic, for about six months. He had to be controlled by several large Maudsley attendants before he could be calmed. Mike Pare and I were responsible for tentatively suggesting that 5-HT might be involved in schizophrenia.[62]

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[58] Nathan S Kline (1916–1983), best known for his work with psychopharmacologic drugs, was the founder and Director of the Rockland Research Institute (now the Nathan S Kline Institute for Psychiatric Research). Professor Merton Sandler wrote: 'He introduced the MAO inhibitor, iproniazid, to psychiatric practice to treat depressive illness.' Note on draft transcript, 12 February 2013. For further comments by Professor Sandler on Nathan Kline, see Tansey, Christie and Reynolds (eds) (1998), page 144.

[59] Professor Arvid Carlsson (b. 1923) is a Swedish pharmacologist best known for his research on the neurotransmitter, dopamine. He was jointly awarded (with Paul Greengard and Eric Kandel) the Nobel Prize in Physiology or Medicine in 2000 'for their discoveries concerning signal transduction in the nervous system'. See www.nobelprize.org/nobel_prizes/medicine/laureates/2000/carlsson-autobio.html (visited 6 March 2013).

[60] Loomer, Saundera and Kline (1957); Kline (1958).

[61] Gaddum and Hameed (1954); Gaddum (1957).

[62] Brengelmann, Pare and Sandler (1958, 1959).

Figure 7: Professor Merton Sandler and Professor Charles Marsden.

Flower: Anybody else want to say anything about the first steps that we took to characterize the metabolic and synthetic pathways?

Green: David Grahame-Smith, whom I worked with for many years, was the first person to identify tryptophan hydroxylase.[63] Everyone had known that there was an hydroxylation step first, but they were not sure whether tryptophan hydroxylase and tyrosine hydroxylase were the same enzyme or not. David, again through the interest he gained at St Mary's on the carcinoid syndrome, was actually able to identify and characterize the enzyme and show it was the rate-limiting enzyme. I think the point to really emphasize about this was that it was his PhD – he was already medically qualified. He did it on his own and when he first presented it in the States he remembers, famously, that some of Brodie's lab who had been working on this for several years, came up to him and said: 'How the hell did you manage to do this when we couldn't?' It's really quite remarkable because the Brodie lab had people like Axelrod and Udenfriend,[64] and I could name many others in that lab, who were real experts in monoamines and he beat them. I think that's worth commenting on very strongly.

Flower: David Grahame-Smith's response is not recorded, I presume?

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[63] Grahame-Smith (1964, 1967).

[64] For biographical details on Julius Axelrod (1912–2004) and Sydney Udenfriend (1918–1999), see pages 141–2 and 157; see also note 21.

Green: He didn't tell me that. [Laughter]

Sandler: Around about the same time that David Grahame-Smith was able to characterize the hydroxylation, there was very similar Japanese input.

Flower: Does anybody else want to talk about early attempts to characterize the synthesis and degradation of 5-HT?

Blackburn: There was one particular monoamine assay at the time, the Welch and Welch spectrofluorescent monoamine assay, which was one of the first neurochemical techniques we were using at ICI Pharmaceuticals in the 1970s.[65] Basically, the practice at the time was to dissect as many rat brain areas as possible and look at the levels of 5-HT, noradrenaline, dopamine and their metabolites, HVA, 5-HIAA and so on. This was the first time I can remember where we were starting to look at monoamine oxidase inhibitors and their effects on different monoamine metabolites. We were looking at action of tricyclic antidepressants, noradrenaline uptake inhibitors, and at the time I was working on a compound called viloxazine, Vivalan, a noradrenaline uptake inhibitor, which also increased 5-HT turnover. So the hypothesis at the time in Dr David Greenwood's and Professor Brian Leonard's lab was to try to understand the importance of 5-HT and its metabolites, looking at the areas associated with mood and emotion and other neurological psychiatric disorders, and trying to pinpoint which of these particular areas of the brain were important. One of the lovely memories I have is working with Brian Leonard.[66] Professor Leonard at the time was being recorded for an *Horizon* television programme. He was dressed all in black with his long silver grey hair and he was demonstrating dissecting the brain of a rat to perform one of his experiments; he placed the brain on a block of dry ice in those days. There were rows and rows of frozen rat brains all ready for the biochemical assay – Welch and Welch assay. However, Brian was dissecting out one brain and it flipped out and went on the floor. He then followed the brain on to the floor with a spatula with the camera looking on all the time. I was really hoping this would be captured on the Horizon programme and it actually was – it just showed him going out of camera shot! However, this was one of the classical bioassay systems being used at the time.

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[65] Welch and Welch (1969).

[66] Professor Brian Leonard was a lecturer in pharmacology in the School of Pharmacy, Nottingham University before joining ICI in 1968 and subsequently moving to Organon International in Holland. From 1974 until his retirement in 1999, he was Professor and Head of Department of Pharmacology at the National University of Ireland, Galway.

Figure 8: Dr Tom Blackburn.

We were trying to understand which areas of the brain were important and being modulated by drugs, but in those days it was like looking at 101 different areas with a 101 different compounds to try to understand their mode of action – it was a nightmare.

Flower: What techniques were you using in those days? Paper chromatography or something like that?

Blackburn: Spectrofluorometric assays.

Flower: Just spectrofluorometric?

Blackburn: Yes, for biochemical assays.

Professor David Clarke: When we come to talking about the clearance and metabolism of 5-HT, we cannot forget Ray Fuller and David Wong at Eli Lilly in the United States (discoverers of Prozac).[67] It was Ray Fuller's work that really characterized the type of monoamine oxidase that was involved in metabolism of 5-HT and it was his work that really set out and defined the uptake mechanism

[67] Dr Ray Fuller (1935–1996) joined Eli Lilly in 1963 as a pharmacologist; Dr David Wong (b. 1935) joined the company in 1968 as a research biochemist; together with Dr Bryan Molloy, a senior organic chemist at Eli Lilly, they developed the compound fluoxetine, introduced into the market as Prozac in 1988. See Fuller *et al.* (1974). See also page 28 and note 91. For further biographical details on Ray Fuller, see page 147.

for 5-HT into neurological tissue. And you know there is a parallel here with the clearance of noradrenaline as depicted by Iversen's Uptake 1 and Uptake 2.[68] However, we never found any evidence whatsoever for an Uptake 2 for 5-HT, it just seemed to go into the nerves. Ray Fuller was certainly a key figure in this field and actually I bear some sort of physical resemblance to him. In meetings, when it was rather dim and dark, I'd be sitting on my own and somebody would come up to me and sit next to me and say: 'Ray, we did get that result. This is the way in which it works. It works like this ....' And I just used to sit there and listen. This was fantastic. And then someone else would come up and say something about science and I'd turn round and say: 'I'm afraid I'm not Ray; I'm Dave Clarke.' And they'd say: 'Who the hell are you?' [Laughter]

Green: One hates to boast, but if we're talking about assays, the first assay was actually native fluorescence, I mean chromatography first and then what was called native fluorescence in strong acid.[69] Then I actually used a Snyder method in about 1966.[70] But Gerald Curzon came to me – I was doing my PhD with him at the time – and said that there was a really interesting new method by Maickel, an American, where 5-HT was reacted with ortho phthaldialdehyde,[71] and he said: 'This ought to be very sensitive. He says it is.' And it was. Then he went on to say: 'And when you've extracted the 5-HT the 5-HIAA ought to still be left behind. You should be able to extract that out and measure that.' And that worked as well. In the end we published this in 1970 and it was, I think, the first method to measure in discrete brain regions both 5-HT and 5-HIAA. I mention this because over the next ten years it was cited nearly a thousand times. It was three pages long in *British Journal of Pharmacology* and is the most cited paper I've ever had.[72] So, it just shows you, a paper can be quite small and still be interesting. Then, of course, that was taken over very much by Charles Marsden's new techniques of high-performance liquid chromatography (HPLC), where they could measure it *in vivo*.[73]

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[68] Iversen (1967).

[69] Bogdanski *et al.* (1956).

[70] Snyder, Axelrod and Zweig (1965).

[71] Maickel *et al.* (1968).

[72] Curzon and Green (1970).

[73] Professor Charles Marsden wrote: 'We could measure it in both in tissue and *in vivo* using microdialysis, Marsden (1981); Wright Upton and Marsden (1992).' Note on draft transcript, 2 September 2013.

Marsden: I was going to go back to Tom's point about the fluorescent histochemistry and what a major role that I think it played in the early 1960s. It was in 1964 that Dahlstrom and Fuxe first identified 5-HT pathways using fluorescence histochemistry.[74] Of course, the difference between dopamine and 5-HT was all in the colour; the dopamine was green and the 5-HT yellow. Hillarp in Sweden developed the fluorescence histochemical method and published it in 1962.[75] I was still an undergraduate at that time and I was very impressed by a *Pharmacological Reviews* article by Kjell Fuxe that led me to completely give up becoming a zoologist and go into pharmacology.[76] My first laboratory work was at Southampton with Gerald Kerkut, using the fluorescence histochemical method to map the 5-HT cells in snail brains. These were very large cells and were subsequently used a lot for the early pharmacological work identifying responses to 5-HT and related compounds and there is a continuum from the development of the tissue assay methods through to the cellular localization of 5-HT and its measurement *in vivo* using microdialysis.[77] But I think that mapping of those pathways really spurred a lot of people's interest, as we could now see where the 5-HT cells were in the brain and where they went to, so we knew which regions to concentrate on in future research.

Sandler: I just want to make sure that 5-HTP decarboxylase, the precursor enzyme responsible for the production of 5-HT, receives a mention and I must say that in the experiments that I mentioned before, about giving LSD and giving 5-HTP to modulate its action, it worked actually, but that's another story.[78] We collected urine samples from the subjects to whom we had given 5-HTP and were surprised to find a very large increase of 5-HT itself in their urine, showing that substantial decarboxylation had almost certainly taken place in the kidney. To this day, peripheral, as opposed to central, decarboxylase inhibition forms part of Parkinson's disease treatment.[79]

Flower: Let's talk a bit about uptake. David [Clarke] introduced the subject. When were 5-HT transporters first characterized? I quoted a sentence from

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[74] Dahlström and Fuxe (1964).

[75] Carlsson, Falck and Hillarp (1962); Falck *et al.* (1962).

[76] Hillarp, Fuxe and Dahlström (1966).

[77] Marsden and Kerkut (1970).

[78] Brengelmann, Pare and Sandler (1958, 1959). See page 20.

[79] Bartholini and Pletscher (1975).

Gaddum's book in 1948, mentioning that the biological activity of clotted blood could be removed by passing it through the lungs. How did this idea of uptake evolve?

Clarke: I'm not sure. This is a long time ago but I suspect and, I'm uncertain about this, that the work arose out of Axelrod's lab originally where he was studying the uptake of noradrenaline and so forth.[80] 5-HT was used there as well. But I'm sure other people in the room will have a more precise idea about that.

Green: There was a very clever experiment, which many people probably don't remember, by Archie Todrick who worked up at Dumfries. They were looking at human platelets and gave uptake inhibitors, and showed that the concentration of 5-HT in the platelets went down over the next week. They correctly interpreted this as the fact that the platelets could no longer take up 5-HT and that this might be how these tricyclic antidepressants work.[81] They also showed the corollary of that, which is if they gave MAO inhibitors then the concentration in the platelets went up. So they looked at two types of antidepressants and showed these different effects. But I suspect that you're right, David, and that it was actually Les Iversen and his catecholamine affinity uptake systems that then made people interested in 5-HT uptake systems. But I don't know more than that.

Clarke: There was a lot of humour about blocking uptake of 5-HT into platelets and relating this to psychiatric illness.[82] People were talking about psychotic platelets and so forth! It wasn't really related to serotonergic nerves in the brain until later; but I think I may be right with Axelrod and Iversen.[83]

Bakhle: That last comment reminds me, I think it was in Grahame-Smith's Clinical Pharmacology Department in Oxford, David Boullin or somebody like that, was selling the idea of the platelet as a model for the brain?[84] A neuronal model because of uptake and storage and, as you said, it developed into the psychotic platelet idea and so on.

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[80] For consistency, the term 'norepinephrine' has been replaced with 'noradrenaline'. For a history of neurotransmitter transporters, see Iversen (2006a); for Axelrod's lab, see Axelrod (1988), Iversen (1992).

[81] Marshall *et al.* (1960).

[82] See, for example, Marazziti *et al.* (2006).

[83] See note 80.

[84] See, for example, Boullin (1979).

Green: That was mainly in Brodie's lab and Costa's lab, before he went to Oxford.

Bakhle: Well, anyway, that model was certainly around but I think the origins of 5-HT uptake must be with Iversen. I remember Hugh Blaschko coming back to Oxford and sitting down to lunch in the department – we used to have lunch all together in the department in those days – and he said: 'Oh you know, there's this amazing finding'; he'd just examined Les Iversen's PhD in Cambridge and he was very, I suppose, excited. I've never really seen Blaschko excited but he was fairly excited. He really thought it was a lovely piece of work, the two uptake systems, and it was, I think, fairly clear. I don't know whether Les ever ran 5-HT as an alternative substrate; if you look in his PhD thesis you'll probably find out. I suspect he probably did, because you know it was a biogenic amine and maybe he ran histamine as well. I certainly would if I'd found out something about catecholamines, I'd throw every amine I could at it.

Green: Les [Iversen] wrote a monograph as the result of his PhD.[85] I bet few PhD students can have a monograph published on their PhD work. It's on uptake and I don't think there's a mention of 5-HT in that. I think it's only catecholamines.

Humphrey: To add to that, Richard, he did actually look at 5-HT and I was always very struck by the fact that 5-HT had an affinity for Uptake 1 in mammalian hearts, rodents. But it was quite potent. It was about one fiftieth of the affinity of noradrenaline, so there you see 5-HT having a not grossly dissimilar affinity to that of noradrenaline, and that follows through on the receptors, that 5-HT will actually activate alpha adrenoreceptors if you give enough of it. I think that confused a lot of the pharmacology in the early days because there's 5-HT activating alpha receptors because pharmacologists have given too big a concentration and stupidly thinking that they were studying a new 5-HT receptor.

Clarke: Someone in the room who's an expert in CNS will probably recall when tricyclic antidepressants came out; drugs such as amitriptyline and imipramine and other related compounds.[86] I think it was Axelrod who showed that 5-HT neuronal uptake was blocked by these drugs.[87] Am I incorrect in saying this?

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[85] Iversen (1967).

[86] For an account of the development of tricyclic antidepressants, see Healy (1997), pages 152–5, and the discussion at the Witness Seminar on drugs in psychiatric practice, Tansey, Christie and Reynolds (eds) (1998).

[87] See, for example, Axelrod and Inscoe (1963).

Green: Iversen and Horn certainly published in that area, but that was long after these drugs were available.[88] That was in about the mid-1970s and a lot of the tricyclics had been around. It was the usual thing in the area of psychiatry, they were found to be clinically effective without really very much idea of how they worked.

Blackburn: When I came back from the States last year (2011), I brought back lots of the boxes that I had taken over there in 1999 and one of things I found recently, but haven't read since then, was the Scrip's *Report* from 1988 and it discusses a lot of the different 5-HT post-synaptic, pre-synaptic uptake inhibitors.[89] The first compound 5-HT reuptake inhibitor (SSRI) to be marketed was from Astra, Zimelidine, which was withdrawn for serious side effects (Guillian-Barré syndrome).[90] But before that, as David quite rightly said, clomipramine, which is a very potent noradrenaline and 5-HT uptake inhibitor, was also very important in those days in trying to understand the 5-HT reuptake mechanism. But it wasn't until the work of the David Wong, Bryan Molloy and Ray Fuller and colleagues at Lilly, who played a key role in the development of fluoxetine, Prozac, in the 1980s, and the pioneering work of Arvid Carlsson and colleagues at the Karolinska that really started to put the 5-HT reuptake mechanism on the map.[91]

Clarke: I remember now that John Fozard and I did an experiment in pithed rats that were reserpinized. You could infuse noradrenaline into them and, of course, because the vesicles were inoperative one couldn't subsequently get

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[88] For an overview, see Iversen and Mackay (1979).

[89] Scrip (1988).

[90] See, for example, Fagius *et al.* (1985).

[91] See pages 23-24 and note 67. Dr Tom Blackburn wrote: 'In 1971 Bryan Molloy at Eli Lilly synthesized a range of new compounds, a group of phenoxyphenyl-propylamines from diphenhydramine, an antihistamine found to inhibit reuptake of the neurotransmitter "serotonin". One of these compounds, Lilly 110140 (later in 1975 called fluoxetine), was found to be highly selective, affecting only the neurotransmitter serotonin. As the chemist who synthesized the new series of compounds, Molloy was in this literal sense Prozac's creator. Years of development and testing finally led to approval of fluoxetine hydrochloride for marketing. In 1976 Eli Lilly begins clinical trials of fluoxetine. In 1983 Lilly applied to US FDA for approval to sell Prozac for treatment of depression. Fluoxetine was initially approved for treatment of depression in Belgium in 1986, and then Eli Lilly's Prozac was approved by the FDA on 29 December 1987 and introduced in the United States at the beginning of 1988. It was the first of a new class of drugs, called selective serotonin reuptake inhibitors (SSRIs), to be approved for use in the United States.' Email to Ms Caroline Overy, 7 June 2013.

a response to tyramine. But if one pretreated these reserpenized rats with a monoamine oxidase inhibitor you could infuse noradrenaline, give tyramine, and restore the tyramine response beautifully. So John and I said: 'Well, let's put in 5-HT', and so we infused 5-HT into reserpenized rats, gave tyramine, and got no response. Put it into reserpenized rats pretreated with a MAO inhibitor – beautiful responses to 5-HT. So this was a clear-cut demonstration, measuring the vasoconstrictor response to 5-HT as a read out, of 5-HT being able to go up into noradrenergic nerves; peripheral noradrenergic nerves. The monoamine oxidase inhibitor that we used was an intraneuronal monoamine oxidase inhibitor, bretylium. It was taken up into the nerves, concentrated in the nerves, inhibited MAO and preserved noradrenaline when it was infused and taken up, and preserved 5-HT when it was infused and taken up. Now that was in the 1960s; this is published in the *Journal of Pharmacy and Pharmacology*[92] or the local newspaper in Bradford.[93] [Laughter].

Green: That leads on easily to some of the major work that David Grahame-Smith started which was giving a monoamine oxidase inhibitor and tryptophan, and the animals show a behavioural syndrome.[94] He showed that if you just gave tryptophan, which increases the turnover of 5-HT, you didn't get the behaviour. If you only gave an MAO inhibitor you didn't get the behaviour, even though the 5-HT concentrations in the brain went up enormously. So he concluded that, in fact, intraneuronal metabolism was very important for controlling function. Again he showed that tricyclics brought the syndrome on earlier and quicker because MAO couldn't be taken back up. Alec Coppen, who is one of the major people involved in the clinical pharmacology/psychiatry of 5-HT, had actually shown that he could potentiate an antidepressant effect in about 1965/6.[95] Giving tryptophan potentiated the antidepressant action of MAO inhibitors, so he'd done the same sort of thing in humans. I think that's really an important thing. Then David and I used this 5-HT model of function to look at every drug we could think about during the 1970s. Moussa Youdim maintained

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[92] Fozard and Clarke (1970).

[93] This is a reference to the research group at Bradford with Professor Robert Naylor and Professor Brenda Costall's work on a 5-HT_3 receptor antagonist and Glaxo's development of the anti-emetic drug ondansetron the expense of which was reported in the *Bradford Telegraph and Argus*. See comments by Professor Naylor in Christie and Tansey (eds) (2007), pages 59 and 61.

[94] Grahame-Smith (1971).

[95] Coppen, Shaw and Farrell (1963). Dr Alec Coppen attended the Witness Seminar on drugs in psychiatric practice; see Tansey, Christie and Reynolds (eds) (1998).

that we just pulled down the Merck Index and then tried to find as many drugs as we could and publish on them. But it's a nice behavioural functional model in animals, some of which has been applied to humans as well.

Marsden: This was about the selective 5-HT uptake inhibitors and when they first appeared. It was my feeling that actually Fuller and Wong synthesized and pharmacologically tested fluoxetine (Lilly 110140) quite early[96] because when, with Ralph Adams, we were trying to develop the voltammetric method to electrochemical monitor 5-HT *in vivo* in Kansas, we used fluoxetine at that point.[97] That was 1977/8 so it was available then as a selective compound but Lilly were not particularly interested in it as a clinical entity at that time, as the emphasis in the US was on noradrenaline and depression. But then, to our embarrassment, for years Ray Fuller always used our data showing an increase in the signal that we obtained, to provide evidence that extracellular 5-HT was increased by fluoxetine when, by that time, in fact, we had discovered that the signal we recorded wasn't actually 5-HT but, most probably, ascorbic acid.[98]

Blackburn: I had the privilege of meeting Ray Fuller on a number of occasions and one of the stories he told – and I think it's very true to the whole of 5-HT research at the time – was that the mind-set of Lilly management wasn't particularly favourable to 5-HT research. When I joined Beecham, they actually in-licensed paroxetine, a 5-HT uptake inhibitor, from Ferrosan in Holland. ICI had turned it down, and this was the same time that Ray was having his problems at Lilly with regard to the market size for SSRIs, which we now know was enormous. But, it was the mind-set of the management at that particular time that they were more comfortable with the noradrenaline reuptake inhibitors rather than the 5-HT drugs.

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[96] See note 67.

[97] Conti *et al.* (1978); Marsden *et al.* (1979).

[98] Professor Charles Marsden wrote: 'The carbon electrodes we used to record the voltammetric signals were very sensitive at a similar potential not only to the amines but also their metabolites and ascorbic acid, the latter which was abundantly present in the brain and readily released. We were probably measuring the release of ascorbic acid and the metabolites of dopamine and 5-HT rather than the amines themselves (for example, Brazell and Marsden (1982)). This problem was subsequently overcome by using nafion-coated carbon fibre electrodes, which excluded ascorbic and uric acid from the electrode surface (for example, Crespi, Martin and Marsden (1988)) and this technique has been further refined and improved in recent years. The technique of *in vivo* microdialysis to measure 5-HT release has also had a major impact on our understanding of the role of 5-HT in both drug action and behaviour (for example, Wright, Upton and Marsden (1992)).' Email to Ms Caroline Overy, 21 June 2013.

Marsden: This demonstrates the point that, at that time, we were interested in serotonin or 5-HT on this side of the Atlantic and the Americans were more into noradrenaline (or norepinephrine, as they called it).[99]

Flower: Let's edge our way towards the early receptor studies now. I can't recall who the workers were, but there were early studies using radioactive 5-HT to identify binding sites. Does anyone want to say anything about these early experiments and maybe discuss Gaddum's early experiments with 'M' and 'D' receptors?

Hoyer: Everyone is citing Peroutka and Snyder,[100] but actually the first to really perform 5-HT binding was a chap called Gilles Fillion at the Institut Pasteur, but the Institut Pasteur had little interest in this sort of thing.[101] J P Changeux was there working on nicotinic receptors, neuropharmacology was rather prominent, and everyone considered that 5-HT was of rather less importance because of J P Changeux's interest in cholinergic receptors. But Fillion did these things and, at the time, he used surprisingly strange material like horse brain; because the horse is fairly large, you can work on one brain for quite some time. So they started using 5-HT, but also LSD, and they were pretty close to saying that there was a relationship between 5-HT and LSD. He was also one of the first to start with second messenger studies, again in the brain (horse brain), and reported 5-HT-induced cyclic AMP (cAMP) accumulation.[102] Inhibition of cAMP was not on the cards in those days because it was difficult in intact tissues, but clearly it was there as well. The nomenclatures were very bizarre; they were talking about S receptors, S1 and S2; and then a little later it was all sorted out when Peroutka and Snyder started using spiperone (spiroperidol), LSD and 5-HT only to show that spiperone, on top of its known dopamine activity, was labelling something that was fairly common to what was labelled by LSD; but then LSD was also labelling a site that was common with 5-HT-labelled sites, so they introduced a distinction between 5-HT_1 and 5-HT_2 sites. 5-HT_1 had high affinity for 5-HT and LSD, whereas 5-HT_2 had high affinity for LSD and spiperone. This opened Pandora's box because then came ketanserin and a number of other ligands with different levels of selectivity for different 5-HT

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[99] For the use of the terms adrenaline and epinephrine, and also noradrenaline and norepinephrine, see Aronson (2000); see also note 80.

[100] See, for example, Peroutka and Snyder (1979).

[101] See, for example, Fillion *et al.* (1978).

[102] See Fillion *et al.* (1979).

receptors.[103] Again, many people had been doing binding studies with ligands that were totally exotic; in the different companies they were using tools like ergotamine, DHE, methysergide, and it was so complicated and dependent on the tissue you were working on, that it was a total mess. It was much later when the selective compounds started to come out. I'm probably the latest latecomer here; I started to work on 5-HT in 1983, and was only in 5-HT research for about nine years before I turned to neuropeptides. When I started, tritiated ketanserin, 5-HT, LSD, and spiperone were available; there had been some playing with iodinated LSD and one of the major contributions at the time was the discovery of 8-OH-DPAT, which was the first 5-HT_1 (5-HT_{1A}) selective ligand.[104] Then we could slowly but surely unravel the mysteries of 5-HT receptor families and sub-families. We are going to go into subtypes later, but this was the beginning of the binding saga with Fillion, Peroutka and Snyder. Everyone remembers Peroutka and Snyder, when actually one of the major contributors was Fillion. This was in 1975/6 when the College de France had a very strong influence in the neurotransmitter field around Jacques Glowinski (although Fillion wasn't at the College de France). Fillion published in 1976, but it was at the time when all these people were coming back from the United States having spent some time in Julie Axelrod's and other labs at NIH.[105] They looked at one receptor after the other; one ligand after the other. Lefkowitz did exactly the same thing at pretty much the same time; in 1977 he published on beta receptor binding with the beta blocker [^{3}H] dihydroalprenolol (DHA).[106] Subsequently there was further work with [^{125}I]HYP, (hydroxybenzylpindolol), [^{3}H]propranolol, [^{3}H]carazolol, and we developed [^{125}I]CYP (cyanopindolol), which not only bound beta receptors but also 5-HT_{1B} receptors (at least in rodents).[107] It was the time when it was still very difficult to get agonists to bind to these receptors (e.g. HBI, [^{3}H]hydroxybenzylisoproterenol, was an exception), whereas antagonists would be binding much better; there was some confusion about high affinity antagonist binding sites and low affinity agonist

[103] Ketanserin, a 5-HT receptor antagonist used to lower blood pressure, developed by the Janssen pharmaceutical company in 1980, blocks 5-HT_{2A} receptors and alpha-1 adrenergic receptors. See Brunton, Chabner and Knollman (eds) (2011), page 350.

[104] Hoyer, Engel and Kalkman (1985b).

[105] Fillion *et al.* (1976).

[106] Lefkowitz and Williams (1977).

[107] See Engel *et al.* (1981); Hoyer, Engel and Kalkman (1985 a and b).

binding, which turned out to be totally irrelevant. But 1976 is when it really started with binding and second messenger studies, primarily cAMP. Inositol phosphates and calcium would come a few years later.

Flower: I want to come back at the end of this session to talk a bit about the '5-HT summit' and the ensuing paper that you [Daniel Hoyer] published, together with others in this room, on 5-HT receptor classification, but at the moment I want to try and gather other reminiscences before the *Pharmacological Reviews* or the IUPHAR classification.

Bakhle: Around 1970, someone asked me if I would write a chapter on 5-HT and bradykinin for a pharmacology textbook.[108] And the reason they were grouped together was that, at that time, certainly from the outside, i.e. someone who hadn't been studying 5-HT all their lives, both were transmitters without a function. Nobody knew what bradykinin was for; it was there, it did a lot of things but what on earth was it really doing? And 5-HT, the only thing I could think about 5-HT in those days as a physiological function was what Edith Bülbring had done to demonstrate that it was involved in the peristaltic reflex.[109] To me, that was the only physiological function of 5-HT. But it was there, all over the body, in enormous amounts. What on earth was it doing? Both 5-HT and bradykinin, as far as I was concerned, were transmitters without a function. Luckily I dallied so long about writing this chapter, because in a year, bingo! There were 53 receptors, well, no, [laughter] at least five or six. I thought, 'thank God', because it would have been so embarrassing to publish this chapter about the 'no-function transmitters' and then it would have blown up in my face. So delay is quite a good idea from time to time.

Flower: When did we begin to get the first intimation that there were more than two receptors?

Humphrey: That's really the topic of the next session and I can tell you how I see it, but coming back to Gaddum and Picarelli, I always remember when I started

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[108] Dr Mick Bakhle wrote: 'I never actually got around to writing it [the chapter] … when I was asked, the topic was "do-able" but within a year or so the number of 5-HT receptors had increased dramatically and I would never have been able to do both in one chapter.' Email to Ms Caroline Overy, 11 June 2013.

[109] Bülbring and Crema (1958).

in 1972 that it was *the* definitive paper.[110] Everybody thought it important because, firstly it was Gaddum, and secondly, it had identified two separate receptor types. So everybody used to say: 'Ah, there are two 5-HT receptors.' And I told them: 'There are at least two, yes. We know these two.' But I wasn't even convinced about those, because the two drugs used to characterize were really, really dirty. Here you have a guinea pig ileum that was contracted by 5-HT, and clearly one response seemed to be a neuronally mediated contraction and the other a smooth muscle contraction, but the first drug used to block the neuronal contraction was morphine. Well, obviously, that was a functional antagonist and inhibited release of acetylcholine. Then dibenzyline was the dirtiest drug going. So you really hadn't got very far when you're dealing with those sorts of drugs. It was all to play for, even though Gaddum had published this paper that just about every pharmacologist or student of pharmacology knew about.

Clarke: May I just jump in on that. The Gaddum and Picarelli paper in 1957 was seminal because we got two 5-HT receptor targets to aim at; one on nerve – the M receptor, and one on muscle – the D receptor.[111] But the trouble was afterwards people couldn't repeat the experiment. In fact it's very difficult in guinea pig ileum to get a response to 5-HT that is mediated directly on the smooth muscle via the D receptor; it's almost impossible. Margaret Day and John Vane failed to do it convincingly;[112] Brownlee at King's failed to do it convincingly.[113] Much later, in 1985, Buchheit, using guinea pig ileum, had to use industrial doses of 5-HT to get a response at the D receptor.[114] It's quite clear that there's a tremendous strain variation of 5-HT receptors within guinea pig gut and maybe young guinea pigs, which Gaddum used, did express the 5-HTD, which is now the 5-HT_2 receptor, but he was extremely lucky. I think this is an important point, that when you do make discoveries, often luck is on your side. It's just lucky to get a piece of guinea pig ileum right next to the caecum that had a reasonable response to 5-HT. Then, as Pat said, he did use dibenzyline and what that did, of course, was to block muscarinic receptors but, in so doing, he wiped out the 5-HT_4 receptor. He had to use very high

[110] Gaddum and Picarelli (1957).

[111] For the equivalence of the M to the 5-HT_3 receptor, see Craig and Clarke (1990).

[112] Vane and Day (1963).

[113] Brownlee and Johnson (1963).

[114] Buchheit *et al.* (1985).

Figure 9: Professor David Clarke.

concentrations of 5-HT and all he picked up was the neuronal M or 5-HT_3 receptor. He missed the high potency neuronal 5-HT_4 receptor, which was at the foot of the dose-effect curve to 5-HT, because it was blocked at the level of the muscarinic receptor by dibenzyline. So it was a messy experiment, as Pat said, but he was lucky and he did pick out two receptors that subsequently appear to have played out.

Humphrey: Just to add to that, those are the practical difficulties. What you haven't mentioned is that there are other 5-HT receptors in those preps as well, on different sites; so you've got a relaxant receptor in there and you've probably got other receptors. I did think about trying to work them all out when we had better ligands but I didn't think it was really worth it. It was a pretty messy situation but it was seminal in the sense that people thought: 'There are two receptors and it's a bit like the catecholamine story all over again. You know, we can use that and move on.' In those days people didn't think about multiple families of receptors; in fact I think a lot of people thought there were two receptors for every neurotransmitter, or later, that there were four for every transmitter. It turned out to be very different.

Wallis: Dirty drugs or not, I still see that as a key historical point when more than two receptors, the S1 and the S2, and the 3 or the M as it was then, were subsequently firmly established in people's minds.

Figure 10: Some members of the 5-HT meeting held on Heron Island, Australia, indicating the number of 5-HT receptor subtypes they believed existed. Pictured left to right: Günter Engel, Toshiro Shibano, Brian Richardson, Ewan Mylecharane, Stephen Peroutka, Ralph Purdey, John Fozard and Pat Humphrey.

Hoyer: Yes, 25 years ago we had the first 5-HT meeting in Heron Island[115] where some famous pharmacologists were present and were asked: 'How many 5-HT receptors do you think exist?' And Pat raised his finger, his single finger, so in those days he still said: 'One, only one.'[116]

Humphrey: Only one receptor but worth several billion dollars.[117] [Laughter]

Hoyer: That's one thing. The other, more importantly, is that in those days people were not shy of using high concentrations of compounds. If you do this today people will say: 'It's totally unselective; what are you doing? You're killing everything around.' But, actually, you're probably setting the right conditions to getting closer to what you want. Obviously, they have missed many of the

[115] The 5-HT meeting was held on Heron Island, Queensland, Australia, 4–6 September 1987. This was a satellite meeting of the International Union of Basic and Clinical Pharmacology (IUPHAR) congress held in Sydney, 23–28 August 1987.

[116] Professor Daniel Hoyer wrote: 'Others, such as. Ewan Mylecharane, were proposing up to ten.' Note on draft transcript, 16 January 2013.

[117] A reference to the numerous drugs affecting 5-HT systems; see also Table 3, page 126.

high affinity receptors. We can talk about 5-HT_4, 5-HT_7, and who knows how many receptors lie in the guinea pig ileum? One of the issues in the ileum, and, I think Gareth should say something about this, is that the composition of the receptor environment in the gut keeps changing from top to bottom. It is very difficult to get a piece of tissue that is replicable, not even between species. In the same animal you will see that the composition of receptor populations, the same receptors, will vary. Also the multiple splice variants (for 5-HT_4 receptors) are making the issue extremely complex. What do you think, Gareth?

Sanger: I completely agree. It depends on which part of the small intestine you study, and this is what most people study. From top of the gut to the bottom there are massive changes in cholinergic and other functions.

Flower: Is that the reason why no one could repeat Gaddum and Picarelli's original data?[118]

Sanger: I don't know is the short answer, but yes, I could easily envisage that. You talked about the terminal ileum next to the caecum, but that behaves more like a sphincter than the main part of the ileum. If you move away from that region you can get a completely different pharmacology to several different receptor ligands. So, yes, very easily; not understanding gastrointestinal (GI) physiology is a real issue.

Green: It's worth mentioning Janssen Pharmaceuticals because they got involved in receptors very early on. You've mentioned ketanserin, but they had ritanserin and pirenperone. They went for what were then called 5-HT_2 receptors. I went for a meeting there, I think in the very late 1970s, and remember that Paul Janssen, who sat there chain-smoking and grunting at various points, didn't really believe the 5-HT_1 story.[119] Even with the existence of 8-OH-DPAT he thought the 5-HT_2 receptor was the interesting and important one and that it was almost a silent receptor, until pathology took over. So, if there was a hemorrhage, the platelet receptors for 5-HT_2 became active, and he felt the brain acted in the same way. There were these 5-HT_2 receptors but they didn't do anything very much unless there was something like psychiatric illness, in which case you should block them because 5-HT then became pathologically functionally active. That drove it. I think that some of the people like Josée Leysen didn't totally believe this, but Paul was in charge of that company.

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[118] See page 34.

[119] Paul Janssen (1926–2003) was the founder of the Belgian pharmaceutical company Janssen Pharmaceutica (part of Johnson and Johnson since 1961); for further biographical information, see page 151.

Humphrey: Paul did push that hypothesis or at least the company did. I got a lot of stick from David Jack at Ware [Allen & Hanburys][120] saying: 'Are you sure that 5-HT's not involved in the aetiology of hypertension?' And I said: 'Yes, David, it's not, because the fact is that ketanserin is an alpha blocker and that's why it lowers blood pressure.' [121]

Green: I went to a quick meeting with Janssen, who had a place down at Wantage, and again David Grahame-Smith was involved with this, and the Medical Director was sort of trying to pooh-pooh the alpha story, saying: 'These drugs don't do very much, even if you give them at high dose.' And David just burst out laughing and said: 'You know, your patients stand up and fall flat on their faces!' Ketanserin wasn't that great at high doses.

Blackburn: Not to lose the M and D nomenclature, which really provided a very important roadmap for pharmacologists, as did Peroutka and Snyder's (S1 and S2) and Fillion's work. All of this work and knowledge gave us sets of pharmacological data: where these sets of data came from, what part of the tissue or organ you're trying to manipulate, its mechanism of action and its receptor subtype. What we tend to do is take these observations in isolation and we use this data to follow a road map, sometimes in the wrong direction, sometimes in the right direction, which may take a number of years to get to the actual receptor and mechanism of action. Jim Black[122] gave an excellent talk several years ago in the States, where he showed pA_2 values for histamine (H1) receptors and that you could get orders of magnitude differences in pA_2s using perhaps the same tissue from the same part of the tissue from different labs – with the same drugs. So there are road maps, which pharmacologists follow, sometimes they lead us in the right direction and sometimes not, but certainly the M and D and the S1, S2 nomenclature provided a very valuable road map for us to move along with into the 1980s.

Flower: We're going to move on to talk about the way in which the field spread and come back to the topic of receptors and classification.

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[120] The pharmaceutical manufacturers Allen & Hanburys are now part of GlaxoSmithKline laboratories at Ware, Hertfordshire. For details of the pharmaceutical companies' mergers, see Appendix 1, note 255.

[121] Humphrey, Feniuk and Watts (1983).

[122] Professor Sir James Black (1924–2010) was Professor of Analytical Pharmacology at King's College Hospital Medical School, London, from 1984 to 1993. For further biographical details, see pages 142–3.

Sandler: Before we move on, we should mention monoamine oxidase (MAO) which is present in two forms, quite different from each other.[123] Only MAOB is present in human platelets, for instance.[124] MAOA is distributed quite differently in rat brain and human brain. So this adds another level of compexity when you're interpreting your data.[125]

Clarke: Merton is absolutely correct and I think I'm right in saying that 5-HT could be stored in platelets, because it isn't a substrate for MAOB and it could not be stored in nerves unless it was in vesicles, because MAOA is inside the nerves. So that's a very important distinction.

Green: Leading on from that, it is worth mentioning Ted Marley because it was known that the MAO inhibitors could cause this hypertensive crisis, the 'cheese reaction', and I think I'm right in that Ted was the first one who really linked this up on major papers.[126] Would you disagree with that?

Flower: Do you want to say something about this, Merton, or do you just want to disagree?

Sandler: The whole situation is complex and species dependent: in rat brain, for instance, dopamine is metabolized by MAOA,[127] but in the human brain it is an MAOB substrate.[128] So we've got to think about this; there are a lot of factors.

Flower: While we're on this topic, when did the association between 5-HT and the carcinoid syndrome become apparent? Was that obvious from the start or was it something that gradually dawned on clinical investigators such as yourself?

Sandler: I'm trying to remember actually. It all seemed to emerge at the beginning and middle of the 1950s. It was certainly known by the time that Mike Pare and I got immersed in this area.[129]

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[123] Johnston (1968).

[124] Collins and Sandler (1971).

[125] Sandler (2004).

[126] See, for example, Blackwell and Marley (1964, 1966).

[127] Waldmeier, Delini-Stula and Maître (1976).

[128] Glover *et al.* (1977).

[129] Goble, Hay and Sandler (1955); Gobel *et al.* (1956). See page 8.

Figure 11: Professor Gavin Reynolds.

Green: I seem to remember that Gerald Curzon published a paper chromatography method showing huge excretion of 5-HIAA from carcinoid patients way back in about 1955, so, very early. [130]

Sandler: Starting with Lembeck's surprise observation of the presence of 5-HT in small ileal carcinoids.[131] It was the people from Bethesda – Sid Udenfriend and Al Sjoerdsma and colleagues – who developed most of the 5-hydroxyindole methodology and particularly the method for 5-HIAA in the urine.[132] They deserve a lot of the credit.

Professor Gavin Reynolds: Not a story, but a compelling question, perhaps to Merton: we mentioned Alec Coppen in the introduction of tryptophan as a treatment for depression,[133] at what stage did we realize that we could actually manipulate 5-HT levels with tryptophan where we can't, of course, manipulate dopamine with tyrosine?

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[130] Curzon (1955).

[131] Lembeck (1953). See pages 8–9.

[132] See, for example, Sjoerdsma *et al.* (1960). Albert Sjoerdsma was head of the Experimental Therapeutics Branch of the National Heart Institute in Bethesda, see Sjoerdsma (2008). For Sydney Udenfriend, see page 157.

[133] See page 29 and note 95. For an interview with Alec Coppen, see Healy (1996), pages 265–86.

Sandler: I'm not sure when precisely, Alec was very smooth and very shrewd; he actually patented the tryptophan treatment of depression. He was a jolly bluff clinician with a foot in both clinical and biochemical camps; I'm sorry he's not here today.

Tansey: He sent his apologies for the meeting.

Flower: We want to move on to discuss the field as it was advancing: what was happening, what sort of people worked in the area, where people published, what 5-HT 'clubs' or societies were formed and how and why they were important. I want to start discussing the classification of 5-HT receptors. When did the increasing interest in 5-HT begin to impact on societies like the British Pharmacological Society (BPS) and the Physiological Society?

Humphrey: I'd like to answer this because it very much focused around myself, in the sense that I was asked to work on migraine at Ware. I joined in 1972 and by 1976 we thought we'd discovered this new receptor, which I alluded to just now, the one that had the commonality between ergot, methysergide, and 5-HT. It was a receptor mainly in cranial blood vessels and we thought that, if we could constrict them selectively, we would actually block the painful distension. At the time there was a theory about carotid arterial venous anastomoses and, funnily enough, although this receptor is in the blood vessels, predominantly cranial blood vessels, we discovered it in the dog saphenous vein. Luckily we had lots of dogs at the time that we used to work on, anaesthetized dogs, and I used to come along and whip out the veins and put them in a gut bath. I went to the BPS at Manchester, I think in 1976, to talk about this and there must have been 300 or 400 people in the audience – it was in the days when we had big audiences at BPS meetings. People said, 'Pat, you're not going to talk about 5-HT again, are you?', because they used to take the 'Mick' as nobody else was talking about 5-HT. I gave a talk about this new receptor we thought we'd discovered in the saphenous vein[134] and I think it went down like a lead balloon except, as I walked up the steps from the podium, there was Michael Owen, who was Head of SmithKline pharmacology department, who had worked on migraine with Novartis. He knew the area well and said: 'That's going to be big.' And it did turn out to be big, because then all we had to do was set about trying to find a selective agonist for this receptor. We knew there were more than two receptors because we had discovered a third, and there was some anticipation

[134] Feniuk, Humphrey and Levy (1977).

Receptor type	S_1	S_2	S_3	S_4
Occurence	Ubiquitious	Some vascular smooth muscle. Some neurones	Neurones	Vascular smooth muscle. Some cardiac and gastro-intestinal muscle
Responses mediated	Generalised vasoconstriction, bronchoconstriction, contraction of gastro-intestinal smooth muscle. Platelet aggregation. Catecholmine release from adrenal medulla.	Selective vasoconstriction of arterio-venous anastomoses. Selective inhition of some sympathetic nerves. Emesis (cat only)	Neuronal stimulation including activation of Bezold-Jarisch reflex and activation of nociceptive reflexes.	Smooth muscle relaxation. Increased force and rate of cardiac muscle.
Selective agonists	AH21068	AH25086 GR32066 Methysergide	CCI 20987	AH21467 AH22308
Selective antagonists	Methysergide Pizotifen Ketanserin	GR32949 (partial agonist)	Metoclopramide GR32985	Methiothepin Methysergide (weak)
Ligand binding site equivalent	$5\text{-}HT_2$	None	None	$5\text{-}HT_1$?
Comments	Originally considered equivalent to Gaddum's D-receptor. However sub-division may be required since ketanserin does not block S_1-receptors in the guinea-pig ileum and rat fundus (Van Nueten, Leyson, Schuurkes & Vanhoutte 1983).		Includes Gaddum's M-receptor (guinea-pig ileum) but data with antagonists indicates sub-division of this receptor type may be necessary (Fozard, 1980)	Linked to adenylate cyclase? (Feniuk Humphrey & Trevethick, 1981)

Figure 12: Classification of peripheral 5-HT (serotonin-S) receptors. Glaxo Group Research Report, 1983, authored and provided by Dr Patrick Humphrey.

that there would be others, so we had to get a selective compound. I had an in-house classification in 1976 and I've got a piece of paper here from an internal report that shows it (Figure 12).

I very reluctantly decided to call them S receptors because of 5-HT. I didn't really want to become an American, I wanted it 5-HT but S just seemed a bit more modern, so in-house we had S1 for the Gaddum D receptor and S2 for our new receptor, and then S3 for the M receptor. Again, that was incredibly naive looking back on it; we were mixing up ion channel receptors and G protein-coupled receptors.[135] But we went through with it, and by 1978 we had found that there was also a smooth muscle 'relaxant' receptor; having made a

[135] For G protein-coupled receptors, see Brunton, Chabner and Knollman (eds) (2011), pages 52–5.

compound we thought was going to be anti-migraine and when we put it in animals, it lowered blood pressure.[136] On investigation we found that there is actually a receptor that, when activated, will relax smooth muscle rather than constrict it. So, by 1978 we had a classification in-house that went S1, S2, S3, which I've just described and then the 'relaxant' receptor we called S4. It was pretty obvious this was getting to be a bit of a mish-mash by now and it needed some resolution and I was quite keen to talk to other people. But I think the bomb really dropped for me when Peroutka and Snyder started publishing because they talked about S1 and S2 binding sites. The problem was that the S1 binding site was our S2 receptor and vice versa, so it was obviously a complete mess. [Laughter] At the time I had a PhD student working with Philip Bradley, who was very keen on 5-HT, having worked with Richard Green, and he was always talking about Richard: 'I know a man who knows about 5-HT.' Suddenly I had kindred spirits to start talking with about 5-HT receptors and we had a student who was looking at platelet release and contraction of smooth muscle, and so on and so on. It was natural that we should start talking about things, so Philip Bradley set up a seminar at Birmingham.[137] I think that the initial thing was probably just for students, but we agreed we would try to set this up at the BPS meeting in Birmingham in 1984 and Philip organized it. That was terrific because we did get people along who had different views about what these things should be called. They had had different experiences in the lab and had published different types of work. I can remember standing on the lawn outside and everybody having really good discussions from the offset. I think there was something unique about the 5-HT area that these guys were all very nice. Dave is still talking to me after years [laughter] and Daniel and I have had punch-ups, but we still talk to each other and go off and have a beer. So I think for some reason, I don't know what it was, experts came together from all disparate areas – Daniel didn't know anything about pharmacology, he was a binder and grinder,[138] I had to teach him some pharmacology [laughter] – and wanted to discuss and debate. We did eventually have a publication that came out from

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[136] Dalton, Feniuk and Humphrey (1986).

[137] See also pages 45–6.

[138] Binding and grinding is a somewhat dismissive label for those who work *in vitro* using biochemical techniques, including grinding up tissues and using radioactively labelled chemicals to bind to putative receptor sites. Whilst providing quantitative data about binding sites, such approaches give no information about the anatomical localization, or functionality of receptor sites.

Figure 13: Poster advertising the 5-HT meeting held on Heron Island, Queensland, Australia, 4–6 September 1987.

the Birmingham meeting in *Neuropharmacology*[139] and it is interesting to look at the names: Phillip Bradley, Gunter Engel, who couldn't unfortunately be here today; Wasyl Feniuk, who is a very close colleague of mine and it's a great shame he isn't here today, because he did a lot of work with me on migraine; John Fozard, another very important person, and it's a very great pity he can't be here either; myself; Derek Middlemiss, again coming from a binding background from what I remember; Ewan Mylecharane, he's an Aussie, we'll forgive him for not being here; Brian Richardson, from Sandoz; and then Pramod Saxena, another very important man in the field of migraine research. So, that was quite a group. I think that after that Birmingham meeting everybody was talking regularly on the phone or at meetings and that was really the start of it. All of us realized, however, that we needed to bring it together into a more authoritative basis and, I suppose, that leads us up to Heron Island.

For those of you who didn't go, hard luck. [Laughter] This was the meeting that was in parallel with the International Union of Basic and Clinical Pharmacology (IUPHAR) meeting in Australia and everybody who was interested in 5-HT and could make it was there. Again, this sort of collegiate interaction was amazing. There was a lot of good, healthy discussion, some of it unhealthy as well, I suspect, but usually offline, and we could get agreement. I was very pleased with the book that came out of this meeting, because Brian Richardson and I wrote a chapter that said: 'This is where we think we are at the moment with 5-HT

[139] Bradley *et al.* (1986).

receptors.'[140] It wasn't just us, because it was a round table discussion – a bit like this meeting – people were jumping up and Brian and I led the discussion and finally collated all the thoughts and put it into a piece of prose. That was in September 1987 and at the same time I went to the IUPHAR meeting, to the vestigial IUPHAR receptor and nomenclature committee that Paul Vanhoutte had set up.[141] Paul had also been very instrumental helping to set up the Heron Island meeting, but unfortunately he wasn't able to make it in the end. But I went to the IUPHAR meeting to represent the 5-HT story so far and report back from Heron Island, and that was the formation of the Serotonin Receptor Nomenclature Committee under the auspices of IUPHAR.[142] I remained chairman of that committee from 1987 to 1993. So that was the beginning. I think Heron Island really set things up because people were marooned on a desert island [laughter], we had days to talk to each other, and old friendships were established, if they hadn't been established before. I think people could see that everybody had different opinions, that was good, but we were all interested in finally getting some sense out of the real mish-mash – there were people with different nomenclatures, 5-HT_{1P} and God knows what else. We got rid of that in the end.

Flower: You mentioned giving a talk to BPS in 1976 or 1978. How many people were interested in 5-HT at the BPS meetings in those days? It sounds like hardly any.

Humphrey: Virtually none.

Green: I remember working through the 1970s, a different era from Pat, and feeling there weren't very many people interested in 5-HT at all. Then the Birmingham meeting was just amazing.[143] Phil Bradley had very much organized this and being used to a great deal of indifference about 5-HT in the

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[140] Humphrey and Richardson (1989).

[141] Professor Paul Vanhoutte (b. 1940) was a consultant in the Departments of Physiology and Biophysics, and Department of Cardiovascular Medicine at the Mayo Clinic, Rochester, Minnesota, from 1981 to 1989, and has been Director of the BioPharmaceutical Development Centre, University of Hong Kong, since 2003 and Chair Professor and Head of the Department of Pharmacology at the Li Ka Shing Faculty of Medicine, University of Hong Kong, since 2006.

[142] The Serotonin Receptor Nomenclature Committee was established in 1990 as a subcommittee of the Serotonin Club, whose chair and members are appointed by its Executive Committee.

[143] See pages 43–4.

brain at things like BPS meetings. I went to that meeting to give a talk and there was this huge lecture theatre, which was absolutely packed out.[144] I said to Les Iversen, who of course had just moved then to Merck: 'What's all this about? Why are all these people interested?' And Les, in his usual slightly hooded-eyed manner, said: 'I've no idea.' Of course, he did have an idea because, as Pat said, the industry was abuzz then, but most of it hadn't been published. It was all happening under the surface and there were huge numbers of industry people at that meeting all writing frantically, you could tell, and that really was a major turning point as far as I'm concerned, from a quiet time to suddenly it all happening.

Humphrey: The meeting was called '5-HT, Peripheral and Central Receptors, and Functions', but it was under the auspices of the BPS, and I suspect that may have been one of the reasons so many people came.[145]

Wallis: I didn't go to the nomenclature meeting, but I remember reading a very adroit and complete description of it written by Paul Hartig and his key point was 'fingerprint criteria' for establishing the receptors.[146] I want to ask Pat how important was that to the discussion?

Humphrey: I think, again, this was interesting because Paul Hartig was coming very much from the second messenger angle, and he brought a lot of new thinking in there. But the concept of the fingerprints was something that was evolving throughout the pharmacological world and, in fact, that's what the IUPHAR nomenclature group set out to do in the first instance: we had an international committee just to talk about the fingerprints you needed to characterize receptors almost as a blueprint[147] before one went off into these different receptor areas. A lot of it was pioneered by the 5-HT group simply because we had so much data and then suddenly we had so many people prepared to have an input. In many ways the 5-HT group carried the thinking around receptor characterization in general anyway. Of course, we had the complexity too of all the molecular biology coming in and some of the molecular biologists were doing their own thing and giving their proteins names unilaterally, but towards the end they were coming

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[144] Green (1984).

[145] Some of the proceedings of this meeting were published in *Neuropharmacology* (1984) **23 (12B):** 1465–569.

[146] See, for example, Hartig (1994).

[147] Vanhoutte *et al.* (1994).

down the IUPHAR track. It was very interesting in the prostaglandin area: the functional characterization and nomenclature had been done long before Narumiya did all his wonderful molecular biology, and the molecular biologists had to go along with the functional nomenclature rather than the other way around.[148] But anyway, I think by then we'd all realized that fingerprints needed everything: it needed second messenger, it needed functional data, it needed the molecular definitive recognition as well.

Hoyer: There are at least four different groups who were extremely important in this. Firstly, the Serotonin Club that was created 25 years ago; we have just celebrated 25 years of the Serotonin Club in Montpellier this summer (2012). The club was an amalgamation of people with very different expertise and horizons – academics, but also people from industry.[149] I think for some reason at that time, there were probably more people from industry than academics. The second important contribution was the support that we got from the BPS from the start. When you look at many of these 5-HT meetings they were in conjunction with the BPS. Actually, the Serotonin Club used to have a lecture at every Christmas BPS meeting, sometimes in a Greek restaurant or at a Christmas party; no one could hear anything, but the whole point was to be there with friends and colleagues. Thirdly, IUPHAR was also important and it started pretty much at the same time. We established the 5-HT nomenclature committee in 1990, which had a leading role for setting the criteria for all the receptor nomenclature committees that were established afterwards, something like 90 committees. The Hartig paper that we published together in 1993 in *Trends in Pharmacological Sciences,* was the result of one of these meetings, it set the scene.[150] So we said that there have to be four criteria for a receptor to be recognized including: a) it has to be relevant to the human situation; b) the pharmacological fingerprint or profile; c) structure, which was about to come because molecular biology was kicking in in the early 1990s; d) function – the function at that time could have been anything, but it was even better if you had a second messenger you could characterize. We haven't talked about splice variants, and strange things like biased signalling at the time (quite often described as poor pharmacology). But we left it open for future adaptation. The good thing is that the group had enough flexibility to keep going. The fourth contribution that was important, I actually think it was probably the first one,

[148] Coleman *et al.* (1984); Coleman, Smith and Narumiya (1994).

[149] See the Serotonin Club website at www.serotoninclub.org/ (visited 26 March 2013).

[150] Humphrey, Hartig and Hoyer (1993).

was the input of the pharmaceutical industry, where 5-HT research was very active, but often people did not know of it because much work in the industry was more underground and was not published immediately. What we knew, of course, was that Pat was working on these targets; similarly Sandoz, which has been a 5-HT company since the start (they worked on LSD),[151] realized in 1978 that 5-HT was important and so they asked Brian Richardson to set up a task force whose only remit was: 'What is 5-HT? How many receptors? What do we know about 5-HT's role? What is the link to the clinic and what can we do to make drugs, whatever the indication?' They started to work on 5-HT_3 (Gaddum's M receptor) and initial indications were pain, because the blister pain model using capsaicin, was sensitive to 5-HT_3 antagonists, e.g. ICS 205,930. This was only the first indication. At some point they also considered migraine but, of course, 5-HT_3 mechanisms in pain are more complex. Somewhat earlier John Fozard had started a group at Merrell Dow in Strasbourg, where they were working specifically on 5-HT. They discovered MDL 72,222, which died, as do many compounds because of toxicology reasons, but it was one of the first selective 5-HT_3 antagonists.[152] Mike Tyers and collaborators in Bradford (Brenda Costall and Robert Naylor, I don't know how many collaborations they had altogether), reported on GR 38032 (ondansetron),[153] the beauty was that industrial chemists were to design new, selective compounds. That was the difference before cloning, once you had the tools you could start working. Today everything is simple: clone and express the receptor and you throw any compound on it; you know it's only mediated by that given receptor. But in those days, whether you used a guinea pig ileum or anything else, you would have to make sure that you had selective compounds, otherwise things were not going to fly. So the interesting part was that then some worked on 5-HT_1, but others worked on 5-HT_2 or 5-HT_3 receptors. Paul Janssen was working on 5-HT_2 and there's much to say about his influence in the field at that time.[154]

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[151] For Sandoz and LSD see page 15 and Snyder (1986), pages 189–93.

[152] Professor David Wallis wrote: 'Between 1983 and 1985, John Fozard collaborated with David Wallis at Cardiff in experiments assessing the action of MDL 72222 on the 5-HT_3 receptors on sympathetic neurons and on vagal afferent neurones, work funded by Merrell Dow.' Note on draft transcript, 14 December 2012.

[153] For a discussion of the use of ondansetron in a paediatric study, see Christie and Tansey (eds) (2007), pages 59–60.

[154] For Janssen, see note 119.

Actually, there was some good influence and some rather bad influence.[155] But it was the involvement of the chemists, by and large, that made the whole process of receptor characterization feasible, because they synthesized more and more selective compounds. Then, at some point, Fozard, Hamon and other colleagues published about 8-OH-DPAT being the first selective 5-HT_{1A} compound.[156] That's when I jumped in and we just kept going, testing more compounds, more radioligands, more tissues and more species. I was supposed to be in cardiovascular research but actually my heart has always been in the brain. So I worked almost 'undercover' with Chema Palacios in CNS who had just come back from Mike Kuhar's lab in Baltimore and we applied techniques that Pat would never use, not at that time; he changed later.[157] We use a combination of binding, autoradiography and second messenger and chemicals, lots of ligands, to sort out the mess. This was how we discovered 5-HT_{1A} versus 5-HT_{1B} and the 5-HT_{1C} that was renamed 5-HT_{2C}. We looked at 5-HT_2 receptors, of course, and then realized that a subtype of 5-HT_2 receptors was in the stomach fundus (to become 5-HT_{2B}). We started to work on 5-HT_3 receptors, then realized there was something in the gut and in the brain that didn't fit to any of these classifications, which was 5-HT_4 at this point, and so on (there was still some confusion about 5-HT_3, 5-HT_4 and the M receptor in the late 1980s).[158] New receptors came out one after the other. An interesting thing is that, shortly afterwards, molecular biology kicked in and we integrated all these cloning people in the 'club'. The first interaction I had with Pat was at the BPS meeting in 1986. I think there were probably 600 people in the audience. Everything went well and I described the 5-HT_{1A} receptor mediated inhibition of cyclic AMP (cAMP) activity;[159] nothing to write home about today, but at that time it was new. Then Pat got up and said: 'This has nothing to do with physiology, you're just talking about a second messenger. We don't know what the second

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[155] Professor Daniel Hoyer wrote: 'There was a strong bias toward supporting ketanserin as an antihypertensive for several years, ignoring findings that showed that this had nothing to do with 5-HT_2 antagonism, as it was all explained by alpha 1 antagonism. Along the same lines, some of Paul's senior collaborators were influencing the field by not recognizing at all 5-HT_1 or 5-HT_3 receptors.' Email to Ms Caroline Overy, 1 July 2013.

[156] Middlemiss and Fozard (1983); Gozlan *et al.* (1983).

[157] See for example, Palacios *et al.* (1990).

[158] Hoyer (1990).

[159] See, for example, Markstein, Hoyer and Engel (1986); Schoeffter and Hoyer (1988).

messenger is doing.' That was going back and forth. Then the chair of the session[160] said: 'Stop. Go to the bar. Sort it out. Then come back.' [Laughter] This was the beginning of a friendship that resulted in the big nomenclature paper,[161] I don't know where the friendship will culminate as we keep seeing each other, even when we're in different parts of the world, and we keep going. But this is what led to the spirit of the 1994 *Pharmacological Reviews* paper. It has been cited about 2500 times now, it keeps being cited, and I think you can re-read this paper, occasionally I do, and much of what we had written then and there is still pretty valid. It's good, it integrates different backgrounds and when you look at it, you can clearly recognize the style of the different authors. John Fozard's writing is different from my writing, which isn't surprising given my background. I will try to improve. The good thing is that everyone's views were accepted and, given that industry was playing a major role, what we tried to do was not to mislead people. That is, we could not give away all the secrets, but at least there was the understanding that if anyone was going on the wrong track we were telling them not to do that, not to mislead, just to be open. We could not say everything, but it worked, and I think it worked remarkably well. I've published papers with people from all over the place, maybe more from the 'competition' than with Sandoz. That was remarkable. Again, it was because of the auspices of the BPS. It would not have happened in France and it would not have happened in the United States, that's for sure.[162]

Humphrey: I have a human perspective on what Daniel has said. Daniel and I took care of the editing of the consensus IUPHAR manuscript[163] but, as Daniel said, all the authors wrote their own chunks and then we had to try to integrate it, which involved quite a lot of time and effort. I'd just like to mention that the authors were: Hoyer; Clarke, sitting there; Fozard; Paul Hartig; Graeme Martin, who unfortunately can't be here today, who went on to take over from me as Chairman of the Nomenclature Committee after I moved onto other

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[160] No one can now recall who was chairing this meeting.

[161] Hoyer *et al.* (1994).

[162] Professor Daniel Hoyer wrote: 'The collegiality between researchers from academia and industry that was so obvious at the BPS was so very different from what was common standard in the other countries and was certainly not experienced between industrial scientists in other countries, for fear of competition and IP (intellectual property) issues.' Email to Ms Caroline Overy, 1 July 2013.

[163] Hoyer *et al.* (1994).

neurotransmitters; Ewan Mylecharane; Pramod Saxena and myself. So it's difficult to know who wrote that paper because everybody had such a massive contribution and the fact that we got everybody to agree, in what was a very large tome. I think we made a rather trite statement at the beginning that, between them, all the authors had got 100 years or more experience in the 5-HT field, but it was true.[164]

Flower: It was a landmark paper; no doubt about that. I want to step back for a second to ask if there were any other influential organizations apart from the BPS?

Green: I think it was the BPS, more than anything else. Certainly not the Physiological Society. Some of these people that Pat and Danny have mentioned – Danny himself, Pramod Saxena – used to come to the BPS winter meetings, and it is notable that when Paul Vanhoutte wanted to set up the Serotonin Club, he had a meeting in December 1986 in London, actually at the School of Pharmacy.[165] I don't know who else was there, but Paul recognized that, as well as setting up the Serotonin Club in the States, coming to the UK in December, because that's when these meetings were held, was another important step in setting up the Serotonin Club.

Clarke: A quick comment that classical pharmacology played an important role in the definition of 5-HT receptors, no doubt about that. Pat's work was classical pharmacology; Fozard's work was started in 1962. I taught him classical pharmacology at Bradford. Without any binding, without any structure, without any second messenger, Fozard defined the 5-HT_3 receptor with cocaine and various isomers of cocaine and so forth.[166] So classical pharmacology was the foundation, but it wasn't enough, and as Daniel says, without the tools, classical pharmacology is quite impotent. But we did have one or two tools

[164] 'It is the role of the biologist to define the receptors of interest and to define the type of ligand required for a particular therapeutic utility. It is for this reason that the authors of this review have spent more than a combined total of 100 years working on 5-HT receptors, to characterize them and to define their function and distribution.' (Hoyer *et al.* (1994), page 159).

[165] See Green (2004), page 3, in which he writes: 'In 1986 I attended a "start up" meeting at the School of Pharmacy in London that Paul Vanhoutte had organised in order to get together scientists who were interested in forming a society that would incorporate anyone interested in serotonin research.' The Serotonin Club was formally founded in 1987, see www.serotoninclub.org/newsletters/Nwsltr64.pdf (visited 8 May 2013).

[166] See, for example, Fozard, Mobarok Ali and Newgrosh (1979).

and classical pharmacology did lay an important foundation for binding and structure, which then led to cementing the whole field.

Blackburn: Pat mentioned the screening cascades he was developing. In the 1980s at ICI Pharmaceuticals, we were developing similar screening cascades based on the 5-HT M & D receptor classification and subsequently the S1 and S2 receptors. Around this time, ICI chemists Bob Pearce and Craig Thornber were synthesizing compounds, which were believed at the time to be selective S2 receptor antagonists.[167] We didn't understand then about 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} receptors, but we had inklings that the receptor from the fundus of the rat stomach was different from the classical 5-HT receptor pharmacology that we were working on at this time. I'll come back to that later with regard to actually identifying selective compounds for the 5-HT_{2B} receptor at SmithKline Beecham. So, the industry was very good at the time in developing tools and ICI 169,369 and ICI 170,809 were some of the early 5-HT_2-like compounds, used worldwide in trying to understand the physiology/pharmacology of the 5-HT_2 receptor. About this time, John Fozard and I were communicating on a selective 5-HT_1 receptor agonist 8-OH-DPAT and it was clear that the ICI chemists' sample of 8-OH-DPAT was more potent than John's sample. So we were swapping actual compounds in those days. Those tools proved to be very valuable in our 5-HT research at the time. A number of these compounds did actually go into the clinic as they didn't possess the alpha-1 receptor properties that the Janssen compound ketanserin possessed.[168] For example, ICI 169,369 went into a migraine prophylactic study and was shown to be active – it reduced the general symptoms of migraine by about 40–50 per cent.

We also went into the clinic with ICI 170,809 in schizophrenia and depression but, unfortunately, the compound failed to show efficacy due to the studies being, in my opinion, underpowered. However, at that time ICI Pharmaceuticals acquired an American company, Stuart Pharmaceuticals, in 1972, which focused on CNS research. It was a little later, that Professor Barry Cox and I presented the Serotonin 2 (now 5-HT_{2A})/dopamine hypothesis to them in Wilmington, with regard to the importance in the basal ganglia area and in ameliorating the

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[167] Blackburn *et al.* (1987).

[168] See note 103.

dyskinesias and psychotic-like side effects in schizophrenia.[169] It was from this early work that the atypical antipsychotic Seroquel (quetiapine) was developed and became one of the biggest selling drugs for AstraZeneca.

So, in those early days, we were providing compounds that allowed the science and the pharmacology of 5-HT to move forward, with a few of them still very successful in the clinic.[170] If you look at the 2010 prescription sales, out of the top ten there are, I think, four or five compounds that are related to 5-HT research;[171] we're talking about billions of prescriptions, which highlights the impact that 5-HT research and development has had on industry and academia.

Sanger: I want to add a comment to David [Clarke's] point because there are only really two occasions when I've wished my first degree was in pharmacology. The first was when my post doc supervisor asked me to define a pA_2 first thing in the morning.[172] [Laughter] The second was reading your [David Clarke] paper in which you used classical pharmacology to define the $5\text{-}HT_4$ receptor using ICS 205,930, then known as a $5\text{-}HT_3$ receptor antagonist. But you protected the receptor and showed that this molecule in high concentrations could actually antagonize a response mediated by a different receptor, later called $5\text{-}HT_4$.[173] It was a wonderful piece of classical pharmacology and I think broke open the area of $5\text{-}HT_4$ receptor research. Until then we were talking about responses and maybe recognition sites – I certainly was. You actually defined it using that nice, classical piece of pharmacology. You were absolutely right.

Marsden: Just going back to that 1984 meeting. I think one of the interesting things for me and people like Richard and others who were involved in some of the behavioural functional read-outs, was that there was an interest in that aspect and that we needed to try to get things in order to be able to classify the receptors. The arrival of 8-OH-DPAT was very important

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[169] Blackburn *et al.* (1980, 1981); Blackburn, Cox and Lee (1982).

[170] See Scrip (1988) and also the comment by Dr Patrick Humphrey on page 36 and note 117.

[171] See Table 3 on page 126.

[172] Professor Gareth Sanger wrote: 'This is a pharmacology term, defined as: "The negative logarithm to the base 10 of the molar concentration of antagonist that makes it necessary to double the concentration of agonist needed to elicit the original submaximal response" (Cammack *et al.* (eds) (2006)). It is a very useful way of quantifying and comparing the functional effects of the antagonist in different experiments.' Email to Ms Caroline Overy, 16 July 2013.

[173] Craig and Clarke (1990).

Figure 14: Professor Gavin Reynolds and Professor Charles Marsden.

because you actually got a defined response, both the temperature response and the behavioural response, so it seemed possible that you could use these as behavioural outcomes. The other thing that occurred at that time, of course, was the expansion of molecular biology. That had an adverse effect, I think, particularly on academic research, because the Thatcher years were not the easiest for academic research and the Government at that time were very keen on having very short-term, quick responses, and molecular biology seemed to provide that opportunity.[174] Those of us who were on the more functional end had quite a struggle at that time. I was extremely lucky because I was protected as I was supported by the Wellcome Trust on a long-term sponsorship. The other advance that occurred then was the development of both the *in vitro* and *in vivo* measurements of 'release' or, at least, transmitter overflow and measurement of extracellular levels.[175] I think that the development of microdialysis, in particular, provided an alternative approach

[174] The mid-1980s saw the launch of the campaign 'Save British Science', which highlighted the difficulties in raising funds for scientific research in Britain. In 2005 this became the Campaign for Science and Engineering in the UK (CaSE); see www.sciencecampaign.org.uk/about/history/index.htm (visited 27 March 2013).

[175] See note 98 and also Marsden (ed.) (1984).

that could be used to look for end points in terms of receptor responses.[176] I do think, however, the very strong impact of molecular biology on research, while terribly important, did have, to some extent, a negative impact on the development of ways of understanding the role of 5-HT in disease and what the true functional consequences of 5-HT were in terms of behaviour. Now, of course, that has to some extent been reversed.[177]

Dr Mike Tyers: I want to have a chance to talk about the 5-HT_3 receptor, since no one seems to be talking about it. It's a sort of forgotten receptor, probably because it appears to have no subtypes and, as far as we know, it's the only ligand-gated ion channel receptor. We started looking at the 5-HT_3 receptor at Glaxo Greenford in the early 1980s, a separate group from Pat's at Allen & Hanburys at Ware. We started looking for a selective 5-HT_3 receptor antagonist. We knew that metoclopramide was a dopamine antagonist, but John Fozard had shown that, at higher concentrations, it was a 5-HT_3 receptor antagonist as well.[178] Several companies were looking at 5-HT_3 receptors at the time and were making compounds related to known molecules that had affinity for the receptor, like metoclopramide and cocaine. At Glaxo, we started with the neurotransmitter and synthesized lots of modified tryptamines and screened them *in vitro* against depolarization of the vagus nerve induced by 5-HT, and *in vivo* against the Bezold-Jarisch reflex bradycardia induced by intravenous injection of 5-HT or a 5-HT_3 selective agonist in the chloralose in the anaesthetized cat.[179] I remember that within a few weeks of starting the project in 1985, we discovered 2-methyl-5-HT, which was a selective 5-HT_3 receptor agonist. Selective 5-HT_3 antagonists soon followed by substituting the 5-OH group with bulk and a substituted -N imidazo group (the chemists involved were Dai Humber, Ian Coates, Alec Oxford and Colin Smith).[180] Our screening test was depolarization of the rat isolated vagus nerve. The vagus nerve is smothered in 5-HT_3 receptors and,

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[176] For an overview, see Chefer *et al.* (2009).

[177] Professor Charles Marsden added: '… by the need to have real understanding of the behavioural consequences of genetic manipulation in mice.' Note on draft transcript, 5 February 2013.

[178] Fozard and Mobarok Ali (1978).

[179] See Ireland and Tyers (1987); Kilpatrick, Bunce and Tyers (1990).

[180] Brittain *et al.* (1987).

being the Xth cranial nerve, arose in the brain stem in the region of the area postrema, also called the vomiting centre.[181] Latterly we identified a 5-HT_3 radio-ligand binding site in the brain and used this as our preferred *in vitro* test.[182] As the Department of Neurophamacology at Glaxo Research we were particularly interested in the central effects of 5-HT receptor-selective ligands. We set up academic collaborations with many groups around the world and gifted our selective compounds to them, asking them to test them in their particular assay systems. Our collaboration with the Bradford group – Brenda Costall, Bob Naylor and Annette Domeney – was particularly productive, leading us to start clinical trials in dementia, memory and anxiety.[183] We soon found it virtually impossible for one company to do evaluation in more than one psychiatric disease because the error was so great, needing studies on many tens of thousands of patients for each arm of the study. Also, it wasn't just one dose needed to produce the effects, but many – the amount of data and subsequent analysis was awesome, even for Glaxo!

Upjohn undertook eleven trials with Prozac to get FDA approval and onto the market, only two of which showed effects in depressed patients. Amazing!

Inspired by John Fozard's work with MDL 72,222 in migraine,[184] we also undertook a trial with one of our selective 5-HT_3 antagonists and found that, as in John's study, the 5-HT_3 antagonism had no effect on headache but did have a moderate effect on sickness. John didn't actually report what effects MDL 72,222 had on vomiting, but has subsequently said that there was a mild effect. Now, Dick Gralla, an oncologist in New York, had reported that high doses of metoclopramide were able to stop sickness in cisplatin-induced vomiting in his cancer patients better than other dopamine antagonists, which had no additional 5-HT_3 actions.[185] Putting two and two together, we postulated that

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[181] For a detailed description and review of the anatomy of the central pathways for nausea and vomiting, see Hornby (2001); Onishi *et al.* (2007); Stern, Koch and Andrews (2011).

[182] Kilpatrick, Jones and Tyers (1988).

[183] For 5-HT and psychiatry, see Sandler, Coppen and Harnett (eds) (1991).

[184] See for example, Loisy *et al.* (1985); see also Fozard (1990).

[185] See Gralla *et al.* (1981); Kris *et al.* (1983); Gralla (1983); see also the Witness Seminar on the discovery, use and impact of platinum salts as chemotherapy agents for cancer, at which Professor Richard Gralla was a participant; Christie and Tansey (eds) (2007).

block of 5-HT_3 receptors should be able to stop sickness induced by cancer chemotherapeutic drugs.[186] Subsequent studies with a selective 5-HT_3 antagonist by Robert Naylor in ferrets [100 per cent effective!][187] and then by John Smyth in Edinburgh in patients, showed this to be true.[188] We went up to John Smyth in Edinburgh and asked him if he would test the compound in his patients. He said: 'I've got very sick patients here,' and so referred us to Bob Naylor at Bradford, who was doing experiments with dopamine antagonists, to do some tests in ferrets. I went up to Bob and said: 'Would you test this compound against cisplatin in your ferrets?' He said: 'It's not going to work, you know.' Anyway he did test it, and two weeks later he said: 'You know, it worked; 100 per cent!'[189] So we went back to John Smyth and said we had the data, and he gave it to one of his most refractory patients. He phoned up the next day, excited, and said: 'This drug has worked effectively. The patient is sitting up in bed eating a hospital breakfast, looking pink and happy.' This was possibly the anti-anxiety effect showing through as well. I think some clinicians started using it off label; one was a patient with bulimia, who said it was the best drug she had ever taken to help her tackle bulimia. But it's not worth developing a drug for bulimia, there are too few cases, so it would be down to the clinician to decide whether to use it or not.

The rest is routine development for any drug, but since we had already conducted clinical trials with a selective 5-HT_3 antagonist in phase 1 and 2, we could go straight into simple phase 2 studies in cancer patients. We had one false start with a compound that, as well as being a potent 5-HT_3 antagonist, also

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[186] Butler *et al.* (1988); Tyers, Bunce and Humphrey (1989). Dr Mike Tyers and Professor Gareth Sanger were jointly awarded the 1998 Pharmaceutical Research and Manufacturers of America (PhRMA) Discoverers Award for the 5-HT_3 receptor/antiemesis research. Further recollections by Dr Mike Tyers on the development of ondansetron are archived with the records of this meeting. See also note 190.

[187] Costall *et al.* (1986, 1987); see also, Florczyk *et al.* (1981); Florczyk, Schurig and Bradner (1982).

[188] Professor Paul Andrews wrote: 'The first paper I can find on PubMed by J F Smyth on ondansetron and cisplatin is Smyth *et al.* (1991). This is not the first clinical paper on ondansetron in chemotherapy (I think that this is Cunningham *et al.* (1987)), nor is it the first on cisplatin and ondansetron in either the US (Kris *et al.* (1988)) or the EU (Marty *et al.* 1989)). He may have done studies that were unpublished or that were presented at a conference – there was a big ondansetron meeting, I think, in 1987...There are basic and clinical papers in the same time window on other 5-HT_3 antagonists and, in particular, granisetron the Beecham/SmithKline compound. The first granisetron paper with cisplatin that I know of is Carmichael *et al.* (1988).' Email to Ms Caroline Overy, 26 June 2013.

[189] Stables *et al.* (1987).

inhibited cytochrome P450, indicating a number of potential drug interactions would be possible. Ondansetron was the next compound to come off the line and was quickly substituted for the 'toxic' compound.[190]

Flower: Would anybody else like to say anything about 5-HT_3 since Mike has started the thread?

Blackburn: In support of Mike, and 5-HT_3's role, particularly in the CNS as being a lost cause, it was following the work from Mike's group at Glaxo and others, that at Beecham we were working on a compound BRL 46470, which we took

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[190] Professor Gareth Sanger wrote: '[at Beechams] we were working on a series of compounds that blocked cisplatin-induced vomiting in ferrets, but we weren't sure exactly how – the mechanism was either because the compound regulated gastric motility (by 5-HT_4 receptor agonism) or because it antagonized at 5-HT_3 receptors. We suspected the latter because (a) John Fozard had demonstrated that relatively high concentrations of a related compound (metoclopramide) antagonized at the 5-HT_3 receptor and because Dr Gralla had previously published a paper that showed that cisplatin-induced vomiting in cancer patients was blocked by high doses of metoclopramide (then assumed to be a better way of accessing dopamine receptors in the brain). The result was that I asked John Fozard for a sample of MDL 72,222, his selective 5-HT_3 receptor antagonist. We found that this compound blocked the vomiting caused by cisplatin and published our data (as the first full paper on the subject, previously abstracted elsewhere, by us). Clearly, our previous abstracts had also alerted the competition! In pouring rain in Melbourne, Brian Richardson (then from Sandoz, later Novartis) apologized to me for reacting to our abstracts as fast as he could, contacting the Bradford group of researchers (Bob Naylor and Brenda Costall) to quickly test their compound (tropisetron) and publish as soon as possible (it came out shortly after ours)! We then had several beers together! At around this time, Glaxo had taken the brave (and wise) decision to develop a 5-HT_3 receptor antagonist and then see what it did, originally focused on several CNS disorders. This approach was clearly evident in the patent on ondansetron. Tough to know what happened next – anecdotal reports that migraine patients were vomiting less + reading our abstracts? Whatever the story, the very efficient Glaxo clinical development and marketing team then took over, accelerated the development of ondansetron and dropped the previous CNS indications (the subsequent PharMA award recognized the discovery of a new drug, which had then been successfully marketed; perhaps we in Beechams could claim more on the discovery side and Glaxo on the development side? It will now always be a moot point). Ondansetron and granisetron then competed, but when SmithKline Beecham and GlaxoWellcome merged to form GSK, ondansetron was retained and granisetron sold off, to mitigate competition laws. A great story! With hindsight, perhaps we shouldn't have alerted the world with our abstracts, so we could have kept the credit for the discovery. However, for cancer patients, maybe it's a good thing that we did!

In addition, however, it is important to note that we in Beecham Pharmaceuticals (soon to be SmithKlineBeecham and then GSK) took a use patent out on the Glaxo compound (ondansetron) after reading their own patent, which did not mention the control of nausea and vomiting. As a result, Glaxo had to pay royalties for many years!' Email to Ms Caroline Overy, 16 July 2013. See also Appendix 1. For further discussion on the development of ondansetron at Glaxo and granisetron at Beechams, see the Witness Seminar on platinum salts as chemotherapy agents for cancer (Christie and Tansey (eds) (2007)), especially pages 51-4.

into a number of clinical studies. Unfortunately, the mindset within the industry and management was that some of these models didn't travel or translate from the Bradford/Glaxo groups' initial findings. That was not the case at Beecham, we actually repeated a lot of the work both *in vitro* and *in vivo.* However, what we found, like many drugs in pharmacology with agonists and antagonists that produce 'bell-shaped' dose response curves, a fact the clinicians couldn't get their head around, these compounds were very potent. So the question was how to make a tablet when you're talking about sub-microgram levels of compound, although clinicians were well aware of the action of, for example, LSD in humans at low concentrations equal to those determined for 5-HT_3 antagonists. This was perceived as a challenge for 5-HT_3/CNS compounds in the clinic when they were active at such low concentrations. It was the initial work of Gareth Sanger on BRL 46470, from which we knew that there was something different about this compound, because you didn't see the same GI effects as with other 5-HT_3 receptor antagonists.[191] Despite much effort, sadly we failed to show efficacy in the clinic with this compound. There were, however, some pluses with this compound in funding a number of PhD students with Jerry Lambert in Dundee and Nick Barnes in Birmingham, looking for subtypes of the 5-HT_3 receptor, with some success. It was following Beecham's merger with SmithKlineFrench in 1989, that the emphasis on this particular therapeutic target soon lost its way. But, in support of Mike, we reproduced a lot of his early data.

Mr Wesley Miner: I'd just like to step back a little bit and return to what Tom was saying, to put things in perspective in 1984, particularly at Beecham. The actual driver of the 5-HT_3 / 5-HT_4 programme was Gareth. He was working hard on the whole thing at the time and knew the pharmacology, that is the classic pharmacology, of 5-HT. He knew 5-HT backwards and forwards, and he was the first one to actually make this quantum leap from 5-HT_3 to the anti-emetic activity on that. But, as Tom was saying, we ran into some very stiff opposition from management. On one occasion, we had a project meeting where our second in command of research sat there and told us that Beecham would never go into anti-emetics again, because they had been burnt in that area before.

Gareth and I sat there and we had all this data produced at the time. We knew exactly what was happening, we had the data right down the line. The compounds, 5-HT_3 antagonists, were so effective against anti-cancer therapy-induced emesis that we both just got up there and, even though the chairman was telling us 'No we're not going to do it', we kept on at it. After we came out

[191] See, for example, Bermudez and Sanger (1994).

Figure 15: Mr Wesley Miner.

of the meeting, one of our colleagues, Christine McClelland, turned to us and said: 'I thought you were both going to get fired on the spot' [laughter], because we just would not give up on it; we knew we had something.[192] It was because of Gareth's drive in the 5-HT_3 area and on into the 5-HT_4 area, that Beecham research really was very focused; and that was where a lot of the drive (5-HT_3 and 5-HT_4) came from on the Beecham side of it. However, for a long time Gareth did not get much support, but ultimately things moved forward.[193]

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[192] Mr Wesley Miner wrote: 'While Gareth (Sanger) and I did have to overcome some pretty high hurdles before senior management bought into our 5-HT_3 anti-emetic work, at one point we were summoned by the chairman of research at Beecham, Dr Keith Mansford, for a private viewing of a video that we produced, which showed the very dramatic effects of a 5-HT_3 antagonist completely inhibiting cisplatin-induced vomiting in a ferret almost instantly after I had dosed the animal intravenously with the anti-emetic. Once Keith (Mansford) saw this amazing anti-emetic activity of the 5-HT_3 antagonist, the company position on anti-emetic research became extremely positive.' Email to Ms Caroline Overy, 17 July 2013.

[193] Miner and Sanger (1986). Mr Wesley Miner wrote: 'At about the same time (around 1983 to 1984) that Gareth Sanger and I were doing early work in the 5-HT_3 (labelled "M" at the time) receptor antiemesis area, Gareth was also working extensively with "*in vitro*" preparations while he elucidated the multiple activities of the drug metoclopramide. It was at this time that he actually identified a "metoclopramide antagonist"; now known to be a 5-HT_4 antagonist. No one at Beecham was exactly sure where this discovery might lead, but along with Gareth, the Head of the Beecham, Harlow, research site, Dr Bob Poyser, was absolutely insistent that this discovery should be followed up and investigated further.' Note on draft transcript, 17 December 2012.

Wallis: The 5-HT_3 effects observed in the intact animal date back to the work of Paintal that I mentioned earlier which was in 1954;[194] he was actually recording responses from nerve cells responding through, what we now know to be, 5-HT_3 receptors. Rod, you just asked who proved it all, who established it was a ligand-gated-ion channel, and I'm not exactly sure who I would credit, but I would suggest it was probably Higashi and Nishi who did intracellular recordings from nodose ganglion cells.[195] A lot of the work on 5-HT_3 receptors is in the periphery because it produces fairly profound and easily recordable large-scale depolarizations – to that extent its effect is dramatic. It was questioned earlier why progress in the CNS physiology and pharmacology of 5-HT apparently went through a period of hiatus. I think it's partly because, when you look for the electrophysiological signal for 5-HT_1 and 5-HT_2 receptors, it is actually difficult to discern, difficult to measure and it tended to be ignored by mainstream physiologists, who wanted to concentrate on the main signalling molecules causing excitation and inhibition, like glutamate, GABA (gamma-aminobutyric acid) and glycine.

To come back to 5-HT_3, we did a lot of work in the 1970s in establishing a technique for recording sizable depolarizations extracellularly and being able to produce dose response curves. The method used was based on one developed by Hans Kosterlitz, Gordon Lees and myself in Aberdeen called the sucrose gap technique.[196] This is essentially a method of extracellular recording, where you diminish the shunt between two recording points on a tissue by using a high resistance solution, such as one that contains sucrose and deionized water. This was work that led to collaboration with Merrell Dow and John Fozard to investigate MDL 72,222; and with Sandoz and some of their 5-HT_3 antagonists.[197] So extracellular methods of recording, like the sucrose gap technique, were important staging posts in investigating the pharmacology of 5-HT_3 receptors. It didn't prove that they were not acting via a second messenger but I think the Higashi and Nishi paper demonstrated the receptor was behaving exactly like a ligand-gated channel.[198]

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[194] See pages 10–11. Paintal (1954, 1955); see also Wallis and Elliott (1991).

[195] Higashi and Nishi (1982); see also Wallis and North (1978).

[196] See, for example, Kosterlitz, Lees and Wallis (1968).

[197] See page 56.

[198] See note 195.

Figure 16: Professor Paul Andrews.

Professor Paul Andrews: I want to come back to a point about the site of action, the 5-HT_3 receptor antagonists in emesis. I have to disagree slightly with Mike, as we've often disagreed; it's embarrassing because he funded quite a bit of my work over the years, for which I'm very grateful. Yes, there are a lot of binding sites within the brain stem, but in the acute phase of cisplatin-induced emesis in the ferret model, the primary action is in the periphery on the activation of the abdominal vagal afferents. This actually was a very important point to demonstrate, because it clearly showed that the peripheral axons of the vagus conveying information from the gut to the brain could be a valid drug target.[199] Of course, if one now thinks of anti-obesity drugs or perhaps drugs for reflux, peripheral terminals, not the central terminals, are seen to be one of the potential targets. So, it was a very important point but clearly at the time, a lot of people thought that because it was an anti-emetic, the site of action must be in the brain stem, but actually I think it caused the paradigm shift in the way that people thought about targeting anti-emetic drugs and that's still true.

Flower: I'd like to move on to my next topic: how did molecular biology impact on the area? Danny, I wanted to ask you whether you felt overwhelmed when molecular biologists started to clone receptor proteins or receptor-like genes?

[199] Andrews, Rapeport and Sanger (1988).

Hoyer: Not at all, because it was all predicted. The first 5-HT receptor to be cloned was actually 5-HT_{1A} and it was by accident. Lefkowitz and Kobilka and the people at Merck had cloned the beta 2 receptor and by homology cloning they were looking for the beta 1 receptor.[200] In between, they got something that was called G21 and had no clue what it was. Bob Lefkowitz is not interested in anything that is not a catecholamine: '5-HT? Never heard of it'. Although, shortly afterwards, we supported Annick Fargin, a post doc in the Lefkowitz lab, who was working specifically on 5-HT_{1A} receptor.[201] And my good friend Chema Palacios spent a sabbatical at Duke with Bob and Marc (Caron). The interesting thing was that they noticed that the G21 receptor was not beta 1 or beta 2 because the pharmacology did not fit any catecholamine receptor. But they didn't look at anything else, except that pindolol was still binding. If we go back, pindolol is an indole and we had described that pindolol and a lot of beta blockers were actually decent 5-HT_1 receptor ligands.[202] When the paper was coming out and they had no clue what it was, we said: 'Well, that's probably a 5-HT_1 receptor.' The point I want to make is that pharmacology, namely the fingerprinting we were doing at that time, predicted much of what was going to happen in molecular biology.[203] So, for instance, at some point we shifted the appellation from 5-HT_{1C} to 5-HT_{2C} because the pharmacology was more 5-HT_2-like. One of the predictions from this was that the 5-HT_{2A} and the 5-HT_{2C} receptor must be very similar. This is precisely what happened: around 1990 we had a meeting in Lucerne and I walked back with Peter Seeburg to the train station, 5-HT_{2C} was halfway cloned and I said: 'My bet is that 5-HT_{2A} is going to be very, very similar.' He asked why I said this. I said: 'Well, this is what pharmacology tells us.' Seeburg went back to the lab, pulled stuff out of the fridge, he had it already but he didn't recognize it, and indeed got 5-HT_{2A}, which was published within just a few months.[204] I understand what Charles is saying about the negative impact that molecular biology had at the time on some of the more functional researchers, because the funding authorities wanted to have molecular biology and if you were not doing this you were not sexy enough. It's like these days, you have to use optogenetics and such

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[200] Dixon *et al.* (1986). Robert Lefkowitz and Brian Kobilka were jointly awarded the Nobel Prize in Chemistry in 2012 'for studies of G-protein-coupled receptors'.

[201] Fargin *et al.* (1988).

[202] Hoyer, Engel and Kalkman (1985 a and b); Engel *et al.* (1986).

[203] See page 46 and note 146.

[204] See, for example, Pritchett *et al.* (1988); Schofield, Shivers and Seeburg (1990).

things; it comes and goes in waves. But, if you read the 1994 paper, the good thing is that many of the things we had put together at the time were later confirmed precisely by molecular biology.[205] This was at the time when, in industry in particular, lots of senior management had just joined. They didn't know much about chemistry and had no clue what functional pharmacology was all about, but molecular biology was there, so you had to have a molecular biology twist. It went on much further, because now you have to show that there's a link between your target and the disease and the link must be genetic, which is a big joke. There are not many diseases where you can establish a clear link, certainly not many monogenetic diseases. There are indeed genetic disease links, as there are epigenetic links, with lots of diseases, but it's not simple. So this was a hindrance. But the good thing was that, whenever we were working on the target, which was poorly defined according to the new wave of senior executives, if you could show that this target was indeed cloned and the result of a gene product that you could then put in a cell system and do high throughput screening (HTS). This was extremely important to get the project off the ground and approved. I'm still waiting for compounds actually coming from HTS to go into the clinic, in most cases medicinal chemistry is still doing the job. [Laughter] It was important to make the point, that what we were talking about was real. You could point a finger at a gene. For instance, when we had this long debate about 5-HT_{1B} and 5-HT_{1D}, the whole situation became messy for about six months because two receptors, 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$, were cloned pretty much at the same time.[206] As we had predicted from the animal work, there is the species difference between rodents and other species, between what was called 1B and 1D; this was perfectly verified using molecular biology. That was making the point again, helping people to work on 'real' targets/gene products. Molecular biology messed up the whole system again, then we found out that the 5-HT_{2C} receptor was undergoing editing and so potentially there are about 25 different forms (more or less edited) that differ between species. Depending on the form, which is edited or non-edited, you will have more or less constitutive activity; this means that the compound you are working on (acting on the same 5-HT_{2C} receptor) may be acting as an agonist, as an inverse agonist, or neutral antagonist at times, depending on the edited form. This becomes important since, in the clinical situation, these edited forms are changing with disease state. The worst of all cases is actually the 5-HT_4 receptor,

[205] Hoyer *et al.* (1994).

[206] See, for example, Harwood *et al.* (1995).

which has so many splice variants that we (still) have no clue what's going on. There's the difference between species in splicing and there are also differences in the splice variants when you move along the gastrointestinal tract, from the oesophagus to the colon, for example. I'm not sure that we know that this explains the differences that we see, but it's one possibility. We don't yet have compounds that are working specifically on different splice variants. Maybe they will come, maybe they will never come, I don't know. But clearly it helped us to make sure that what we had said was real and so it's the final proof. When we said 16, or 15 or 14 5-HT receptors, people were jumping up and down saying it wasn't possible. Well, molecular biology nailed it.

Coming back to what we said before about the influence of industry. At some point Janssen Pharmaceuticals were only working on the 5-HT_2 receptor and everything else was not relevant. Dr Pierre Laduron, who was very influential at the time, would tell us the 5-HT_3 receptor was of no importance because no-one cared about the electrophysiology of these receptors. A fast ligand-gated channel was of no relevance. Everyone knew that glutamate, glycine or GABA for that matter, were unimportant! It was the same thing for 5-HT. I'm sorry, they seem to be important targets in the clinic. For 5-HT_1 it was the same. 5-HT_1 just did not exist. It was only at a meeting we had in Houston in 1991 that Dr Paul Janssen stood up and told us the wonderful stories about the cloning of these receptors. The point I wanted to make is about Fillion, who was working at the Institut Pasteur, specifically on 5-HT_{1B} and 5-HT_{1D} receptors, was undergoing some scrutiny by his research management, as is normal. Pasteur called in external reviewers, I will not name names, but some of these people claimed to be experts. They came round and said that this 5-HT_1 receptor did not exist. The net result was that, based on these experts, his INSERM lab was closed.[207] Pasteur was more liberal, they kept it going and then two people, Rene Hen and myself, got called upon. Rene, who is really a cloner, came in to tell them that actually these receptors existed and for all we know, from Pat's work and everyone else, 5-HT_1, what we called 1B and 1D receptors, were clinically of high importance. But the people at Pasteur and INSERM hadn't a clue about this, because some of the self-proclaimed leaders in the field were ignoring everything. Just another point: I happen to be French; no one is perfect. [**Sanger**: 'True']. [Laughter] Only once in my life did I go to any French meeting and it was in 1986 when I presented 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1C} receptors. Laduron stated: 'There's only one receptor; this

[207] See also comments on page 31.

Figure 17: Professor Paul Andrews and Dr Mike Tyers.

is the 5-HT_2 receptor, just like the D2 receptor.' I can remember all these old professors, excuse me to the professors, standing up, applauding saying: 'This is real; we don't need these complexities.' So this is why the molecular biology is important, because if anything it confirmed these complexities. Of course, it added more complexities, but we can deal with that. We've been around for some time; it's part of the job.

Flower: Mike, did you want to respond to Paul's earlier remark?

Tyers: I always respond to Paul, my friend. [Laughter] I think that the site of action of 5-HT_3 anti-emetics is not critical, clearly it still works by blocking 5-HT_3 receptors, which are all over the body on nerves where emesis can arise. Wherever it blocks them it is effective. The vomiting caused by cisplatin and other cancer chemotherapeutic drugs is probably caused by release of 5-HT from enterochromafin cells in the gut wall, which activates 5-HT_3 receptors located locally on the vagus nerve, which projects to the chemoreceptor trigger zone that we showed to have the densest population of 5-HT_3 receptors in the brain – the emetic centre.[208]

Nausea and emesis from any cause, even including pregnancy, are mediated via that centre. So perhaps because the vagus nerve arises as the Xth cranial nerve in

[208] See Ireland and Tyers (1987).

the area postrema this is probably the source of 5-HT_3 receptors, which migrate down the vagus nerve into its vast field of innervations in the gut.[209]

Blackburn: To follow on from what Danny and Charles were saying earlier about disabling and enabling technologies: molecular biology is extremely important. However, in the 1990s, Dr Peter Goodfellow[210] joined SmithKline Beecham and I think he/we were all seduced by Bill Haseltine and others who had started Human Genome Sciences (HGS),[211] and to quote Haseltine: 'Genomics will change drug discovery overnight and we'll all have new medicines by tomorrow.' Well, not quite in those words. [Laughter]

Flower: Almost.

Blackburn: SmithKline Beecham were very much leaders in genomics research in the 1990s and were de-orphanizing G protein-coupled receptors (GPCR) hand-over-fist, trying to keep up with HGS and the Human Genome Project.[212] However, to my knowledge, only one compound has come out of that particular genomic collaboration with HGS and they have only one in-licensed compound in their development portfolio to date![213] As a disabling/enabling technology, molecular biology resulted in scientists shooting off one orphan receptor after another, which basically caused a major distraction of focus in various therapeutic areas, one of which was the 5-HT area. My lasting memory of Peter was when I left for America in 1999. It was my last winter BPS meeting as President and I was sitting on the dinner table platform, next

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[209] See note 181.

[210] Professor Peter Goodfellow (b. 1951) was Balfour Professor of Genetics at Cambridge University from 1992 to 1996. He was Senior Vice President at SmithKline Beecham (1996–2001) and Senior Vice President, Discovery Research, at GlaxoSmithKline from 2001 until his retirement in 2006.

[211] William Haseltine (b. 1944), was Professor at Harvard Medical School from 1976 to 1993 and Chief of Human Retrovirology at the Dana Farber Cancer Institute (1988–1993); he founded the biopharmaceutical organization Human Genome Sciences (HGS) in 1992, of which he was chairman and CEO from 1993 until his retirement in 2004. HGS was acquired by GlaxoSmithKline in 2012.

[212] For an introduction to the Human Genome Project, see Fletcher and Porter (1997) and the main Human Genome Project information website at www.ornl.gov/sci/techresources/Human_Genome/home.shtml (visited 16 April 2013).

[213] Dr Tom Blackburn wrote: 'Benlysta (belimumab) is the company's lead drug, and it is an antibody created for the treatment of lupus (systemic lupus erythematosus), and when it was approved in 2011, it became the first new lupus treatment approved by the FDA in 50 years. Human Genome Sciences also sells raxibacumab, an inhalation anthrax treatment, to the American government for use in the Strategic National Stockpile.' Email to Ms Caroline Overy, 7 June 2013.

to Jimmy Black and John Fozard, who was sitting next to my wife Jacqui. Peter Goodfellow was presenting a prize to the late Dr Rob Kerwin for his excellent clinical pharmacology studies.[214]

This was one of the most embarrassing times of my BPS career, as I had to introduce Dr Goodfellow to present the clinical prize. Before presenting the prize, he went on to ask why the BPS wasn't embracing molecular biology. To cut a long story short, a young PhD student came up to me after the dinner and said: 'Dr Blackburn, was Dr Goodfellow trying to influence us with regard to the importance of molecular biology? because he failed miserably.' [Laughter] All he had to do was to look at the BPS abstract book where 70 per cent of the abstracts in that book were all related to molecular biology, in some form or other. So, yes, molecular biology has been, and is, extremely important, not only in 5-HT research. But in certain places at certain times with certain people, it can be very disabling. [215]

Flower: I think we can all agree with that!

Humphrey: I want to stick with 5-HT_3, as we seem to have gone on to molecular biology.

Green: I'd like to link the molecular and Tom back to Charles because in the 1970s, Grahame-Smith came up to me and said that there had been a paper in the *BMJ* saying that propranolol was good in schizophrenia.[216] It turned out to be wrong, but he said: 'Well, wouldn't it be interesting to try it in our 5-HT model?' We gave propranolol and it blocked the behavioural syndrome and we published it in *Nature*.[217] Then I was invited up to ICI, as they were at that time, and they said: 'Oh, well, we knew it is a 5-HT blocker, but we've never published it because the company might want to do something with producing

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[214] Dr Robert Kerwin (1955–2007) was a psychiatrist and neuropharmacologist who pioneered treatments for schizophrenia.

[215] Dr Tom Blackburn wrote: 'Without doubt the "Genomics Revolution" and the fast pace of molecular biology in the 1990s was transformational and had both positive and negative effects on 5-HT research at SmithKline Beecham and the industry in general. The focus then was on deorphanizing novel (GPCR) receptors and trying to relate these genes to a pathophysiology at the demise of several 5-HT neuroscience projects, where we knew much more about the physiology and pharmacology.' Email to Ms Caroline Overy, 7 June 2013.

[216] Yorkston *et al.* (1974).

[217] Green and Grahame-Smith (1976).

Figure 18: Professor David Clarke and Professor Alberto Kaumann.

derivatives. So, yes, they might be interested now that you've actually published this.' But we then went on to show that pretty well all the non-selective beta adrenergic blockers were actually 5-HT antagonists.[218] This then went on, and so was all functional, and went on, of course, to pindolol being used. You [Hoyer] mentioned it being used in molecular biology[219] and, of course, for a while, it was also tried clinically to block the 5-HT_{1A} pre-synaptic receptor to increase 5-HT function. So, in fact, the molecular biology and the function can work well together, but without function you're not anywhere, and that just happened to be one area where the function appeared well before the molecular biology. It's never worked clinically, has it? But we can't have it all.

Professor Alberto Kaumann: I'd like to tell you how the work with vagal 5-HT_3 receptors in the heart inspired me to discover the 5-HT_4 receptor of human heart. Basically, in the 1980s, we did some experiments on cat heart and we were interested in the Bezold-Jarisch reflex elicited by 5-HT. We measured bradycardia and also sympathetic nerve activity at the level of the renal nerves. During the reflex, induced by 5-HT injected into the pericardial sac, we observed not only bradycardia, but also that the renal nerve firing was abolished. Vagotomy prevented the 5-HT-evoked bradycardia and suppression

[218] See Costain and Green (1978).

[219] See page 63.

of renal nerve activity, but now 5-HT produced tachycardia.[220] The reflex was also prevented by Fozard's compound MDL 72,222, which was consistent with mediation through 5-HT_3 receptors. The cardiostimulation observed in vagotomized cats with 5-HT prompted the thought that 5-HT could cause cardiostimulation in human heart, which was indeed detected in the human atrium and later ventricle.[221] At that time I had been working for ten years with the pharmacology and biochemistry of β1- and β2-adrenoreceptors in human atrium and ventricle. We found that 5-HT also increased cyclic AMP (cAMP) and the activity of cAMP-dependent protein kinase in human atrium. My second point is that MDL 72,222 and granisetron did not antagonize the inotropic and biochemical effects of 5-HT in human atrium, ruling out mediation through 5-HT_3 receptors. I also obtained a potent 5-HT_3 receptor antagonist (pKB ~ 9) from Sandoz called ICS 205,930, nowadays tropisetron, which at micromolar concentrations caused competitive antagonism of the cardiostimulant effects of 5-HT with a moderate affinity around 200 nM (i.e. a pKB ~ 6.7) on human atrium. At that, it had become apparent that ICS 205,930 antagonized both intestinal contractions induced by 5-HT through acetylcholine release[222] and the 5-HT-evoked increase in neuronal cAMP through 5-HT_4 receptors.[223] This is how working with 5-HT_3 receptors and 5-HT_3 antagonists triggered the discovery of the human cardiac 5-HT_4 receptor.

Humphrey: I want to come back to 5-HT_3 because I think it's very interesting. I remember talking to John Fozard years ago, in 1980 or so, and he told me his idea about getting a 5-HT_3 antagonist to work in migraine and he was very enthusiastic about it. I think John did some terrific pioneering work to find compounds and get out there,[224] and obviously tropisetron was finally the deluxe 5-HT_3 antagonist that didn't work in migraine. I must admit I didn't believe in it simply because it was a brilliant idea that John had of 5-HT_3 receptors on afferent nerves as well as on motor nerves, you can imagine if 5-HT_3 was released on afferent nerve terminals those receptive terminals could be on cranial nociceptive neurones. But I always felt, 'where's the 5-HT coming from?' What we did do at Glaxo, following on from having a whole cupboard

[220] Mohr *et al.* (1987).

[221] See, for example, Kaumann *et al.* (1990, 1991).

[222] See, for example, Craig and Clarke (1991).

[223] Dumuis *et al.* (1988).

[224] See Fozard and Kalkman (1992, 1994).

full of 5-HT_3 antagonists, was to think about irritable bowel syndrome (IBS) because I've often thought of this as migraine of the gut. You can think there about proprioceptor and nociceptor afferents, and wow, where's all the 5-HT? There's tons of it – 95 per cent of 5-HT is in the gut. You've got all these enterochromaffin cells, you can imagine some kind of damage, inflammation and you could have a very important role for 5-HT_3 receptors. We had actually developed one of Mike's compounds that came out the CNS cupboard, which was alosetron.[225] We already knew that 5-HT_3 antagonists are constipating and that's probably through blocking cholinergic motor nerves, so we thought we should study IBS patients who had a predominant bowel habit of diarrhoea. These were people who were really in a terrible way; they couldn't get to work. There were stories of people in the US buying a second house that was halfway to work so that they could stop off – it's a very debilitating condition and very painful as well. With alosetron, which became Lotronex, we got good efficacy. Not only did it block the diarrhoea, but people said they'd never felt so well. This looked like a very exciting, potentially important drug. Unfortunately very soon into the drug's life on the market, less than a year, I think, there were several patients who had ischemic colitis, a very serious side effect, and the drug was stopped by the FDA, or GSK probably withdrew it before the FDA stopped it. Interestingly though, this drug is very effective and to this day we don't know what causes the ischemic colitis, but we do know that a lot of people said that this drug was so important that now it's been brought back, but it's under very, very tight specialist control.[226] So this is an interesting example of where a drug has worked and is very effective, but we've suddenly come up with a side effect that we think is related to a 5-HT_3 mechanism, as opposed to the drug itself, but nobody knows what the mechanism is. I think somebody should get in the lab and find out, because if you could circumvent that, or understand it, maybe there's another important clinical indication for 5-HT_3 antagonists.

Flower: Gareth's got his hand up, he knows the answer. [Laughter]

Sanger: It's an interesting point, because I teach a little bit of drug discovery, believe it or not, to students now. I can cite the 5-HT_3 receptor antagonist story as saving so much human misery if you get the patient population right, in this case, cancer patients needing anti-emetic treatment. However, if you get the patient population wrong, as in the case of patients suffering from IBS, drugs

[225] Humphrey *et al.* (1999).

[226] For a discussion on the withdrawal and subsequent reintroduction of alosetron, see Lievre (2002). See also note 229.

acting at the same receptor are thought to be associated with deaths. What I really want to draw attention to is that it is this withdrawal of alosetron, perhaps coupled with cisapride's withdrawal, because of its ability to block the HERG channel (potassium ion channel) on the heart, perhaps also coupled with the withdrawal of tegaserod (a 5-HT_4 agonist), because of poor efficacy and some apparent cardiovascular effects,[227] that has combined to make the regulatory authorities and drug companies as a whole, scared of the word 5-HT. Everybody I know who plays in that area cannot get management support, because they are aware that the regulatory authorities will make life so difficult. Last week we saw the Shire close down the former Movetis company (now owned by Shire) with the loss of 60 jobs in Belgium, because prucalopride, the world's first selective 5-HT_4 receptor agonist – demonstrated to have good intrinsic activity using native tissues, not molecular, because that's the only way you can do it – failed to live up to expectations.[228] They can't get it in the US; the regulatory authorities still want trial after trial to demonstrate that there is no cardiac side effect. So there's been a sort of legacy now from those three compounds, in particular, that the industry, and 5-HT as a whole, is still suffering from. We cannot seem to move forward.

Hoyer: I was going to say something similar to what Gareth has already said. The problem was that once the FDA had understood that there was a problem with 5-HT_3 and alosetron, everything else that came after that and should work through a 5-HT mechanism in IBS, was bound for failure, because they just remember 5-HT. So this is the bad thing for 5-HT_3 and 5-HT_4 and I think we should revisit these compounds. In fact alosetron is still on the market, but not with Glaxo.[229] 5-HT_4 seems to be forgotten and yet I think it's an important mechanism. Basically what you need is to identify the right patient and give the right compound. When we started looking at 5-HT_3 in the brain, we did autoradiography, since we had found that ICS 205,930 was working on neuroblastoma/glioma cells. When we did the first autoradiography experiment, we exposed for one month, no result; two months, no result; three months, no results. After five-and-a-half months of exposure we saw the receptor to

[227] For cisapride, see, for example, Mohammad *et al.* (1997) and for notice of its withdrawal, Anon (2000); for a discussion of tegaserod and alosetron, see Fayyaz and Lackner (2008). See also, Sanger (2009).

[228] See comments on page 109.

[229] Prometheus Laboratories in San Diego, CA, acquired Lotronex from GlaxoSmithKline in 2007. Due to the risks of developing ischemic colitis the drug can only be prescribed by those who have enrolled in the Prometheus Prescribing Program. See page 71 and note 226.

be indeed present in the vagus complex and area postrema and another bit of binding in the hippocampus. The interesting thing was that when the first papers were published, we were told that this is almost impossible, because everyone knows that the 5-HT_3 receptor is a peripheral receptor, it has nothing to do with the brain. This is what the dogma told us.[230] But anyway, the good point was that in those days we could play and perform the kind of experiment, which today is almost impossible, at least in the non-academic set up. This is why and how industry is suffering from short-term vision.

Flower: We've been joined by Jackie Hunter and Gerald Curzon and I'm going to ask them in a minute if there's anything they want to say about what we've already discussed. David, did you want to make a remark about what we were talking about earlier?

Clarke: I wanted to go back and say that it's important to recognize the work of Joel Bockaert in the discovery of the 5-HT_4. He did it by measuring adenylate cyclase in colliculi neurones from mouse brain, and we did it quite independently in the gut. Our work was really based on Gareth's years of trying to find out how prokinetic agents worked in the gut. He never quite got there, but it was his pioneering efforts that led me to move into the gut and have a look to see what the receptor really was. Plus, I was always fascinated by some of the 5-HT dose effect curves I used to see coming out of John Fozard's and other people's labs. They were biphasic curves and the first phase of the dose response curve was very small, very variable, but nobody took the slightest bit of notice of it. John started his curves halfway up the dose response curve and so I thought: 'Well what is this receptor?' That question, plus Gareth's work, led to looking at 5-HT receptors in gut and led to finding the 5-HT_4.

Dr Colin Dourish: I have a couple of comments. First of all responding to Gareth's pessimism about the 5-HT area and the attitude of regulators. I shared his pessimism until relatively recently, because one of the most difficult areas to convince regulators is in obesity and for many years a number of companies have struggled because of all the side effects with obesity compounds, the recent example being the withdrawal of the cannabinoid antagonist rimonabant. The gratifying thing was just three months ago the FDA approved the first

[230] See, for example, Bradley (1987). Professor Paul Andrews wrote: 'There was lot of confusion at the time about central 5-HT_3 receptors, at least in the brainstem, and this resulted in a publication in *Trends in Pharmacological Sciences* on a consensus view (Pratt *et al.* (1990)).' Note on draft transcript, 7 January 2013.

compound for many years, lorcaserin, which is a selective 5-HT_{2C} agonist.[231] That finally suggests that the regulators are starting to look at risk–benefit again, which is a big boon to all of us if they start to do that. Clearly what happens to that compound in the market is going to be very important over the next few years, but at least that's one slight glimmer of hope. Coming back to something we were discussing earlier, we talked a lot about the prototype selective 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) and I'd just like to give credit to the Swedish group that developed that compound. It was originally synthesized by Lars Erik Arvidsson at Uppsala in Sweden.[232] That group provided the compound initially to a number of other groups, and it was also synthesized by a number of other labs, like Merrell in Strasbourg, and I believe that's where we got it from. I was working with Gerald Curzon at the time in 1984 and I think we got it from Merrell. What was really interesting about that compound, and we've heard this from a number of people already, is that it helped us to really understand function for the first time with receptor subtypes. We were interested in Gerald's lab in both neurochemistry and behaviour and trying to tie the two together, so we were getting into, like Charles was at the time, *in vivo* microdialysis using HPLC detection. But also we wanted to try to link function with that neurochemical change and when we got hold of the compound we didn't really know what it was going to do, so we gave it to some rats and observed their behaviour. What we knew about 5-HT effects on behaviour from previous studies was that 5-HT generally had an inhibitory effect on feeding, so we were rather shocked to find that these animals seemed to be looking for something to eat.[233] We started giving them some food and all of a sudden what we found was that 8-OH-DPAT, a compound that apparently was a 5-HT_{1A} agonist, was having the opposite effect to any other serotonergic agonist we knew about that generally decreased food intake. That led to an understanding, or towards an understanding, of pre- versus post-synaptic 5-HT_{1A} receptor localization. It turned out that the reason the animals were increasing their eating, rather than decreasing, was that this compound at a low dose was selectively activating the 5-HT_{1A} receptors on the cell bodies of 5-HT neurones in the raphe nuclei and this was later borne out in studies we did using microdialysis and studies by other people, such as Trevor Sharp, who

[231] For a discussion of the FDA's approval of lorcaserin, see Colman *et al.* (2012).

[232] Arvidsson *et al.* (1981).

[233] See, for example, Dourish *et al.* (1986).

Figure 19: Dr Colin Dourish.

unfortunately couldn't be here today. Again, the Swedish group led by Stephan Hjorth showed that 8-OH-DPAT and other 5-HT_{1A} agonists at low selective doses would decrease raphe firing and thereby decrease 5-HT release.[234]

Flower: So, Jackie and Gerald, we had a good session this morning when we tried to collect, amongst other things, some reminiscences of the very early days of 5-HT research and went over this era in a bit of detail. But I'd like to give you two the opportunity to contribute to the discussion. Is there anything you'd like to add?

Dr Jackie Hunter: I think this gathering here is for people far closer to a lot of the early discoveries than I was. In fact the earliest work was carried out when I was working with Cathy Wilson in the Department of Obstetrics and Gynaecology at St George's Hospital and that was on the effects of selective receptor subtype agonists and antagonists on the reproductive system. Perhaps one of the most interesting times was working at, what was then, Glaxo with Mike Tyers, and Pat Humphrey was there, looking at the whole story of 5-HT_3 antagonists in cognition and actually showing that there were, in the pre-clinical species, effects of the 5-HT_3 compounds on memory and learning. That interest in cognition is something that has stayed with me throughout my

[234] Hjorth and Sharp (1991).

Figure 20: Dr Jackie Hunter.

career within the industry and we can come back and talk about some of the later developments afterwards. That's all I wanted to say in terms of the early study.

Professor Gerald Curzon: Who funded my group's 5-HT research? That was one of the main questions of this session. Initially, I was interviewed at Queen Square by Dick Pratt for a research fellowship.[235] He showed me the structure and formula of something I'd never heard of, LSD (lysergic acid diethylamide). That was about 1953. He said: 'How do you think this acts on the brain?' I said: 'Well it looks like something called serotonin that's recently been found in blood serum.' He asked if there was any in the brain. I answered, not as far as I know. In fact Marthe Vogt had just detected it in brain but it had not yet been published.[236]

On another point, the job that I was applying for had already been offered to two people. Both turned it down. Dick Pratt was then a mere senior registrar and those who turned it down decided instead, not unreasonably, to take jobs

[235] Dr Richard Pratt (1917–1983) was senior registrar in the Department of Psychiatry at Queen Square from 1952 to 1954 when he was appointed consultant in psychological medicine to the National Hospitals for Nervous Diseases, London.

[236] Dr Marthe Vogt (1903–2003) was a pharmacologist whose research focused on neurotransmitters. See Cuthbert (2005).

with Fellows of the Royal Society. They both eventually became FRSs themselves and one of them got a Nobel Prize.[237] As for me, I took the fellowship at Queen Square, which later became a lectureship. My lab was mainly supported in those years by the MRC with three research grants followed in succession by three five-year programme grants, all centred on 5-HT. There were also smaller grants from the Migraine Trust and the Brain Research Trust. Looking back, the research of my group was mainly driven by the emerging availability of new laboratory techniques. At first there was something that seems very ancient now, paper chromatography, but it seemed revolutionary in the early 1950s. As Wordsworth said: 'Bliss was it in that dawn to be alive.'[238] Sir Charles Dent, who worked down the road from Queen Square at University College London, encouraged my work. He said: 'With paper chromatography the world will be at your feet.' Well, not entirely. [Laughter] After paper chromatography there was colorimetry, fluorimetry, HPLC and *in vivo* dialysis. We put a lot of effort into *in vivo* voltammetry, which turned out to be a lot more difficult than I first imagined. Something perhaps of historical interest was the small grant given by Pfizers in 1986 for me to prepare a lecture and a poster demonstration on Frederick Gowland Hopkins, discoverer of tryptophan.[239] This was using information from Hopkins' daughter, Jacquetta Hawkes. The posters on this are now in the Science Museum. If I can go back just for a moment to what Colin [Dourish] was talking about: he really had get up and go – doing an experiment with his right hand and writing it up for a journal with his left hand. He worked with Peter Hutson, who was an absolutely superb observer, but wasn't at all keen to write things up. So between them it was really a good combination. The other things I want to talk about are on the question of industry and academia: tensions and collaborations.

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[237] Professor Ivan Roitt and Professor Sir John Vane. The latter was awarded a Nobel Prize (with Sune. Bergström and Bengt I. Samuelsson) 'for their discoveries concerning prostaglandins and related biologically active substances'.

[238] William Wordsworth wrote the line in his poem, 'French Revolution, As it Appeared to Enthusiasts at its Commencement in 1805', first published in *The Friend* in 1809. It is part of his autobiographical poem, *The Prelude*, book XI. 'France (concluded)', line 108.

[239] Frederick Gowland Hopkins (1861–1947), Professor of Biochemistry at the University of Cambridge (1914–1943), isolated tryptophan in 1901. He was awarded the Nobel Prize in Physiology or Medicine (shared with Christiaan Eijkman) in 1929 'for his discovery of the growth-stimulating vitamins'; see Dale (1948). Professor Gerald Curzon wrote: 'Hopkins isolated tryptophan but got the structure wrong, see Curzon (1987).' Email to Professor Tilli Tansey, 16 August 2013.

Figure 21: Professor Gerald Curzon.

Flower: We'll come back to that in a minute if we might, Gerald, because there is something I just want to raise. A couple of other people have touched on this topic, so can we discuss to what extent invertebrate models contributed towards progress in the 5-HT area. There was quite a lot of activity: Charles already mentioned the snail, but there was a lot of work done on C. *elegans,* looking at feeding and appetite suppression and that sort of thing. So I want to ask whether that was something that had an impact or not.

Wallis: Well, two important and long papers from 1974, were by Gerschenfeld and Paupardin-Tritsch,[240] who analyzed synaptic responses in snail neurons and did quite a lot of work in analyzing what might be the receptor, or more than one receptor, involved, but I'm not sure who followed up on that work. I guess now those receptors are recognized as being part of the panoply of G-protein linked receptors. They were important and provocative papers at the time.

Marsden: To reiterate what I said before: there was an advantage of using neurons in species like the snail in the early days because you could very clearly identify large nerve cells that contained 5-HT. That had an impact at that stage. What impact it had in the 1980s and 1990s, which is the time we've been talking

[240] Gerschenfeld and Paupardin-Tritsch (1974 a and b).

about more recently, I don't think it was that important because molecular biology essentially took over at that stage, in terms of the identification of individual receptors.

Sanger: I'd agree. I used to collect all these papers and read them and I honestly don't think they had any value whatsoever in interpreting mammalian physiology. Even now, I'd question the translational value of some of these models that are held up as something that will solve all our problems.

Wallis: A point I should perhaps have added: as far as I can see the invertebrates retained the amines like 5-HT as major transmitters in their signalling pathways throughout evolution, whereas mammals and vertebrates seem to have not so much abandoned them, but used them as modulators. Amino acids became the rapid, direct signalling molecules.

Humphrey: Following on from that, I think molluscan hearts and things like that were incredibly sensitive to 5-HT, so were very good as bioassay preparations.[241] I could never make head or tail of all the work that was done with drugs on invertebrate receptors. I remember Michael Berridge had a very erudite paper in, I think it was the *Journal of Physiology,* on 5-HT receptors in blowfly salivary glands and he used all sorts of drugs and it just didn't equate with anything we knew in terms of mammalian pharmacology.[242] In the end, out of intellectual curiosity, I actually had a PhD student working on the snail receptors and it just did not make much sense. The only thing that seemed to work was the ergots, they seemed to have some potency but it just didn't relate to our mammalian work. I know nothing about the molecular biology, but I suspect they're very different receptors.

Flower: I thought it would be useful to talk about the question of who funded research in the field. Gerald mentioned the importance of discreet funds; did you mention the Brain Research Trust? And what about industry? You mentioned Pfizer?

Curzon: The Brain Research Trust funded research over quite a wide area but I think the only person, as far as I can remember, who was supported by them for 5-HT research was myself. Most of my funding at that time came from the

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[241] See page 13.

[242] Berridge, Lindley and Prince (1975).

MRC. It was then so much easier getting money out of them than now. One sat down, wrote an application in an afternoon and quite often they granted it. Not like it was even 20 years ago.

Green: Unless I'm wrong on this, the Brain Research Trust will only support research conducted at Queen Square.[243]

Flower: Oh, is that right? Okay. So, other academics, where did you get your funding from?

Andrews: From my perspective, with the 5-HT_3 work that we did on emesis, there's no doubt that it was funded mainly by industry. Quite a variety of companies supported it over the years, I think that was true for a number of us. Glaxo and, as it was originally, Beecham and then as it became SmithKline Beecham, probably were the two major funders, but then others came later. That made a very important contribution because, as far as I can recall looking back at the papers that were published in this area, there were almost never acknowledgements to the Wellcome Trust or the MRC for funding. I think I'm only aware of one grant, maybe two that they funded in that whole period that involved emesis in any of this pharmacological work. So it was really industry that drove it.

Sanger: Is it worth commenting on the opinions that fellow academic colleagues had about the receipt of so much industry money?

Andrews: Yes. I think the attitude clearly has changed and now it's seen as quite favourable to have links with industry and be seen to be collaborative and having work that's translational, but it was certainly not viewed quite so well in those days, let's put it that way. Even though, of course, it led to peer review publications and other things. Attitudes have changed.

Flower: The problem these days is there's no industry left to collaborate with. [Laughter]

Andrews: Well, that's the problem and, of course, the other problem is that, in a way, the golden goose has been killed because a lot of people perceive that the problem of emesis is solved because we've got 5-HT_3 and NK1 antagonists.

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[243] The Brain Research Trust is a charity established in 1971 to fund research at the Institute of Neurology, University of London, 'to promote and support research into the causes, treatment, prevention and cure of neurological diseases', see www.brt.org.uk (visited 17 April 2013).

So for people who don't look clearly at the small print it's an area that's shut off and, I think, there's a perception in other areas that is rather similar.

Hunter: When I first started working with Cathy [Wilson], Wyeth funded some research and also gave a lot of compounds that were really important in terms of dissecting out the pharmacology. There was also a charity, I might be wrong, the Neuroscience and Mental Health Foundation that actually went because of Baring's bank; it had all its funds in Baring's bank and they used to fund quite a lot on the charitable side.[244] It's unfortunate that Robert Naylor isn't here because obviously, Costall and Naylor were important in defining certain 5-HT_3 pharmacology and Glaxo funded them to quite an extent. Subsequently over the years, when I was working with SmithKline, we had very good links with Nottingham and some of the work around the 5-HT_6 receptor and defining its role in cognition was done in collaboration.[245] There was a lot of industry funding and also a lot of provision in kind, in terms of tools as well as for imaging. A lot of important work was done in, for example, positron emission tomography (PET) to be able to look at occupancy; you've probably touched on that this morning so I won't harp on it. In terms of advancing our knowledge of 5-HT pharmacology, industry funding played a big role and it would be interesting to actually think what proportion that represented over the years.

Marsden: I was also going to mention the Mental Health Foundation and I think both Richard and I served on their committee as well, at some stage, being recipients of grants from the Foundation.

Green: They were called the Mental Health Research Fund and I had a year of my PhD with Gerald on that. Then they became, I think, the Mental Health Foundation and I was on their research committee for a while with Trevor Robbins. They did fund both pre-clinical and clinical research but the amount of money they had wasn't great, and they switched to supporting only clinical type of work from psychology through to psychiatry; they stopped supporting any pre-clinical work at all.[246]

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[244] In 1972 the Mental Health Research Fund merged with the Mental Health Trust and in 1973 changed its name to the Mental Health Foundation.

[245] See, for example, King *et al.* (2009).

[246] The charity moved away from laboratory research to work directly with people with mental health problems. See Mental Health Foundation (2009); see also note 244.

Marsden: As regards my other sources, as an academic there was the MRC, of course, but also the Wellcome Trust, which had a very significant interest in mental health and had earmarked funds for mental health and as that was the area that I was in, the Trust was another one of our major funders.[247] One of the most helpful sources of funding were the Biotechnology and Biological Sciences Research Council Case Awards in terms of training PhD students. That was a marvellous scheme and I had a lot of links with companies both in the UK and in Europe. It was a very effective means of educating PhD students because they got a feel for both sides of the business, both the academic and the industrial.

Clarke: I must be unique here because I was funded by the NIH. I was at the University of Houston and put in a grant to characterize 5-HT receptors plus some other receptor targets and they were delighted. There was no biochemistry in it; no hint of molecular biology; they said: 'Give him the money.' I got that grant and thought: 'This is so damned easy', so I thought I'd write another one and I more or less got the same response. But at that time I moved from academia into what was Syntex, later Roche, in California, and the NIH were terrific. They allowed me to take my grant with me and I had a lab with two PhD students in it and a post doc and I could run that NIH grant in industry. Of course, they wouldn't renew it after that, but they were very good to me; they weren't big grants but I don't think they got that sort of functional pharmacological approach in other grant applications. The molecular biology aspects of 5-HT came from America, functional pharmacology from Europe and the binding is sort of mixed. Thus my grants were unusual grants and they were the easiest grants I ever got. [Laughter]

Flower: I guess, of course, it wasn't only funding from industry that helped the field along, but also the provision by them of highly selective agonists and antagonists. One question I have for you all is whether there were any really important pharmacological tools that came from industrial labs that enabled you to do all these sophisticated studies with receptor subtypes that were so crucial in the development of the area?

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[247] Professor David Wallis wrote: 'I should like to record my thanks to the Wellcome Trust, who funded my research into 5-HT_3 receptors on peripheral neurons and subsequently on 5-HT receptors present on spinal motoneurones and reflex spinal cord pathways in the years 1983, 1985–6, 1988, 1990, 1991, 1992 and 1993. The Welsh Scheme for Development of Health and Social Research also provided support. Brian Richardson and Gunther Engel from Sandoz sponsored work at my laboratory in Cardiff (1985–86) on the blockade by ICS 205,930 of the depolarizing actions through 5-HT_3 receptor on sympathetic and vagal afferent neurons; and Beechams funded research in my laboratory to quantify the antagonism of BRL 43694 at 5-HT_3 receptors in rabbit vagal afferent neurons (1987–88).' Note on draft transcript, 14 December 2012.

Dourish: We've already talked in the 5-HT_{1A} field about 8-OH-DPAT. The other important compound in the 5-HT_{1A} field was the Wyeth compound, WAY 100,635, which not only was used in binding studies pre-clinically, but also was used in a lot of pharmacology and *in vivo* behavioural studies. Crucially, it was also then developed as a PET radio ligand and was used in studies at Hammersmith and other centres to visualize and map the 5-HT_{1A} receptors in the human brain for the first time.[248] I think Phil [Cowen], you and Paul Grasby were then involved in some of the subsequent studies with WAY 100,635 looking at 5-HT_{1A} receptors in depression.[249]

Andrews: Just a comment: my perception was that it was much easier to get compounds in those days. The amount of bureaucracy to get a compound to try something in your model to see if it worked was a lot simpler. The speed with which compounds circulated was probably a lot faster then than it would be now if a similar situation arose.

Tyers: Supplying compounds wasn't only between industry and academia, it was also between industry and industry, because most of us had exciting compounds to work on that were in the public domain.[250]

Blackburn: I think the relationship between industry and academia has always been very strong. There seems to be this notion that perhaps things weren't right in the early days or perhaps are not much better now, but certainly as far as the companies I've worked for, they've always been strong, culminating in excellent PhD students from Nottingham, Birmingham, Dundee and other universities.

Dr Guy Kennett came out of Gerald's laboratory, and in my lab at Beecham and SmithKline Beecham he helped to develop several 5-HT_{2C} selective compounds.[251] Dr Gordon Baxter in my lab was another classical pharmacologist trained by the likes of Dave Clarke. Gordon developed a number of 5-HT_{2B}

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[248] Fletcher *et al.* (1995); Pike *et al.* (1995).

[249] See for example, Sargent *et al.* (2000).

[250] Dr Mike Tyers added: 'Our Intellectual Property Department always made us get a Confidential Disclosure Agreement signed, which we always thought was a little excessive amongst such nice people! But, 20 years later, the importance of this became apparent in the law courts of the USA! It is also surprising that any of us were able to publish anything. Where would we be if we had published nothing?' Note on draft transcript, 20 December 2012.

[251] See, for example, Kennett *et al.* (1994).

selective compounds, so there were some very good selective 5-HT compounds and pharmacological tools that were developed at SmithKline Beecham at that time.[252]

Sanger: A small point about the generosity of people working in this area, which you've touched on before, but the first 5-HT_3 receptor antagonist I had was from John Fozard. I was in industry, he was in industry; he sent me a sample so we could actually explore our ideas in the laboratory before we'd made our own. So there was industry-to-industry contact. You've talked a lot so far about academics finding funding; industry people have to find funding too. They have to get acceptance from whatever the organization is, in order to get the ideas progressed; some found it difficult; we found it difficult, I think, to get things going.[253] I don't know about the then Glaxo group, Pat and Mike, but I have always been impressed by the fact that it seemed to me that you'd taken all the receptors and you were just going to go for them all and figure out what they did later. And, if that was correct, I think that was a wonderfully brave thing to have done.

Marsden: I was just going to give an example of an academic/industry collaboration, which I think worked very well and that was in more recent years with the 5-HT_6 receptor. We had a long-term link with Hofmann and so got very immediate approach to the new compounds they developed. This collaboration was a sort of wheels within wheels situation because the person responsible for the link on the industrial side was an ex-PhD CASE award student of mine, Andrew Sleight, and I think that's the way a lot of these links worked.

Humphrey: Yes, it may seem like that from the outside [laughter] but I don't think it was 'tons of money, do what you like.' David Jack was very determined that we should be very applied and I think we got things right, therefore we were successful and therefore the money came in. It's as simple as that. I was waiting for an opportunity to give you a bit of an anecdote, and I think it fits in here. David Jack said: 'You know, we should be like chess analysts, watching all the world's chess games and we're looking for a game that's in the end game, we think we can take on and win.' I said to David: 'Well, that's great, but if you want good chess analysts you've got to let them play chess.' He went pale at that point [laughter] because he didn't like people messing around on the side.

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[252] See, for example, Forbes *et al.* (1995).

[253] See also comments by Mr Wesley Miner on pages 59–60.

In general we were allowed to do about ten per cent basic research at least, and we probably did a lot more, because it was always focused on trying to make sure that our project delivered somehow. It wasn't a question of having tons of money; it was a question about focusing the money we had in the right places.

Hoyer: Across the board it's the same thing that industry was doing in those days, looking for new targets, meaning indications. If you were to have indications first and you knew what the target was, it was simple, but sometimes the target was ill defined, then you had to make sure that you defined the target. That's precisely what happened for 5-HT_3, 5-HT_{1A} or 5-$HT_{1B/D}$ and 5-HT_{2C} eventually. The bottom line was that you can play with these targets but make sure that you get a compound, a tool, first, followed by a development candidate. The best way to finish a programme early is to get a compound that doesn't work in any kind of a clinical setting, because suddenly the trust in the whole approach is gone. Unfortunately it takes about ten to twelve years to go into the clinic and eventually into market, or at least that's what it used to be. More recently you would do early proof of concept and if for whatever reason your compound doesn't have the right pharmacokinetics (PK), you are in trouble. PK is very difficult to predict, as you know, from mouse to man you can do allometric scaling, but that doesn't add much, because of species variation etc. From the outside it looked like we could play, and indeed we did play in the very early days, there was much more freedom in those days than is currently available. Another good thing was that, and again this is where the BPS is very important, on the continent we had students from England. They were from Manchester, Cambridge and other places and would come for a year and do these placement studies before their Masters and PhD. They didn't cost much, they were pretty bright because they were coming out of the right universities, they would speak English and write it occasionally, which is important because you have to write, and they would go back and then attract the next generation that we met at the BPS meeting. We kept doing this on a regular basis. Of course, having lots of Brits on the Continent helped to have students from the UK. So again, it's an indirect but major contribution of the BPS – we went to the BPS meetings, met these people in the meeting itself or at the bar, which was at least as important, and then you have already selected the next brilliant student to come over. Quite often these students came back to England to finish their year and then realized that the Continent wasn't bad at all, so they would come to Switzerland, and finish their PhD. This has happened repeatedly. And so it was feed forward and that was great. This has changed, PhD students are now less considered than post docs, probably a big mistake.

With respect to compounds, yes, some were made available to select groups and not to others and so you had to figure out how to get the compound. Fortunately in those days we had chemists who were prepared to synthesize compounds as tools and not just as a final end product that you would make a patent and then enter the clinic with. We would quite often replicate chemistry made at Glaxo or ICI or SmithKline, etc. Occasionally we would get the compound from the real source and I know that John Fozard had been distributing MDL 72,222 and others; we used to give ICS 205,930 to many investigators, but eventually it stopped. I had been distributing 5- carboxamidotryptamine (5-CT), which was a Glaxo compound and I think that legally this was just about at the limit of what we could do. I remember a Brighton Christmas BPS meeting where Pramod [Saxena] was presenting some data with the 5-HT_{1B} triptan from Merck at the time and, of course, it was not Merck who supplied the compound. We know who it was but it was never revealed. Eventually, we had to save Pramod from being kicked off the stage because Merck didn't want an abstract to be published as long as he wouldn't reveal the source of the compound. Pat played a major role in saying that Pramod actually could be trusted [laughter] and the abstract was accepted. [254] We all agree that the industry has played a major role in providing the tools and this is what we should have done anyway because this is how we made progress. Occasionally, industrial groups were biasing the research, probably to an extent that I think is at the limit of ethics. I will stop here [laughter] but I would think that one should go back to the basics and make sure that even if the money is being provided by whoever it is, that these people have no influence on what you publish or what you don't publish, because quite often the important thing is what you don't publish. Just to remind you about the ketanserin antihypertensive story. Hans Kalkman's thesis was showing that ketanserin was not working via 5-HT_2, because although it's a good 5-HT_2 antagonist, it is also an alpha 1 adrenergic antagonist.[255] This was largely neglected by people for the next eight years until Janssen realized that actually most of the 5-HT_2 agonists they were developing had no cardiovascular effects in the first place. A surprise!

Curzon: The economics of clinical trials has changed tremendously over the years. I remember Merton once remarking about some compound of which there was a lot lying around that looked as if it might be a monoamine oxidase inhibitor. It was given to one or two patients without any kind of ethical trial

[254] VanDenBrink *et al.* (1997).

[255] See Kalkman, Timmermans and Van Zwieten (1982).

and it worked.[256] That was how the monoamine oxidase inhibitor field started. There was another crucial stage, I don't know whether there's been a proper study done on it, that was the influence of the thalidomide disaster.[257] After that happened, it became much more laborious and expensive to do clinical trials of any kind.

Hunter: I wanted to come back to industry funding, which you may have discussed this morning, the role of the commercial organization in defining how you position a programme of research and what you can and can't do. I think sometimes that really constrains what you do. So, for example, Carol Routledge was leading the programme on 5-HT_6 compounds at SmithKline Beecham. A compound was being developed as an antipsychotic agent, that indication was very much on commercial grounds, the first molecule was SB 271046.[258] Luckily, because of Kevin Fone's work, it shifted to Alzheimer's.[259] There are other potential indications that are less well characterized and, because of the costs of clinical trials, could not be pursued even though they might be more likely to succeed or to work in subsets of patients and populations. That has the potential to hinder research within industry and that's why it's so important to try to get compounds out and people using them outside of industry, either in clinical or pre-clinical settings. But you're right, there are a lot of barriers now to sharing compounds and there are barriers to doing the clinical studies, with both the sponsorship and ethical issues, that have to be overcome. So in some ways we are a lot less free, even when we've got very selective and potent compounds, to be able to pursue them in perhaps what might be the most logical indications. I think it is good when people make compounds independently and go off as they did with SB 271046 because that validates your view. If you can get more laboratories independently to confirm what you see, then you feel much more comfortable about moving forward.

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[256] For monoamine oxidase inhibitors, see, for example, Pare (1985).

[257] Thalidomide was introduced in 1958 in the UK as a sedative and anti-emetic in pregnancy. It was withdrawn in 1961 following widespread malformations in children of mothers who had taken the drug. This tragedy accelerated the establishment in 1963 of the Committee on the Safety of Drugs, chaired by Sir Derrick Dunlop, which resulted in the Medicines Act of 1968. See the Witness Seminar on the Committee of the Safety of Drugs, Tansey *et al.* (eds) (1997), *passim*.

[258] Routledge *et al.* (2000).

[259] Professor Kevin Fone has been Professor of Neuroscience in the School of Biomedical Sciences, University of Nottingham, since 2006. See his review of 5-HT_6 receptors (Fone (2008)).

Bakhle: All this discussion has created in my brain the impression that certainly the whole area has moved forward because of, and due to, industrial pharmaceutical companies' research rather than the academic research. Most of the academics perhaps felt a little bit *vox clamantis in deserto,* left on the fringes of everything. It wasn't until the companies became interested in and started to make compounds and drive research and give out grants, that the field really moved forward. Now is this a usual pattern? Are there other areas of pharmacology in which this has happened? As an academic all my time, I've always had this romantic notion that the real advances, the new discoveries that you didn't quite know what to do with, all came out of academic labs, and what happened was that the companies saw a new idea and said that they could do something with it, and did it. Whereas it seems to be quite different in this particular case. If you look in this area of pharmacological research again, is it the companies who actually are leading, and are driving the field or is it in fact my romantic idea which is correct? I just wondered about that because it's a general fundamental question and I'd be very interested to hear from people how they feel on that general topic.[260]

The other practical question that I have is: in the early days, say for instance when Pat (Humphrey) started trying to convince David Jack, and everybody in their own industrial company tried to persuade their directors to take up 5-HT, the forgotten compound as it was, what point of 5-HT action did they use in order to convince them? Was it always a CNS aspect for which there was, I don't know, good or bad evidence? Or was it a peripheral aspect? What was the initial driver to convince the companies to get into this area?

Flower: Two tough questions.

Miner: I think actually the way I look at it, in the past, particularly coming from the 5-HT_3 side of it, the industry/academia interaction has always been a real two-way street. I know in the first instance that we in industry got the selective 5-HT_3 antagonists, but without Paul (Andrews) pushing us on a little bit and doing some really interesting work on the physiology side of it, which was purely academic, I don't think the story would have come out quite as nicely as it really did in the end. So I feel that there is not just one side to this story, it really is a partnership between academia and industry.

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[260] For recollections on the relationship between academia and pharmaceutical companies, see the Witness Seminar on clinical pharmacology (Reynolds and Tansey (eds) (2008b)).

Blackburn: In my experience data trumps everything, whether that data comes internally or externally. I spent my research life in Pharma doing a lot of work externally because it was sometimes difficult to get a slot for a particular experiment within the Pharma matrix management system. So you went outside and you knew where to focus your research. Like Pat said, you know the areas you want to go, you work with the academic departments, you build up a trust within the academic department where both groups work well together, whether it's on 5-HT_6, 5-HT_{2C} receptors, whatever. That is the way it happens, you bring back the carrot into the organization to get the funding for you to move on. As in academia, I was growing projects each day, month, year, basically trying to move each project forward internally. In my time, before I left SmithKline Beecham, we had several projects running at the same time to deliver two development compounds into the clinic per year, which was a major task. So you were looking at all ways and means to try to fund and manage that research, whether it be from your own project internally or externally.

Curzon: On the question of industry and academic funding, when I used to have visitors from the old Soviet Union in my lab, I'd say to them: 'The best thing that I can do for you is let you look along the shelves and if there are any compounds of interest to you there, take a little of them.' The fine chemicals industry was much, much more advanced in the West than in the East – an advantage of capitalism with the competition between drug companies leading to all these nice, new compounds. On the other hand, they put a tremendous amount of effort into persuading themselves – and the rest of us – that their compound is a lot better than anybody else's compound. When it comes down to it, it can be very, very difficult to demonstrate whether any particular monoamine oxidase inhibitor is better than any other monoamine oxidase inhibitor. It often comes down to the question of side effects and compliance. The MAOI antidepressants first came onto the market 50 years ago or more, but is there any great difference between the newer drugs and the older drugs in their effects on depression?

Tyers: I want to come back to a comment about research of subtypes, whether it's the research that comes first or the application. At Glaxo, we were very much of the mind that we needed to look for a receptor antagonist first and then find a disease for it afterwards. We knew that 5-HT_3 receptors were present in the brain and so there must be a clinical target there somewhere. That's why we collaborated with Brenda Costall and Robert Naylor at Bradford University because they had a lot of animal models that predicted activity in the brain,

and several other neuroscientists around the world were working on models of diseases of the brain. So we sent them all a number of highly selective 5-HT_3 antagonists and said: 'Go and test these compounds in your CNS models and see what emerges.'

Flower: That makes sense.

Green: Having been on both sides, I found industry was very generous when I was with the MRC Clinical Pharmacology Unit, including the fact that we managed to publish on one of the 5-HT_2 antagonists from Janssen before their own internal people published it, which caused a bit of aggression for a while.[261] I think the situation changed because, like Tom, I got involved in doing quite a lot of work for AstraZeneca by trying to get a drug we had got, not a 5-HT drug but I'm sure it's a generality, worked on in specific models in universities. By the very late 1990s, early 2000s, the university had really got serious about making money in every direction. You would ask them to do something fairly straightforward, you know: 'Will you do this and we'll pay you for it?', and then you would get tied up for months because the university's department officers would be saying: 'But if we find anything unexpected, we expect to take the patent; we expect to take 25 per cent of any money you make if you get it onto the market.' Suddenly it was almost on the other foot. It wasn't that academia was grateful for getting these things and would be paid, but the university was trying to actually take intellectual rights and all sorts of things off you at an early stage. On one or two occasions we gave up because we could never actually get agreement: even the things we knew about they were trying to get a hook into you, that if they got a positive result with this they would expect to get royalties from it and things like that. I think academia for a while made it very difficult; it wasn't industry being difficult, it was academia.

Flower: Still is, I'm afraid.

Hoyer: Richard raised the point I wanted to make as well. It has become increasingly difficult to get academics to understand that if we have a compound or product that is made available and they play with it, if it's contract research, what's the point? Getting a patent out is ludicrous: who is going to write the patent and who will accept it? So, it's become more and more difficult. But to answer Mick's point, 25 years ago the people in 5-HT were just nice people. It sounds a bit over the top but that's what it was. I think most of us here are friends and yet we've been in different companies, we've been in competition

[261] Green *et al.* (1983).

and you don't see this very often. Now, of course, things have changed. For one thing, from the 1990s, chemists were less and less prepared to synthesize tools; they prefer compounds that go into the clinic, therefore it's very difficult to get just tool compounds, and then to give them away for free. This attitude has changed. Management doesn't like that concept anyway, because if a compound is going to make it to the clinic, and an academic reports something that could be negative for the compound, then that's bad news. The other thing is that compounds in those days were distributed just out of the synthesis lab; there were no good laboratory controls or good laboratory protocols. They may be 99 per cent pure but not 99.99 per cent, so there could be some impurity that is detrimental. And if you have a toxic finding it has to be reported. In essence, life has not become easier. My final point is that the field has changed with molecular biology; biologics have made their way. No one cares about just another small molecular weight (SMW) compound; they want to have a specific short interfering RNA or an antisense or a transgenic mouse and the like; if you don't have a transgenic, people are not going to buy what you have shown using a SMW drug. This is where attitude and emphasis have changed. But coming back to Mick's point: the 5-HT field is an exception just because these people were nice.

Dr Jeffrey Aronson: I think that 5-HT probably is an exception, but there are formal studies of this question. The classic text on this is a book called *The Sources of Invention,* which is now something like 50 years old, by Jewkes and others.[262] There have been other studies since then and covering a wide range of technologies, not just drugs. On balance, my reading of that literature is that it is about 50/50 industry and academe. A lot of this information comes indirectly from the balance (a false dichotomy in my view) between basic and applied science. But there is quite a lot of actual information on this that you can read – my impression is it's about 50/50. As Richard has said, however, there are tensions and I don't think they are all in the one direction necessarily, they have, at different times, been in both directions.

Humphrey: Following on from Daniel's point, yes, I think everybody in the 5-HT area did happen to be nice and was that a coincidence? I don't know. Part of me thinks it was something to do with the era in which we were. I was in academia before I went into industry but I wanted to discover a drug and I

[262] Jewkes, Sawers and Stillerman (1969).

Figure 22: Dr Jeffrey Aronson

think most people in the industry in those days were very altruistic about their mission in life. They weren't there to make money, they wanted a job obviously, but their main mission was to find a medicine that would benefit patients. That's why working with David Jack was so inspirational because he told us that's what our job was – to find new drugs, better drugs that would benefit patients. Today, I think of the pharmaceutical industry just like the bankers – put the wrong people in charge and the motivation is entirely wrong. The motivation today seems to be to make money for yourself and that's not just the guy at the top but all the way down. That's all that counts. So all the good things that come from altruism are being lost.

Sanger: At least for some of the larger companies the influence of molecular biology and the human genome changed things dramatically. We would be told to take advantage of this wealth of molecular targets and try to make a new drug every two years! But what happened in the end was that a process developed and people began to ask where the creativity was within that process. We lost creativity. All we did was take a target and process it; we put it up for high-throughput screening, developed a molecule for it, and put it into, perhaps, a standard animal model, before taking it to the clinic to find out if it would work or not. Suddenly invention and creativity were lost. I remember at some

stage being interviewed about what I thought had improved since we were able to mine the human genome for new targets and I said: 'Well the process is bad. It's good, obviously, because you get new targets to work on but the process kills creativity.' The message I got back from the guy interviewing me was: 'Yes, that's what I hear consistently.'[263] You can see that in other parts of the industry, the process kills biological creativity. And maybe that's been a big problem with some of the big pharmaceutical industries, they've had tools but no invention.

Flower: Are you saying they are being de-skilled, in a sense?

Sanger: In a sense – although I'm being a bit 'over the top' to make a point.

Hunter: I think it's really apposite that Gareth who is the least process person I know would make that comment. Partly it isn't always down to individuals because, as a personal reflection on Gareth, Gareth has the little drug discovery genie that sits on his shoulder and tells him what's the right question to ask and the right hypothesis. That was coming back to the original question: I would say that there is a role, it is 50/50, but perhaps you can say predominantly in academia it's knowing what question to ask and industry is providing the resources, for example, the tools and technologies, to be able to answer that question. Now is 5-HT different? I would actually argue that it isn't. If you look at the era of the NMDA receptor and neuroprotection, the work that was done by companies to provide selective compounds really drove a huge amount of research in that area. When those compounds failed, I would argue potentially because the trials were not appropriate in the clinic, neuroprotection in terms of funded research crashed.[264] If you look at the number of sessions at the Society for Neuroscience, for example, versus ten years ago, you can see it's hugely reduced from what it was. So I don't think it's unique. Deeply wonderful though you all are, I'm not sure it's just because people who work in 5-HT are nice people. I do wonder whether it's something like the Serotonin Club, which brought people together around a particular topic, in this case 5-HT that actually fostered that cross-creativity between companies and people and industry and academia. That could be, perhaps, something to think about. I also see a move in the industry now, not so much away from the industrialization

[263] Professor Gareth Sanger wrote: 'He [the interviewer] was a senior American academic, employed for a while by GSK (Dr Allen Roses). Among others, I was interviewed as part of an internal review of activities conducted on behalf of senior management. Difficult to remember, but this took place maybe 10–15 years ago?' Email to Ms Caroline Overy, 16 July 2013.

[264] See, for example, Palmer (2001).

but a realization that, until we find a way of improving our chance of success, we're going to have to cut the cost of failure. Therefore you do see many more precompetitive activities. But when you get the medicinal chemistry or the actual biologics, I think that's probably a step too far. So, a slightly different perspective.

Andrews: I want to come back to what Richard said. I agree very much from an academic perspective that the difficulties of getting compounds have increased immensely on both sides and also what you said about universities, that's been precisely my experience. We've got IP officers and business officers and I think what we have to try to do on both sides, if you call it that, is to learn the lessons from this. Because I think this is a fairly unique set of circumstances that have happened around 5-HT and really the question would be: could we do this now? Certainly in my own small area the answer would be 'no', because it would just be too difficult for multiple reasons. I think there was a particular time when it all just seemed to work in a lot of people's favours for reasons on both sides of the fence. I do wonder whether we're losing something, so I think somehow we need to try to distill a few of the positive lessons for both industry and academe, as we're supposed to work more closely together now officially and with more blessing than before, and try to work out what it was that was really good about this period that made it work. Clearly there are going to be other circumstances where we need this and I'm worried that something has been lost. Maybe it's just getting older, you begin to feel that. There may be some parallels here with NK1 receptor antagonists as well, where there was a lot of background data on substance P, but really I think that it was the availability of small molecules that again advanced this further. So there may be some other parallels.

Blackburn: Apart from this sort of parochial view with regard to 5-HT and it all being very nice, Gareth's comment about process, and Jackie saying it's much wider: well, it is much wider in the sense that the late 1980s and the 1990s were a very important era with regards to Pharma and the way the whole industry was thinking. It's a fact that McKinsey, like many consulting companies, came out and promoted: 'This is the way to follow.'[265] And we all did! We followed with 'me-too ism', so you had many companies all jumping on the same

[265] McKinsey and Company is a global management consulting firm. See Booth *et al.* (2002), which states: 'Our research indicates that first-in-class drugs don't always deliver the highest returns…For the long-term sustainability of the business, it is crucial to improve the pipelines' productivity. To that end, most drugmakers will have to orient more of their drug development efforts toward best-in-class rather than first-in-class approaches.'

bandwagon. What we've seen from that is a destruction of creativity. I asked a question at a New York meeting a few years back because everyone showed these wonderful graphs of New Chemical Entities (NCE) disappearing over decades. I asked: 'Is there a correlation, a graph, showing the amount of money we've spent on consultancy companies over these years with regard the number of NCEs?' And one of the luminaries of the pharmaceutical industry said: 'Oh yes, but they've taught us how to write reports well.' Well, if you haven't got a compound to write a report on, you don't have an industry. The dependence on management processes, whether it was matrix management, proved to be a failure in many industries and was one of the undermining problems that I saw within the pharmaceutical industry in the 1990s, in destroying that creativity of individuals or scientists like Gareth and others around me.

Marsden: My interest was in mental disorders and there was a difference in approach between the academic and the industrial side during the 1980s and the 1990s in particular. With all these 5-HT receptors being identified, the industry thought very much of a single target approach but it always seemed hard for me, and many others in the academic field, to think that you could explain a mental illness by attacking a single, very specific receptor. It is interesting when you think of Bill Deakin's work on anxiety, which implicated at least two 5-HT receptors in this disorder, that a single target approach could ring true when trying to treat mental disease.[266] Understanding has moved on now and people are beginning to think of these disorders as being more complex. Maybe the 'magic bullet' approach did hold research up in the 1980s and the 1990s, as we had a too simplistic approach about how you might treat a mental disorder.

Clarke: When we're talking about academia and the pharmaceutical business, we've got to consider three things and I think there's always an uneasy relationship between these. One is the businessman: I admire businessmen but I don't understand them. They're willing to put everything on the line for an idea and sometimes I don't get the reasoning behind it. Then there's the applied scientist: now he's a man who wants to discover a drug, discover and develop a molecule for a defined medical application, if he's in the pharmaceutical industry. His brain works differently; it's always thinking about trying to get a molecule for the target, going down the road to try to get to that point where he wants to be and that is make a compound that hits the target, that is clean, and that one can get into the clinic. Then you've got the academic:

[266] Bill Deakin is Professor of Psychiatry and Head of the Neuroscience and Psychiatry Unit at the University of Manchester. For his work on receptors, see, for example, Mekli *et al.* (2011).

now the academic is often a blue-sky researcher; he's not interested in an end effect. He's a reductionist researcher, he's goes into it and into it and into it because it's interesting, not because he's going to hit a target that is valuable and therapeutic. He's just interested in science and discovery and what nature is all about. So you've got the academic, you've got the applied scientist and you've got the businessman, all in an uneasy relationship with one another. The businessman wants something now; the applied scientist says: 'You can't have it now; we haven't got the molecule'; the academic doesn't really want anything now, he just wants to do some research that's paid for and to find out how things work. This has always been the case: their brains are different. The academic brain is different from the applied scientist's brain in industry and it's different from the businessman's brain. What happened years ago in my opinion, and it's only my opinion, that despite these brain differences there was trust. I think we've lost that very important element: a trust that the businessman would trust the applied scientist. The applied scientist who needed help at Bradford would send out his compounds; he'd trust Bob Naylor and Brenda Costall. That is gone. As Dan says, now the academic is more like the businessman. He is there, he wants money for what he's doing, he wants rights for what he's doing, and all this undermines trust between these three elements. And that removes freedom. If you're going to get creativity, you've got to have freedom; you've got to be able to say to somebody: 'We trust you, we think you're good, your idea is good. Here's some money, go in the lab, get stuck in and do the work and don't even bother to give me a report for two years. I trust you. Come out with an answer.' That's gone. Now you can get into a lab for two weeks and if you haven't got an answer, they stop the project in industry these days. I think these are very important elements that pervade current drug discovery, universities and applied science. And that's why we haven't got new chemical entities coming out.

Flower: I'd just like to make one comment and that is it's not actually the academics it's the university administrators who are responsible for all these rules and regulations. It will kill everything.

Curzon: Again and again, people here have said 5-HT workers are so nice. There are few of us in this room who are under 60 and there are quite a few who are over 80. We come from a different world. When I graduated, less than about one per cent of British graduates got PhDs. Only a tiny fraction of society was involved in research. Because far more people are now doing research, they are

recruited from a more ordinary pool. I'm not saying we're better people than the newer generation but we're different to them.[267]

It was easier in our day to help other scientists but things nowadays are more grim and competitive. Scientists are under greater pressure to get the next grant and are much less relaxed. Tony Blair wanted 50 per cent of the population to have degrees, which is fine, but this is altering what it means to be a scientist.

Flower: I certainly agree with that.

Professor Helen Cox: Two points: one is to echo what you've just said Rod, in terms of the tensions that exist in academia, they are between academics and the enterprise arm. I would like to emphasize the fact that there is trust, a lot of trust, between scientists on both the academic and the pharmaceutical side. Although I'm not a 5-HT expert, certainly in my area of neuropeptides I know that I can communicate with my compatriots in Pharma companies and, with material transfer agreements in place, still get compounds readily, but I'm sworn to secrecy on that. So there is a degree of trust but it is challenged by internal 'hurdles' along the way. I'll leave it at that.

Bakhle: In your particular area, Helen, where are the advances coming from? Are they coming from industry that you can identify in this crude way, or are they coming from the academic sphere? That's what I really want to find out: is 5-HT different from other research areas? We've heard from Jackie about the NMDA area; is that common?

Cox: I'd say that in the neuropeptide Y (NPY) receptor field, we're also very communicative and supportive people, but largely this is driven by the fact that we've had meetings, a bit like the BPS, once every two years for pretty much the last twenty years.[268] The same Primary Investigators turn up to these meetings with a core group of us in academe and Pharma who end up writing IUPHAR recommendations in *Pharmacological Reviews*.[269] When a group of people do

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[267] Professor Gerald Curzon wrote: 'Research is becoming just another profession like accountancy or law. But some of us saw ourselves as almost a kind of scholarly knighthood. A band of brothers (and sisters). We were proud to be research scientists.' Note on draft transcript, 22 January 2013.

[268] Professor Helen Cox wrote: 'To clarify, the neuropeptide Y meetings I referred to have been organized in an *ad hoc* way, and have occurred on average every two to three years since 1989, largely due to the common interests of a proactive group of scientists working in different countries in this area (of which I am one). There's no organizational entity as such.' Email to Ms Caroline Overy, 12 June 2013.

[269] See Michel *et al.* (1998).

Figure 23: Professor Helen Cox

meet on a regular basis, those links are maintained and I'd like to think that that's true in the Y receptor field just as much as I've heard today that it obviously exists in the 5-HT field. So, in answer to your question, Mick [Bakhle]: what is driving it? In the 1990s when NPY receptors were being cloned and when Pharma was really interested in anti-hypertensives and anti-obesities, there was a preponderance of work going on in Pharma. But then as a consequence of the compound attrition, those compounds came into academic circles and this helped significantly in the classification of the receptors. So, research in this area is cyclical as I see it and now with the anti-obesity drug targets in the limelight again Pharma is contributing significantly again, ten to fifteen years later.

Andrews: A final point about funding, we've talked about funding research directly, but I think we shouldn't forget that the industry has also funded a large number of meetings in this area in general, and particularly in 5-HT_3 at the time. Those regular meetings of pretty much the same people but sharing data almost in real time, played a very important role in keeping the area going, giving a momentum to the area and in some ways keeping some aspects of the science alive. We shouldn't forget those meetings because they're the ways, in a sense, in which we can plot the course of the development of the area. Many of those were funded by industry, and I think that is not likely to be the case

now where funding for a meeting from industry is very difficult to get hold of; small sponsorship but not exclusively funding from two or three companies and making it a very open, international meeting. So that's another aspect of this.

Flower: We ought to move on a bit and discuss the advent of specific drugs in the 5-HT field. It was Tom who mentioned four or five of the top twenty drugs acted on the 5-HT system. Is that right, Tom?

Blackburn: In a recent article from the American Chemical Society it was interesting to note that neuroscience attrition rate was less than that for anti-cancer and anti-infective drugs, yet neuroscience is seen as a high risk therapeutic area![270] I mentioned Seroquel earlier, which is coming off patent and was a $4–5 billion drug in 2010. Duloxetine, a 5-HT uptake plus noradrenaline uptake was a $4 billion drug in 2010 and there are one or two others that are still highly efficacious and highly profitable drugs.

Flower: I'd like to come onto that a bit later because I think that's a very important question. What I'd like to do now is to record and capture personal anecdotes or reminiscences about the introduction of particular groups of specific 5-HT drugs. Pat, I wonder whether you could say a few words about the triptans for us. Maybe some personal reminiscences about their introduction and so on and then we'll go on to talk about others.

Humphrey: Well, that could be a long one or a short one, I don't know how to deal with this. From the reminiscence side, as I told you, I was a lecturer at St Mary's Medical School in the Physiology Department and I didn't really want to just teach medical students and end up with a line in a textbook, so I thought I wanted to discover a drug, and I was very fortunate and was asked to go down to Ware and find an anti-migraine drug. When I got there I found an empty lab and a girl sitting on a stool saying: 'What are we going to do?' I said: 'Well, I don't know; we'll have to think about this' because there were no preconceived ideas about how we should proceed. That would never happen today, to be given that freedom. I don't think I would have discovered anything if I'd gone to Glaxo 20 years later. So the empty room is the first thing you need if you want innovation and what did I do? I went and spent three months talking to clinicians while I was waiting for equipment to arrive, finding out about migraine. I don't think I want to bore everybody with the details, but there were two or three clinical people to this day who I think are brilliant because they understood their patients, they knew which drugs worked. But

[270] Lindsley (2012). See also Table 3 on page 126.

as I said, the key for me, the seminal observation, was James Lance who said that there was a prophylactic drug, methysergide, which was a 5-HT_2 blocker or a D receptor blocker, whichever terminology you want to use. It was given prophylactically; it was taken every day for months and months and didn't do very much. However he noticed that some of his patients took a tablet and while they were in his clinic, his office, with a migraine, suddenly it went away.[271] In other words, it had another action that the other 5-HT_2 antagonists didn't. So I was studying what it was that methysergide did. What we discovered was that there was another receptor at which methysergide was a potent agonist, and so that turned out to be the 5-HT_{1B} receptor.[272] So clinical observation is absolutely critical. Another part of the mix is really intimate discussion, trust and interaction with the clinical field, really find out about the disease first. Then all bets are open. It could be that you want to look at it in a complex way. When I first started, I used to work on prostaglandins and 5-HT because there was a story that if you infused prostaglandins into people, I think it was PGE1, it caused migraine-like headaches. So we were going to measure prostaglandins in jugular venous blood during an attack. Unfortunately we couldn't find a medic who was prepared to do it, so we never did that experiment. We had all sorts of bioassays worked out and everything. I quickly moved onto 5-HT in preference over prostaglandins because of this clinical observation that I've just described, and then it was just about looking at blood vessels and we were actually lucky enough to be able to have identified a receptor through using different tryptamine analogues prior to the molecular revolution.[273] What we discovered turned out to be correct. It's interesting that we knew this receptor was also on nerve terminals and would inhibit nerve terminals and it looked like the identical receptor: everything we did, hundreds of compounds, couldn't differentiate them. I'm pretty confident now that that was probably the 5-HT_{1D} receptor and so we discovered two receptor types in reality but they were so similar pharmacologically and, as it happens, molecularly. Of course, the proof of the pudding then was in the eating and that was 'get hold of a migraineur and find out whether it works.' And to be fair, it's analogous to getting an asthmatic who's wheezing and giving them something to inhale, 'Does it work?' You know when your bronchodilator works.[274] In the same way with a migraine attack:

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[271] Curran and Lance (1964). See note 52.

[272] Apperley, Humphrey and Levy (1976).

[273] See, for example, Apperley *et al.* (1980).

[274] For discussions on bronchodilators, see Reynolds and Tansey (eds) (2001), *passim*.

with a severe migraine I think it's pretty obvious if your drug has worked or not. That was the exciting thing about it, that there were patients who were really ill and they were just getting off the bed and going home happy.

Flower: Bearing in mind some of the comments other people have raised, what battles did you have to fight internally in order to keep this project going – or was it plain sailing?

Humphrey: Well, it was a bit of an open door because at Glaxo at the time, it was led by David Jack, who was not a micromanager, but you were pretty clear what he wanted of you and that was to do what you were supposed to do. All he asked of you was that for every experiment you did you had to have a reason, and knowing if it worked out, where it would take you. That would take you to the next step, on to the next step, to the final end, which was always the drug: the medicine that would benefit patients. I think that was absolutely critical. What was also lucky was that I had an academic interest in 5-HT receptors as a consequence of getting in through that door and you could see that 5-HT was everywhere, and in the brain and in the gut and one just felt that this had to be an opportunity to find other drugs. Now that wasn't something that convinced David at the time particularly, he didn't like that blunderbuss approach but it didn't matter. The thing was, if you were always doing the right things, that was fine. But I just can't imagine how such a drug would be discovered today. First of all if someone said: 'Well, there are 14 different 5-HT receptor types and we know that 5-HT aborts a migraine attack, you go and find the right one.' You know with just the molecular biology and paucity of whole tissue and *in vivo* pharmacology, it just wouldn't work. Then if you have the Clipboard Charlies going around telling you how to run your project and how you should be doing it, that would kill it as well. So I think I was very, very fortunate in being at the right time in the right place with the right organization.

Flower: And the right person, too.

Humphrey: That's what I mean about the right organization, it was the leader at the top.[275]

Flower: I mean you actually.

Humphrey: Oh right, well, that's very nice of you. Thank you.

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[275] i.e. Sir David Jack. For biographical details see page 151.

Hunter: I talked to the guy who ran the clinical study[276] and in the first 12 patients, you know, it was almost like you said, it was almost like a Lazarus moment, so that must have helped as well that you were able to show that so quickly.

Humphrey: There was one person in which it didn't work but they later found that he had a broken jaw.

Flower: You mean it doesn't fix broken jaws as well? [Laughter]

Green: I think Pat has brought up a vital point, which is that he went and talked to clinicians. One of the great things of working in the Clinical Pharmacology Unit in Oxford, and if you go back and look at the NIH in the 1960s and people like Sjoerdsma, is that they worked together closely. I found it invaluable being with Phil Cowen and Dave Nutt and others because I was working mainly on depression and I would say something like: 'Oh, you know, I believe most depressives have this and that', and I'd get people like Phil saying: 'Well, yes, the books often say that but I almost never see it' – actually picking up what the vital components are and this goes exactly with what Charles has said as well, one size fits all, one receptor will do everything. If we actually knew much more about the problems of things like depression and schizophrenia and could break them down because we were working and talking with clinicians, we would then be producing much better animal models. To give you an example, for years I worked on neuroprotection and stroke. When I look back now, why were we using young, healthy male animals for almost everything when, in fact, the stroke patient, and if we'd had a stroke clinician on the pre-clinical group this would have been pointed out, is mainly an elderly hypertensive diabetic. We should have been using hypertensive animals, diabetic animals, elderly animals. I think this is something that we have lost, that happened much more in the early 5-HT research, meeting people like Merton Sandler, Mike Pare and Alec Coppen.[277] Every time we met these people and talked with them, they told us what the clinical problems were and what they wanted. I think we were much

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[276] Referring to Dr Malcolm Thomas. See the interview 'Sir David Jack CBE FRS FRSE in interview with Dr Max Blythe (Interview III) and in conversation with Professor Patrick Humphrey, Oxford, 6 August 1997', which can be accessed at the Medical Sciences Video Archive at Oxford Brookes University, ref MSVA 173/174, and at the Wellcome Library, Moving image and Sound Collections 1843V.

[277] Michael Pare (1925–2002) was a Consultant Psychiatrist at St Bartholomew's Hospital, London, from 1959 until his retirement in 1984. His work centred on the treatment of depression. See Professor Merton Sandler's comments on pages 8 and 20. Alec Coppen (b. 1923) is a British psychopharmacologist who worked at the MRC's Neuropsychiatric Research Unit in Epsom, Surrey. See pages 29, 40 and note 133.

more aware than a lot of the young scientists are now, particularly in industry, trying to develop a specific antidepressant drug or something like that, because they don't get the clinical input. I really would love to see, and Jeff Aronson and I have talked about this, clinical pharmacologists and the basic pharmacologists interacting much more closely again.[278]

Hoyer: When I started, and my background is in beta receptors and alpha receptors, I had no clue what 5-HT was all about. However on the day I presented my PhD in Strasbourg, in the afternoon I went to Merrell Dow and made a presentation to Dr Fozard and we have kept in touch ever since. This was 1981. In 1983, I was asked to join Sandoz, at the time I was at Penn University of Pennsylvania, to work on 5-HT. I said that I still didn't know anything about 5-HT, and one person said that this was important because I was unbiased. The way 5-HT research started at Sandoz was in 1978, when Brian Richardson was asked to lead a 5-HT task force. We knew that the receptors were complicated, the goal then was to characterize receptors, compounds, tools first and then go into the clinic with the best ones. This is how the 5-HT programme started, pretty much at the same time as John [Fozard at Merrell Dow] was doing it and presumably Mike [Tyers at Glaxo]. The good thing then is that once they realized that there was mileage, and there was quite some mileage, they said: 'Go and look for more, and go into other indications.' Initially we were talking about pain, migraine, of course in both cases it failed but actually we were the first ones to ever try a 5-HT_3 antagonist in a clinical set-up with cancer patients: chemotherapy induced vomiting, all these things were happening at the same time in different places.[279] The problem is that, quite often, by the time you have the clinical data the company will not follow because in the meantime the management or strategy has changed. This is one of the major disappointments that you experience. But at least at that time the freedom was given: for example, we had one of these 5-HT_1-like receptors to play with because we had a compound that was reducing blood pressure to the extent that we couldn't really believe it.[280] Nothing else would match the profile: it was working in rats, in dogs and in other species and so we went on a fishing expedition to find out what this compound was doing on which receptor. Note that this would not be feasible today. Eventually we found out it was actually 5-HT_7-mediated, it

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[278] Green and Aronson (2012).

[279] See Christie and Tansey (eds) (2007).

[280] See comments by Dr Patrick Humphrey on pages 42–3.

was not a 5-HT_1 effect. The so-called 5-HT_1-like receptor was actually a 5-HT_7 receptor.[281] It took quite some efforts chemically to sort this thing out, until the receptor eventually was cloned, but this was many, many years later. It turned out that this compound never made it, for again PK issues etc – PK is one of many critical issues in drug development. In one of my latest teams, the first thing I did was to hire a clinician because he knew what he was talking about, actually he had already developed a compound in the indication we were pursuing, but on another mechanism. This was an eye-opener, we knew precisely what we were looking for and, importantly, we also knew what we were not looking for. The side effects, depending on the indication, are going to kill your compound so you'd better know early what you don't want. One of the major issues that we have experienced more recently is that clinical research and pre-clinical research have been totally separated, I don't know if it was a McKinsey or whoever's effect, but there was a wall.[282] In the old days we had clinical pharmacology, these clinicians would take compounds and put them into probands/volunteers. Actually I've been testing beta blockers on the bike and I can tell you that some of them don't help you to go up the hill [laughter], others are a bit better. This sort of expertise had totally left the company because they thought they could subcontract all these studies and then the link between pre-clinic and clinic was totally lost. So one of my first things in another team, around the end of 2002, was to create a translational biology group in neuropsychiatry; I made sure that clinicians would be at the meetings, as quite often the doctors are busy, because without clinicians, pre-clinical people are lost. This is important, it has to be fixed, so in my new job, I will have to convince my friends in the clinic that what people do in research departments is important too.[283] I remember at the BPS meetings in the old days, clinicians and pre-clinical people would be together and talk happily. Toxicology was a bit different, it has always been a bit different, but at least clinical and pre-clinical were very much linked and we would go all to the bars and restaurants together, because clinicians know the good places! Now we have more and more molecular biologists who don't care about the other end of the spectrum. One of the hurdles that we have with respect to academic–industry collaborations is that, in America, every scientist,

[281] Villalón *et al.* (1997, 2000).

[282] See page 94.

[283] Professor Daniel Hoyer became Chair and Head of the Department of Pharmacology in the School of Medicine at the University of Melbourne in December 2012.

at some point or another, thinks that he's going to be able to create a biotech company and become a millionaire. This leads to information retention because he always thinks about his future, when actually the future is rather grim for most biotechs. This has become a major issue as well.

Sanger: In some ways my experience is rather similar to yours, Pat, in that, when I started in industry, I was given an empty room and I was told to help the programme develop new dopamine receptor antagonists. At that time they were working on metoclopramide, which was deemed to be the lead dopamine receptor antagonist. It quickly became apparent that it wasn't just a dopamine receptor antagonist, it had something to do with 5-HT as well. I had to go through the process of defining its ability to stimulate a 5-HT receptor in the gut – ultimately named externally as 5-HT_4[284] – and also identifying, for the first time, the clinical significance of its ability to antagonize at the 5-HT_3 receptor and from here developing anti-emetic drugs. Part of that process was reading the literature and there were clinical observations that said: 'There's something peculiar going on here.' Gralla's work on the anti-emetic activity of high doses of metoclopramide was particularly important in our discovery of the anti-emetic role of the 5-HT_3 receptor.[285] Another part was reading competitor activity, in particular by John Fozard, who identified the receptor pharmacologically and showed that metoclopramide antagonized at this receptor.[286] So it was then possible to read these two areas of literature and test the hypothesis that metoclopramide exerted anti-emetic activity by antagonizing at the 5-HT_3 receptor – in terms of new anti-emetic drugs, the rest is history! New pharmacology and drugs came out of that kind of research, but today we don't have extensive literature on any of the new drug targets that we work on, the ones that create the high impact papers. It's very difficult to go out and find the clues. You've got to do it yourself or you do it in a very limited way. You may choose a knock-out mouse, which may or may not be relevant. So Danny's point about trying to pull the clinicians in is a good one, I can see

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[284] Professor Gareth Sanger wrote: 'After publishing papers which suggested the existence of a 5-HT receptor mediating the abilities of drugs such as metoclopramide to stimulate gastrointestinal motility (for example, Sanger G J (1987)), I received a phone call in the lab from Joël Bockaert who announced, in his rich French accent, that he had found my receptor in the brain! This was amazing! Joël then went on to publish his findings and named the receptor as 5-HT_4 (Dumuis *et al.* (1988)).' Email to Ms Caroline Overy, 9 October 2013.

[285] For Gralla's work see note 185.

[286] Fozard and Mobarok Ali (1978).

it helps, I don't know how much, because even they don't know what this new molecular target might be because they haven't got ten years of literature behind them on that target, which I certainly did and others did at the time. You had that literature behind you; you don't have it so much now, so it's more difficult.

Tyers: I'll tell you a couple of anecdotes. Before ondansetron was approved in the States by the FDA it was possible to use it off-label with the Surgeon General's permission. There was a report through from our clinical trial researchers, who said that this woman was suffering from severe nausea and vomiting and could she take ondansetron as a means of overcoming it and the Surgeon General said, 'Yes she could.' Well, she took it and it worked very, very effectively. She said: 'If I ever meet the guy who discovered this drug I want to give him a big kiss.' And the researcher told her, 'Don't look forward to it.' [Laughter] Another one is after ondansetron (Zofran) had been on the market in the UK for only a couple of months. I have a cousin who is an oncologist in Gloucester Hospital and she said one day she visited the oncology ward after their daily doses of chemotherapy and everyone was vomiting indiscriminately, the nurses were running around with mops and buckets and things. That night they were all given ondansetron and the next day when she went in for her ward round at the same time of day all the patients were sitting up in bed having their breakfast and the nurses were just standing around wondering what to do. So, one of the rewards of discovering a useful drug is that it that does what it is supposed to do.[287]

Blackburn: To address Danny's question: in my days at ICI, I was thankfully working alongside clinicians like Steve Howard and David Milson and we were developing a trust in the project with regard to their clinical buy-in and enthusiasm for the science. In those days, we were looking at biomarkers, looking at pupillary constriction, platelet aggregation and EEG changes and several other models, which were hoping to determine the dose to take us into the clinic. We were interested in migraine prophylaxis, whereas our competitors in Glaxo were really going full-steam for the intervention therapy,[288] so the marketing people at ICI were basically saying 'no to prophylaxis treatment and that intervention therapy is going to sweep the board and you guys have got it wrong.' Okay, fair enough at the time, but migraine prophylaxic treatment is a

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[287] Dr Mike Tyers wrote: 'Now just about every cancer patient in the world given chemotherapy or radiotherapy receives ondansetron or a 5-HT_3 antagonist to treat the sickness.' Note on draft transcript, 7 January 2013. For a discussion of a paediatric study of ondansetron, see Christie and Tansey (eds) (2007), pages 59–60.

[288] Intervention therapy using the Glaxo drug sumatriptan.

big market and still is, if you have the right compound. An anecdote, and Pat might remember this; it was at the Migraine Trust Symposium in 1992, where Glaxo made a major sumatriptan marketing presentation with all their excellent science and marketing guys culminating in a top-class PR presentation. Then there were these poor guys from ICI pharmaceuticals, Barry Cox and myself, with Clifford Rose in the chair, giving their presentation. After my presentation using one of those huge lantern projectors, Dr Wasyl Feniuk from Glaxo, a good friend of us all, came to me and said: 'How did you do that, Tom?, I said, 'What?' 'You presented a slide talking about spreading depression in migraine and all of a sudden on the picture of the brain you could see this shadow moving across the slide'[289] [Laughter] It's just what we do best at ICI.

Flower: You were ahead of the curve as always, Tom.

Curzon: Those who are 25 years or more younger than I am have no idea of the enormous gulf of mutual ignorance between the laboratory workers and the clinicians, due to the overlaps between their trainings being so slight. There was also the tremendous prestige and self-confidence of the top clinicians, while good research scientists are cautious and self-doubting. I remember an eminent neurologist, now dead, saying quite dogmatically that pharmacology had very little to teach the neurologist. Then levodopa appeared and I stood up at a meeting at Queen Square saying very diffidently: 'There's this new thing called levodopa and it helps people with Parkinson's disease.' A comparably eminent neurologist, now dead, said through clenched teeth: 'If Dr Curzon had been a clinician he'd know that biochemistry or pharmacology have nothing to do with Parkinson's disease.'[290] [Laughter]

Kaumann: I'd just like to comment how surgeons and clinicians influenced the design of my experiments. I often fetched human coronary arteries, atrial and ventricular tissues from explanted hearts at Papworth Hospital and also human atria from patients undergoing coronary bypass surgery. I used to get notice about three hours before the next operation. Before receiving cardiac tissues I used to have time for chats with the clinicians and surgeons and I'd like to give you two examples how this influenced the experimental design and hence results with adrenaline and 5-HT. For example, I was told by a surgeon

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[289] Heat from the beam of the projector sometimes caused condensation in glass-mounted 35mm slides or burnt those mounted in cardboard.

[290] Professor Gerald Curzon wrote: 'The "eminent neurologist" was Roger Gilliatt. The "comparably eminent neurologist" was John St Clair Elkington.' Email to Ms Caroline Overy, 3 July 2013.

that, on occasion, some patients undergoing coronary bypass surgery and treated with atenolol, a selective β1-blocker, developed transient post-surgical atrial fibrillation. This was surprising because it was known that propranolol reduced the incidence of these arrhythmias. That prompted me to compare carefully results from patients treated with β-blockers, usually β1-selective, such as atenolol or metoprolol, with non-β-blocker-treated. Paradoxically, we discovered on isolated atria from β1-blocker-treated patients that the β2-adrenoreceptor function was enhanced and that the latter receptors mediate as many experimental arrhythmias as β1-adrenoreceptors. During my experiments with human atrial tissues, I had also noticed that 5-HT, on occasion, elicited arrhythmias. Louise Sanders, Sian Harding and I discovered that the 5-HT_4 receptor function of human atrium was increased in β1-selective-treated patients and that these receptors mediated more arrhythmias in β-blocker-treated than in non-β-blocker-treated patients.[291] The other example is coronary arteries. With one particular case, I was shown the contrast radiography of the coronary tree and I could clearly see atheroma in certain sections with stenosis of the patient that was going to be transplanted that night and going to receive a new heart. I was fortunate to experiment with those bits of coronary artery and discovered that the prestenotic and atheromatous section of the artery responded to 5-HT with a contraction through 5-HT_{1B} receptors, whilst on the non-atheromatous poststenotic segment a 5-HT-evoked contraction occurred through 5-HT_{2A} receptors. These findings were prompted by conversations experienced at cardiac surgery in Papworth. I learnt enormously from these contacts.

Aronson: I don't have a drug discovery story, but I'd like to comment on the clinical scientist interface from the clinician's point of view. Notwithstanding Gerald's story, I was very impressed by Pat's story that he took three months out to talk to clinicians and discovered a drug that I keep permanently in my pocket. The story that we've just heard about the coronary arteries, I think it's hugely important that basic and clinical pharmacologists – or let's avoid words like that – pharmacologists and clinicians should speak together, but then as Danny says, the clinicians are not always available. We can't always find them. They're not always interested, perhaps. That, I think, is a real problem that we do need to tackle. These days clinicians are expected to be innovative, I'm talking about academic clinicians, we're expected to be innovative researchers, effective clinicians, and inspiring teachers in addition to all the other things that

[291] Sanders *et al.* (1995). Professor Alberto Kaumann wrote: 'It is still an open question whether transient post-surgical atrial fibrillation can be initiated by 5-HT.' Note on draft transcript, 9 December 2012.

one does: policies, committees, all kinds of things. I'm not sure that it was ever possible for a clinician to do all of those three things. I think some clinicians whom I've admired were good at pretending they were doing all three things, but the pressures are greater nowadays. Clinical medicine is much more difficult to practise than it was, people are living longer and have more complicated illnesses, there's specialization, and so on. I think it's now not possible, even if it ever was, for a clinician to do all three things to a high standard. I do think we need to tackle this, and my suggestion has been to take any two activities out of three and develop people who are good clinical researchers, or people who are good research teachers, or people who are good clinical teachers, mix and match those disciplines and get them all talking to each other and with the scientists.[292] We really do have to do something about encouraging clinicians to take part in the process that you've all been discussing.

Clarke: To take the opposing view about clinicians, a little warning: management takes a lot of notice of clinicians. The more eminent they are the more notice they take. Syntex/Roche was developing prokinetic drugs based on 5-HT_4 agonists and they'd gone down the road quite a long way, although I was not in charge of this programme, I never was; I handed 5-HT over to other people immediately I got into industry. But the company moved that programme forward and then they brought in some very eminent gastroenterologists after an awful lot of pre-clinical work and one of them asked in front of management: 'Does this compound prevent pain? Gastrointestinal pain,' and the answer was: 'No, it doesn't.' The clinicians said: 'Well, that's it, it's useless. We must have a drug that is analgesic for these IBS patients.' The company called him in and no matter what we said to management it was of no avail – the programme was stopped. As we know, although it's got a chequered history, Resolor is on the market as a prokinetic agent for IBS despite a big question mark as to why some of these prokinetic agents cause cardiovascular adverse effects, it's not at all clear.[293] So there is room there for further work. It can be very damning how very quickly a whole programme can come to an end.

Hoyer: My point was to speak to clinicians early and not in the presence of management!

Clarke: I think the point is that I should have been more like Pat.

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[292] Aronson (2011a).

[293] Resolor (prucalopride) is manufactured by Shire Pharmaceuticals. See comments by Professor Gareth Sanger on page 72.

Flower: And gone to the bar?

Clarke: And more like Dan, and more like everyone else in this room, but as it is, it's usual for me to be about 50 years behind everybody else.

Sanger: Very quick empathy with both points and the difficulty of getting good clinical advice into development. I was at the World Health Organization a month ago where we were discussing prokinetic compounds and laxatives. The prokinetic drug prucalopride, for example, is not registered for the treatment of IBS and the proposal was to reclassify it as a laxative. However, a separate group of prokinetics – which also included alosetron, a drug which inhibits colonic motility – would have been separately classified as drugs for treatment of IBS, even though the pharmacological mechanisms were similar. We had the 5-HT_4 agonist tegaserod in the IBS box; the 5-HT_4 agonist prucalopride in the laxative box and the 5-HT_4 agonist metoclopramide in the gastric prokinetic box. To me it was utter chaos, and so we had half a day's discussion on this. I talked to the woman running the session afterwards and she admitted that it was imperfect, but the problem was that she found it difficult to get good, clinical gastroenterologists who understood both the science and the pharmacology. And this is the World Health Organization. So I'm empathizing with both of you.

Hunter: One comment on the clinical side. A lot of companies are trying to fix this by bringing clinical people in to run things, but I actually think that there are different phenotypes: you need good clinical researchers in your company, but you don't want to take the clinician out of the environment in which it's most valuable for you to interact with them, i.e. the clinic. Just a couple of personal reminiscences about the 5-HT_6 programme: SB 271046 was about to go into Phase II trials when the six-months toxicology came in and it said there was a retinal problem in the dog and so there was a huge thing about killing the project. Luckily we had the transgenic mouse and were able to show that this wasn't a 5-HT_6 specific effect, that it actually was a compound specific effect and that allowed us to go on and carry out further work.[294] The other thing I want to mention, *vis à vis* clinical understanding, is that I was lucky within the set structure we had at Glaxo, I could be fairly autonomous in my decision-making process. I actually wanted to do a dose

[294] Dr Jackie Hunter wrote: 'The retinal stuff was never formally published, although it has been mentioned in talks – the compound that was a 5-HT_6 antagonist that made it into Phase II clinical trials was published in Maher-Edwards *et al.* (2010, 2011); Upton *et al.* (2008).' Email to Ms Caroline Overy, 18 June 2013.

Phase I	Initial studies to determine the tolerability, metabolism and pharmacological actions of a drug in humans; the adverse effects associated with increasing doses; and to gain early evidence of effectiveness. May include healthy participants and/or patients (*c.* 20–80 people).
Phase II	Controlled clinical studies conducted to evaluate the effectiveness of a drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term adverse effects and risks (*c.* 100–300 people).
Phase III	Expanded controlled and uncontrolled trials to evaluate the overall benefit/harm balance of the drug and provide a basis for labelling (*c.* 1000–3000 people).
Phase IV	Post-marketing studies to delineate additional information, including the drug's long-term adverse effects, benefits and optimal use.

Table 2: A summary of the organization of clinical trials. Adapted from: www.clinicaltrials.gov/ct2/info/glossary (visited 5 June 2013), and reprinted from Reynolds and Tansey (eds) (2008), page 10.

ranging study, a Phase IIB study with that molecule, thinking it might fail because we had seen no signal in the Phase I studies that there was a positive effect on cognition. It's very hard in Phase I to see an effect on cognition, but we hadn't seen any signal at all. I wanted to have a clear-cut result, and there were a lot of people within GlaxoSmithKline at the time who were saying that I should do a small, IIA study, and what you would have got was 'Junk In and Junk Out'. Because of the variability with Alzheimer's in a mild to moderate population, you needed to do a big enough study. Amazingly enough it worked. I think that points to the fact that you've got to really understand your patient population to be able to test the hypothesis, and sometimes it does mean doing a larger study. I've seen studies done by industry where they've done a one month, one dose, 40 patient group study in mild to moderate dementia. You will never, ever see a positive effect, even if you've got a compound that works. The clinical knowledge is very important but also it's having some of the other tools that you can use to really test whether your molecule has the right legs to make it.

Flower: Tom, you mentioned earlier that such a high proportion of the top 20 drugs came from the 5-HT programme and you said that it would be interesting to know what other 5-HT drugs there are in people's pipelines.

Blackburn: How many of us are still actively involved in 5-HT research would be interesting to hear. Jackie, with the 5-HT_6 or other people who know about compounds moving forward, because if you look at that Scrip *Report* for 1988, there's a vast array of different 5-HT compounds, but very few, if any, actually made it to market.[295] Certainly the 5-HT_3 antagonists have been a spectacular success in their own right, as has sumatriptan. But the 5-HT_{2A}/dopamine D_2 pharmacology has obviously been a very important area too in schizophrenia and it would be just interesting to hear more about the successes, did anything even come out of 5-HT_{1A} area? These are the sort of questions we should address.

Flower: Let's talk a bit about the legacy of the area and what's coming.

Dourish: To address the 5-HT_{1A} receptor, Tom, as far as I'm aware buspirone, which is used to treat anxiety, was obviously not discovered as a 5-HT_{1A} compound but subsequently, when we started characterizing 5-HT_{1A} receptors, it looked like that was one of its main effects. Then Bayer went on to develop ipsapirone as an anti-anxiety drug and Bristol-Myers' buspirone follow-up was gepirone. But none of these compounds were really any more effective than buspirone. So, a lot of companies – Wyeth were the leaders at one point, obviously now it's Pfizer – tried to develop 5-HT_{1A} antagonists with the idea that they'd either be effective as anxiolytics or antidepressants or potentially cognitive enhancers, or have other beneficial effects in the CNS. Again none of those compounds has ever got beyond late Phase II and so this area has not been terribly successful. Whether any drug that acts at the 5-HT_{1A} receptor (with the exception of buspirone) is likely to be marketed to treat CNS disorders, I think the evidence that I've seen would suggest not at the moment.[296] In terms of other compounds that are in development, I think we mentioned the 5-HT_{2C} approach; clearly that's being looked at in a lot of different areas including psychiatric disorders, such as anxiety and depression.[297] But for now where those 5-HT_{2C} agonists seem to have found a place is in the treatment of obesity, where the first agonist lorcaserin has got on the market.[298] In terms of the other things we haven't discussed very much, for depression there are the SSRIs and then the SNRIs and the add-ons, and that's certainly still a fruitful area for a number of companies.

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[295] Scrip (1988).

[296] Dourish (1987); Fletcher, Cliffe and Dourish (1993).

[297] See, for example, Stahl *et al.* (2013).

[298] Dourish (1995). Belviq (lorcaserin), manufactured by Arena Pharmaceuticals, was approved in the US in June 2012 to treat overweight or obese adults.

A number of companies have got compounds that are add-ons to the SSRIs in development with interesting components that the SSRIs may not have. So in fact Phil [Cowen] and I were just discussing a compound that Lundbeck have developed called vortioxetine, which looks interesting, and they've submitted for regulatory approval so it may be approved next year. We were discussing how this compound has been described and there's a new term apparently called a multimodal antidepressant. We used to call it a dirty drug. Hopefully it's without some of the unwanted effects of SSRIs and SNRIs. Vortioxetine has got a whole range of receptor affinities and the interesting thing is that it may have some cognitive-enhancing properties that, if you can add that into treatment of depression, clearly is going to be very interesting.

Blackburn: I know this compound very well because when my first biotech company, Synaptic Pharmaceuticals, was bought out by Lundbeck in 2004, the compound which I was developing at the time lost out because it was too innovative. It was a galanin R3 receptor antagonist that has a very similar profile to an SSRI, with hopefully fewer side effects associated with SSRIs. Because this compound was too innovative, the multimodal LU AA21,004 (vortioxetine), which was a mixed SSRI, 5-HT_3, went ahead.[299] However, thankfully the galanin R3 compound is still alive today with another company and in a Phase II study for depression, so I still know of a compound which modulates 5-HT, somewhere in development.

Sanger: One of the ways forward is, perhaps, to avoid concentrating just on 5-HT but to look at the whole tryptophan pathway, and in the GI area there are tryptophan hydroxylase inhibitors that have gone into Phase 2, although I'm not sure where they are now. People are getting more interested in melatonin and its receptors and the kynurenine metabolism pathway.[300] It's a way of broadening out from just 5-HT and avoiding the regulators and finding other ways of making drugs.

Miner: I would like to make a comment. I worked on the periphery of a 5-HT_{1A} project in industry and we were looking at 5-HT_{1A} antagonists for visceral pain. It was a terrific concept, but about a year down the line we found several of our compounds were agonists.

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[299] See, for example, Baldwin, Hansen and Florea (2012).

[300] For melatonin in the GI tract see, for example, Zagajewski *et al.* (2012); for depression and kynurenine pathways, see, for example, Oxenkrug (2013).

Green: We've currently got quite a lot of interest for one reason or other with MDMA and Dave Nutt's trial.[301] We've got a terrific 5-HT releasing drug there that he's now looking for post-traumatic stress. He was asking what else we can release 5-HT with, and I said that he has fenfluramine, but he said that it doesn't work in the same way clinically. So again there's something special about MDMA, but that may be because it also releases dopamine. We're getting to a generality of hitting the brain with everything and 5-HT has to be playing a role there somewhere. If David [Nutt] and the other people in the States can show that MDMA really does have clinical efficacy, it's important.

Hoyer: 5-HT_{1A} may not be completely dead, since Adrian Newman-Tancredi still thinks that 1A compounds have a great prospect in pain and other indications.[302] We will see, he has just created a company to elaborate on this.[303] The 5-HT_2 story, actually 5-HT_{2A} story continues, iloperidone was recently registered as a dopamine D2, 5-HT_{2A} antagonist (with many other activities like a number of atypical antipsychotics). Whether it's going to be the best antipsychotic on earth, I have serious doubts, but at least they managed to register it; I don't know how they did it. Furthermore, Servier registered a drug with melatonin 1 and 2 agonist combined with 5-HT_{2C} antagonism, agomelatin.[304] Their argument is that 5-HT_{2C} antagonists will increase dopamine in the right place and have antidepressant effects, which is a very twisted way of achieving it. The melatonin component should, of course, be beneficial for sleep. If you can treat sleep in depressed patients you may have some mileage as well, because most depressed people don't sleep very well, or sleep too much, or at the wrong time of the day. The problem with a melatonin agonist is that you have to administer it at the right time. If you give it in the morning then it may not work, you have to give it in the evening. 5-HT_4 is still ongoing. Pat can tell us more, one of his compounds from Theravance is undergoing development.

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[301] Professor David Nutt and Professor Val Curran carried out a trial to look at the effects of MDMA (ecstasy) on 25 healthy volunteers under laboratory conditions. *Drugs Live: The Ecstasy Trial* was televised on Channel 4 in September 2012. For a discussion of the potential medical uses of MDMA, see Sessa and Nutt (2007) and the subsequent discussion (Green, Marsden and Fone (2008); Sessa and Nutt (2008)).

[302] Newman-Tancredi (2010).

[303] Dr Adrian Newman-Tancredi is co-founder and Chief Scientific Officer of the biopharmaceutical company, Neurolixis Inc, which was founded in 2011 to carry out research 'focused on the discovery, development and commercialization of novel drugs for the treatment of human central nervous system diseases including depression, schizophrenia, Parkinson's disease, ADHD and autism.' See www.neurolixis.com visited (24 April 2013).

[304] Carney and Shelton (2011).

Humphrey: Theravance has a very good compound, velusetrag; clean as a whistle, does what it's supposed to do and it's a full agonist rather than a partial agonist like the prototypes, metoclopramide and cisapride, but the problem is that big Pharma is reluctant to develop such a compound because of the perception that there's likely to be an issue with the FDA, stemming from cardiovascular concerns with tegaserod.[305] Nevertheless it's been in a lot of patients and careful cardiovascular studies have been done and they are continuing their efforts to attract a partner. I do believe that they may have done a deal, but I can't talk about it and I don't know anything about it anyway.[306]

Flower: Colin mentioned the SSRIs and we haven't really paid any attention to those and we should. So far we've concentrated on receptor agonists and antagonists, but would anyone like to say something about the uptake inhibitors?

Professor Phillip Cowen: I'm the tame psychiatrist here and I think that SSRIs have transformed the treatment of major depression, in the sense that they're now a first-line pharmacological treatment in any depression guideline.[307] I suppose it wasn't too surprising that SSRIs worked in depression because we had the example of the tricyclic antidepressants, we knew that they blocked the uptake of 5-HT and I think clinicians seemed to prefer using the tricyclics, like amitriptyline that had a rather more prominent effect on 5-HT, than they did on noradrenaline.

SSRIs are not just antidepressants – they've become a cultural issue that you could have a whole meeting about anyway, you know, *Listening to Prozac* and all that.[308] I guess SSRIs are rather better tolerated than the older antidepressants and I would say that they're perhaps a little less effective. On the other hand they're safe in overdose and they work very well in anxiety. Also I was just thinking about Charles' comment that: 'How can a simple pharmacological action translate into efficacy in such a complex condition' in terms of something like major depression, because if you think about it, there are abnormalities in so many neuropsychological and biological domains. Really an SSRI isn't doing

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[305] Manabe, Wong and Camilleri (2010). See also page 72 and note 227.

[306] Theravance, Inc. and Alfa Wassermann announced in October 2012 that they had entered into an agreement to develop velusetrag, Theravance's investigational 5-HT_4 agonist for the treatment of gastroparesis. The phase 2 proof-of-concept study was announced in January 2013.

[307] Harmer and Cowen (2013).

[308] Kramer (1993); Wurtzel (1994); Metzl (2003).

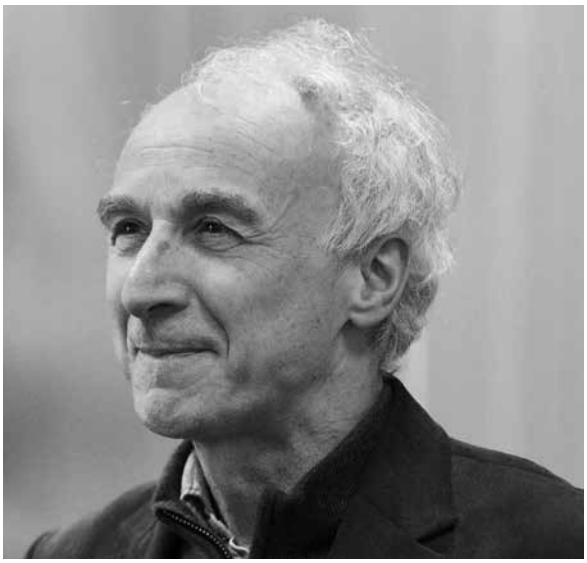

Figure 24: Professor Phillip Cowen.

very much, it's just boosting the action of 5-HT a bit in a rather general way, and somehow, surprisingly, this simple effect can sometimes be enough to make all of those really nasty psychological and biological symptoms go away.

We don't know much about the neuropsychological effects of SSRIs at the moment. However, there are some quite interesting effects on other psychological processes that we don't normally think about, such as emotional processing and pro-social behaviour. We've talked about how people researching in 5-HT tend to be rather kind and community-minded and, of course, in animals and in some human trials, if you boost 5-HT, animals and people behave rather more nicely. It does tie in with my own experience in that I once took Seroxat for three or four weeks for a study and at the end of it I didn't notice any difference in how I felt, but my wife asked if I could stay on it. [Laughter]

Blackburn: I spent about ten years as a sort of 'front person' for paroxetine (Seroxat/Paxil) at SmithKline. Visiting psychiatrists, from Europe and America, were presented with pre-clinical and clinical data. Sometimes it was very difficult to find a clinician who would actually step up to the mark, which often left me presenting the pre-clinical and the clinical pharmacology. However, it was fascinating to get the feedback from the neurologists and psychiatrists on their clinical observations, like the effects on sexual dysfunction, seen more in the garlic-eating southern European countries rather than north European countries.

With such observations, how do you design a test, to look at sexual dysfunction in garlic-fed rats? But, apart from that, it was all good clinical feedback.

Flower: I can see that would be a challenge.

Blackburn: There were lots of other observations coming out of the clinic. I remember one Dutch neurology group who were very interested in whiplash syndrome in their specialist centre in Holland, and they swore by SSRIs for the treatment of whiplash injury. Now whether the drug was relieving depression associated with severe whiplash syndrome or increasing the pain threshold which 5-HT is well known to do within the spinal cord, is something that is still unclear. So there were lots of observations coming out of the clinic with these compounds, which were helping us basically to design the next generation of 5-HT compounds.

Clarke: There may be room for dual uptake inhibitors, even triple uptake inhibitors. Duloxetine, which Tom mentioned, is earning a lot of money,[309] it's a terrible drug to take for many people and nausea is a big problem with it, 16 to 19 per cent of patients are nauseous. The other thing is sweating, you get a lot of sweating when on the drug. But the interesting thing is that, although it is an antidepressant, it's also one of the very few drugs that will work in neuropathic pain and it's on the market for neuropathic pain in the United States, and in addition it is a drug that works in the lower urinary tract for stress urinary incontinence. That area, for instance, hasn't had a really effective new drug mechanism in years, except mirabegron, so there may well be room for a new compound. But the key would be: how do you stop nausea, or how is it mediated, and when you block noradrenaline uptake one gets noradrenergic cholinergic sweating and what are you going to do about that? So those are two questions but I wouldn't necessarily write off new dual uptake inhibitors.

Wallis: Of course, what an SSRI does depends on the activity of the neurons it targets. I just wondered, and this is a question really for the psychiatrists, what use they have been able to make of the studies done by Barry Jacobs where he records from single serotonergic neurons in conscious cats under various behavioural situations and charts the change in activity and relates them to behaviour.[310] Has this been of any help in deciding what SSRIs are doing to a human?

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[309] See page 99.

[310] Professor Barry Jacobs is Professor of Psychology at Princeton University; see, for example, Horvitz, Stewart and Jacobs (1997).

Cowen: There's a short answer, which is unfortunately 'no'. I think what Barry pioneered was the goal of conceptualizing the action of 5-HT in a single neuropsychological formulation. This is hard to do because, as we've said, 5-HT has got so many actions in the brain and affects so many processes. I think Barry also said that 5-HT is involved in everything but responsible for nothing.[311] People have tried to capture that complexity in a single overarching function, as Barry did himself. However, because Barry's concept focuses on motor behaviour, it doesn't fit in very easily with the kind of emotional disorders that SSRIs are used to treat. The formulations you see done by people working in computational neuroscience now would be more like the notion that 5-HT has the role of signalling aversive experience and for dealing with it. That's another overall way of conceptualizing its function.

Wallis: Barry Jacobs' emphasis on exercise and the effect on motor neurons being facilitated has prompted him to promote exercise as a way of increasing your 5-HT levels and treating depression.[312]

Aronson: I'm interested in adverse reactions to the SSRIs. If a drug turns up an adverse effect that translates into an adverse reaction, everybody throws up their hands in horror and the drug is withdrawn or it's contraindicated or restricted. Sometimes you can learn something from the adverse reaction, and I'm particularly interested in the suicidal ideation that young people get from this. Older people don't seem to, if the evidence is the way it is. I wonder if we can learn something from that observation. Phil's reply to the last question makes me not too sanguine about that, but nonetheless I think we should turn adverse reactions to our advantage by thinking about what causes them and whether we might learn something from them.

Blackburn: That was my question. I really want to understand from our clinical colleagues why suicidality was perceived as such an issue for 5-HT CNS compounds. It appears that the regulatory authorities are now seeing this with many classes of CNS compounds, including anticonvulsants, so it may not be specifically related to 5-HT compounds?

Cowen: As always with SSRIs you can take a number of different positions. At a population level increased SSRI prescribing seems to be associated with lower suicide rates, if anything. On the other hand, you see individual case

[311] 'Serotonin is an enigma. It is at once implicated in virtually everything, but responsible for nothing', Jacobs and Fornal (1995), page 461.

[312] Jacobs (1994).

reports where people seem to become agitated and distressed and do something dreadful when they first go on treatment.

I think Jeff's point is a good one, that if you look at older depressed people SSRIs are protective against suicide, but in people under 25 there's an increase of suicidal behaviour on SSRIs.[313] At the moment the controlled trials don't show an increase in what's mistakenly called 'successful suicide', what you see is an increase in suicidal acts and it's hard to know what to make of that. Is it that the 5-HT system is differentially developed in young people, so the drugs have a different effect; or, is it that if young people get a bit revved up by any kind of antidepressant drug they're more likely to harm themselves impulsively? So I don't think people understand the mechanism, but there certainly is a phenomenon to explain.

Hunter: Jeff's point is a good one and it would be interesting to explore that more. In an age where reimbursement is king, I'd like to challenge how much mileage there actually is in serotonin reuptake inhibitors and whether or not the comments made earlier about more selectively targeting release through intermediate mechanisms is something to focus on. There are obviously issues in depression trials anyway, where you have to do three trials to get one or two working. That's something that, if it's not sorted out, will not really encourage Pharma companies to invest, considering large-scale Phase III failures like the Targacept AstraZeneca nicotinic agonist, and it is a real issue.[314] Maybe we are deluding ourselves that somehow there is more mileage in the serotonin uptake inhibitor area?

Andrews: To pick up on the point about looking at the side effects, particularly in relationship to nausea, because this is something I've been working on, looking at why certain drugs have a particular nausea or vomiting liability and trying to find ways of identifying this much earlier in the pre-clinical studies,[315] bearing in mind, of course, rats and mice don't vomit.[316] Also to say that there are studies on-going at Queen Mary, University of London that Gareth and I are both involved in, brain imaging in human subjects, looking at the central

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[313] Barbui, Esposito and Cipriani (2009).

[314] AstraZeneca and Targacept announced in 2012 the failure of the drug TC-5214 in the randomized, double blind, placebo controlled Phase III studies.

[315] Percie du Sert *et al.* (2012).

[316] Horn *et al.* (2013); Sanger, Holbrook and Andrews (2011).

pathways involved in nausea, so if it works we can identify particular areas that, in theory, one could then go on and look at whether these areas are or aren't activated in certain pharmacological treatments.[317] So I agree with you, looking at side effects of well-characterized drugs gives us a map if you look at it systematically.

Reynolds: Implicit in all this discussion about side effects and responses is the concept of individual variability, which brings us to personalized medicine, which of course some drug companies are beginning to embrace, though somewhat reluctantly. It's interesting that it's the 5-HT transporter that has really been central to individualized medicine in psychiatry. It was Lesch's work on the short/long variants polymorphism in that area that's really sparked a huge development of pharmacogenetics.[318] And we see that 5-HT_{1A} has a very important polymorphism too that may well explain quite a lot of the differences between individuals in responses to drugs. So I think this is where the field is developing and we would hope that the pharmaceutical industry might embrace personalized medicine rather more strongly than they have done in the past.

Flower: With 14 receptors to pick from there's a lot of work on polymorphisms to be done.

Reynolds: There is, and there are a lot of people doing it, of course.

Marsden: I was just going to say that most of the pre-clinical work on SSRIs in rats is done on sexually mature rats. There's very little work that has compared the treatment in young, non-sexually mature with the sexually mature rat. If you look through the limited data available, there is evidence for differences in behavioural response to certain SSRIs between the young and mature rat that might have clinical relevance. We did do some of this type of work that was funded by a drug company and unfortunately we were unable to publish the results. We found, and there's now stuff which has appeared, that says the same thing, that you get a greater aversive affect in a young rat treated with an SSRI in the acute phase than you do in a mature rat.[319] So maybe there should be more work along that line?

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[317] See Ng *et al.* (2012).

[318] Lesch *et al.* (1993, 1996); Costafreda *et al.* (2013).

[319] See, for example, Fernández-Guasti, Ulloa and Nicolini (2003); Herrera-Pérez, Martínez-Mota and Fernández-Guasti (2010); Iñiguez, Warren and Bolaños-Guzmán (2010).

Green: The other problem, it seems to me, and we've known this since about 1970 at least, is that if you take a normal rat and you give it an SSRI, the first thing that happens is 5-HT synthesis shuts down. We still have even Phil saying: 'Well, we give SSRI and we increase 5-HT function.' I don't think we really know what is going on. Certainly that happens acutely but I've never heard anyone explain it. We give the drug, something acute happens, and then there's this sort of black box for about two weeks, which is what the psychiatrists say is about the time these drugs take to work, and then we get an effect. What's happening during that period? Is it just that the brain takes a long time to adapt and for us to see an overt antidepressant effect? Or is the brain altering very fundamentally as the result of this insult and something else much more important is going on? I've never heard anyone explain why there is this long interval between starting to give the drugs, measuring various biological markers like inhibition of uptake in platelets and things like that, and then the clear antidepressant effect. We know that some patients will change almost overnight, it's rare, but it happens. We know you can get a mood change happening quickly but these drugs don't do it, do they?

Cowen: No. I think if someone switches mood very quickly after starting SSRIs, it normally means that you've made them manic. Obviously some kind of manipulations can produce very rapid changes: sleep deprivation and more recently IV ketamine. In David Grahame-Smith's lab we spent many years trying to identify what neuroadaptive changes might underpin antidepressant action, we went through beta receptors and alpha 2 receptors, then the desensitization of the 5-HT_{1A} receptor.[320] Current activity focuses on changes in brain-derived neurotrophic factor (BDNF) and synaptic plasticity.[321] We're always searching for the molecular secret that underpins the antidepressant action. More recent work looking at the neuropsychology of antidepressant action suggests that emotional processing changes very rapidly after treatment initiation so, at an implicit level, one is rather emotionally different but you don't feel better. One reason for the delay in feeling subjectively better is that you have to, in a sense, learn where you are again in an emotionally transformed world. So that's a psychological explanation of why it takes a long time for SSRIs to work.

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[320] Cowen *et al.* (1982); Metz *et al.* (1983).

[321] See, for example, Dwivedi (2013).

Sanger: This is a naive observation, but since the SSRIs hit the market, has CNS research really moved on very much in terms of 5-HT research? What's actually come out of it and why do I keep hearing of receptor studies that have not worked or not gone beyond a rat. Is it time to move on?

Blackburn: Gareth used to ask this question of me in the 1990s, so nothing's changed! We're talking about understanding multiple receptor subtypes and the pharmacology associated with them, whether it's in the periphery or the CNS. One of the articles I read some years ago and I always try to relate to regarding neurohormonal changes, is the work of Bruce McEwen from Rockefeller, New York, where he talks about non genomic and genomic activity where there's a receptor event, however transient or prolonged, and then there's a more prolonged effect through transcription factors.[322] We're only just starting to get to grips with a lot of these mechanisms of action. To answer your question, Gareth, there are a number of compounds, one of which was mentioned earlier, lorcaserin (Belviq), a 5-HT_{2C} agonist for obesity, that has cost Arena Pharmaceuticals over $1 billion to develop to overcome the safety problems related to the 5-HT_{2B} affinity of the compound that's been associated with cardiac hypertrophy.[323] So like Lorcaserin, there are other compounds coming through as we've heard today, for 5-HT_6 and 5-HT_7 and others we're still waiting on.

Clarke: This is just for my own interest: do you know whether ondansetron blocks nausea with duloxetine? Does anyone know?

Cowen: There's been some work showing that if you give ondansetron you can block nausea induced by fluvoxamine.[324] On the other hand, the drug we just mentioned, vortioxetine,[325] is an SSRI, it also blocks 5-HT_3 receptors and causes as much nausea as a standard SSRI. As Colin said, vortioxetine has other actions too that complicate interpretation. What we need is a proper study with more selective compounds.

Clarke: It seems pretty basic.

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[322] McEwen (1991). Professor Bruce McEwen has been Head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at Rockefeller University since 1981 and Alfred E. Mirsky Professor since 1999. His research focuses on how stress and sex hormones react on the brain.

[323] See pages 74 and 112 and notes 231 and 298.

[324] Bailey *et al.* (1995).

[325] See page 113.

Dourish: I was just going to address Gareth's question about SSRIs. Most companies in the area have moved on from SSRIs, with the exception perhaps of vortioxetine, and what's really driving the depression field now is the observation that Phil mentioned, which is the rapid onset antidepressant effects of IV ketamine. Many companies are very interested in that and clearly the issue with ketamine is that it has other effects apart from an antidepressant effect, but there are NMDA compounds such as AZD 6765 now that are in late phase trials that appear to have the antidepressant effects without having these sort of dysphoric or euphoric effects.[326] In response to the original question, no, these compounds don't act on 5-HT receptors. I think the common view is that that the SSRI path is exhausted and that's why they're now looking at excitatory amino acids.[327]

Flower: 5-HT has obviously been a very highly successful area. Is it a general model for drug discovery, do you think? It does seem to have been characterized by an unusually good rapport between the academics, the clinicians, the industrial scientists, the Pharma companies and everybody else. Is this a sort of exemplar of how drugs should be discovered, given the fact that we have such a fantastic output from the area in terms of blockbuster drugs? What do you think?

Bakhle: We now have 14 receptors and perhaps an unknown number of uptake mechanisms – and how many drugs do we have out of it? I mean usable medicines – really rather few. We think that one of the successes, practically speaking, is an SSRI which, by definition, doesn't affect any particular receptor. Is pharmacology becoming too obsessed with 'the receptor' and the unique single action drug? Have we done all we can with that one specific drug idea? Do we now have to change and say that we have to go for what we used to call, and still do call, 'dirty drugs' with all the things that we feel as wrong?' Polypharmacy – Joe Collier used to spit upon its grave.[328] Okay, he was a pretty aggressive guy but there are lots of clinical pharmacologists who think that polypharmacy is trash; should not be allowed, etc. However we have also been told about the polypill, me included, I'm a 'mild hypertensive' but I've got

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[326] Zarate *et al.* (2013).

[327] Hashimoto *et al.* (2013).

[328] Professor Joe Collier (b. 1942) was Professor of Medicines Policy and Clinical Pharmacology at St George's Hospital and Medical School, London, until his retirement in 2007. He was a participant at the Witness Seminar on clinical pharmacology (Reynolds and Tansey (eds) (2008)).

four drugs to take, including a statin. Now are we too obsessed? Should we now think of pharmacology no longer in terms of single receptors, but accept the fact that we should go functionally for an effect, a physiological and/or pharmacological effect? In a sense, damn the torpedoes, let's go for the effect. Because if you were to look at this area of pharmacology, you would say: 'I've got 14 receptors beautifully categorized, but what good are they doing me in terms of medicine?'

Flower: Okay, that's a very provocative thought.

Humphrey: You've just woken me up, Mick. Seriously, that's a real challenge, and I'm horrified by what you say. Combination therapies are very, very important. Look at asthma – you inhale a steroid and you inhale a bronchodilator and you transform the treatment. Hypertension – most people have more than one form of hypertensive drug and it transforms the tolerability and the efficacy and everything. So combination therapy is a good idea, but the minute you move away from Ehrlich's magic bullet, i.e. not using specific and selective drugs in any combination, it is at your own peril because you don't know what you're doing.[329] You don't know what you're dosing, you don't know what you're giving anybody. The challenge is that we've got to work out what these receptors do and how we can harness them, but just because they're there doesn't mean God put them there so we can make a drug. They're there for other reasons, maybe, and they may not be functional. So don't get too hung up on: 'We've got to find a drug for every receptor.' We've got to work out the physiology and pharmacology *in vivo* and then harness what we can.

Hunter: I think we're entering an era where I personally believe that with human genomics, transcription genomics, the data coming out of human biology will be much more powerful than doing a lot of transgenic models, etc. The question for us is how to get that information into making a compound that affects that pathway and then iteratively going back into the clinic to test whether that has a significant action. That's going to be a challenge because it's a very different way of thinking about things. We may find from the computing power of the big data sets that the potential for optimal combinations, rather than random screening, is going to be very interesting. That's one area where we may see progress in terms of thinking about different combinations. Like all paradigms,

[329] Paul Ehrlich (1854–1915) was a German immunologist whose concept of drugs designed to attack specific targets, or 'magic bullets', revolutionized the treatment of disease. He shared the Nobel Prize in Physiology or Medicine in 1908 with Ilya Ilyich Mechnikov 'in recognition of their work on immunity'.

there are aspects that are good but it will also need champions as all successful molecules do. For example, paroxetine was an in-licensed molecule and as such had champions within the organization which promoted it at times when it would have been usual to stop development or 'kill off' the molecule. It was only the fact that it was an in-licensed molecule that meant that people had to do something with it, that really pushed it ahead to be the success that it was.[330] There are champions and circumstances that can change things. So there are aspects that are good, but there are a lot of receptors and a lot of money is being spent on trying to find those particular tools and the actual disease they may be useful for. Maybe there are some lessons to be learnt and actually are there some areas where one is better doing things precompetitively rather than alone?

Blackburn: I mentioned earlier the American Chemical Society article that looked at the top psychiatric medicines prescribed in 2011 to address Mick's question: 'How good have these been?' (see Table 3)[331] Number one is alprazolam, Xanax, and that drug achieved 47 million prescriptions in 2011. Celexa and Zoloft are numbers two and three and between them they've achieved 70 million prescriptions in 2011. Then we get another benzodiazepine, number four, and then Prozac, which is still selling 24 million prescriptions a year. After Prozac comes Lexapro and then trazadone (Desyrel), a trazidole that is a 5-HT_2 blocker plus SSRI which is used mainly for its antidepressant–sedative properties and a number of other properties, achieving 22 million prescriptions in 2011. Then there is duloxetine (Cymbalta) at 17 million and then Seroquel at number ten, with 14 million prescriptions. Thus, of the top ten drugs prescribed in 2011 the majority of them have a 5-HT-related mechanism of action. So I think it is obvious that 5-HT-like drugs have had a major impact, particularly in psychiatric medicine.

Bakhle: Because there are a zillion prescriptions doesn't mean anything in my context. The question I'm really asking is: are we treating the diseases for which we use these 5-HT drugs as well, in terms of patient outcome, as we treat hypertension? You may prescribe as much duloxetine as you like, but if half of the people who take it are puking and the other half are committing suicide or whatever, I'm saying the actual prescription rate, the fact that you use these compounds, doesn't answer the question: is the disease actually being treated

[330] Dr Jackie Hunter wrote: 'The fact that it was an in-licensed compound meant it was visible and much harder not to commit to solving development issues – in turn this focus, and the fact it was effective, made it into the successful drug it was.' Email to Ms Caroline Overy, 18 June 2013.

[331] Lindsley (2012). See also page 99.

Brand name drug (generic name)	Prescribed / indicated for	2011 prescriptions (in millions)
Xanax (alprazolam)	Short-term use in anxiety	47.7
Celexa (citalopram)	Depressive illness; panic disorder	37.8
Zoloft (sertraline)	Depressive illness; OCD; panic disorder; PTSD; social anxiety disorder	37.2
Ativan (lorazepam)	Short-term use in anxiety or insomnia; status epilepticus; peri-operative use	27.1
Prozac (fluoxetine HCl)	Major depression; bulimia nervosa; OCD	24.5
Lexapro (escitalopram)	Depressive illness; generalized anxiety disorder; OCD; panic disorder; social anxiety disorder	23.7
Desyrel (trazodone HCl)	Depressive illness especially where sedation required; anxiety	22.6
Cymbalta (duloxetine)	Major depressive disorder; generalized anxiety disorder; diabetic neuropathy; stress urinary incontinence	17.7
Valium (diazepam)	Short-term use in anxiety or insomnia; acute alcohol withdrawal; status epilepticus; febrile convulsions; muscle spasm; peri-operative use	14.6
Seroquel (quetiapine)	Schizophrenia; mania; depression in bipolar disorder	14.2

Table 3: The top psychiatric medicines prescribed in 2011 using information adapted from the *British National Formulary* and 2011 prescription data from Lindsley (2012), page 631.

adequately or better than we could, say, ten years ago? Maybe there is a real advantage; if there is, fine. I'm putting a question to you and I'd like to see it in terms of patient outcome rather in terms of prescription.

Hoyer: Mick has a point, actually he has several points. But the proof of the pudding is in the clinic. We can do as much as we want with normal animals in pre-clinical studies, but it is the clinic that will give you the answer. The problem is that not so long ago most of these diseases, at least the brain diseases, had very poor clinical or biological definitions in the first place. The *DSM-V*

will come out some time next year with a more, bigger emphasis on biology.[332] So far most of that stuff was purely descriptive, so we talk about depression; it doesn't mean anything to me. 'Hypertension' doesn't mean anything to me: some guy will react to a calcium antagonist, another guy will react to beta blockers and another guy will need diuretics, an angiotensin antagonist, or a renin antagonist. When I started, I was told repeatedly by marketing that what we need is monotherapy because that's the only way you can sell compounds. And guess what? We've gone full circle. Now we're prescribing fixed combinations of angiotensin antagonists, calcium antagonists and maybe renin antagonists to patients, only to find out that occasionally we do too much, so you should perhaps take one away. The fixed combination is not going to be the answer. We do have compounds that are, what are called, 'dirty', but even these dirty compounds will work on some part of the population; how well or not well described is the population. Personalized medicine will work once we know the biological basis for the disease and then we will know what we will need to get to patients. Asthma is the perfect example, where a long-acting beta 2 agonist is great, yet will not work in isolation. I'm not sure I would take one, given what I know. But you take these steroids and you take this and you take that, so we go to chronic obstructive pulmonary disease (COPD) and we add a long-acting muscarinic compound and then it will work. We know that in these indications monotherapy does not work. Hypertension is pretty much the same, monotherapy is useless. I don't know of any patient that suffers from hypertension that has a monotherapy that works effectively, so they take more and more. In depression we know by tradition that people are just mixed bags, it's the cocktail. Again, the question that we are trying to answer is: what is the disease you want to treat and what is the biological basis for this disease? In many cases we don't know yet what it is. We do guesswork and by the end of the day the smart clinician will try compounds, sometimes even off label, in combinations and find out what works best for the patient. Epilepsy is another: there's no single treatment for epilepsy, although I can mention two or three that would work perfectly well, except that the compounds are probably in the clinic. So what we do is combination. Every patient has combination treatment and yet 40 per cent of these guys eventually will undergo surgery to get a piece of the frontal lobe or hippocampus taken out and this is the thing that works best. In Parkinson's disease you also have combination treatments because monotherapy doesn't work; l-DOPA alone doesn't do anything, you have to

[332] The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) was published in May 2013 by the American Psychiatric Association. It is the standard classification for mental disorders.

help with a DOPA decarboxylase inhibitor, and then you put the D2 agonist and you keep going. After about ten years of treatment these people are in a bad shape and there's nothing you can do, and for some people what we do then is deep brain stimulation. So personalized medicine is coming but we need to know what the disease is all about, so we're still searching and there's hope. Coming back to the question asked by Mick: single treatment will work in some cases and we know perfectly well that some people with migraine react extremely well to sumatriptan or to zolmitriptan, but I do know some people don't react to zolmitriptan, when sumatriptan works. How is that feasible? In principle, it's the same mechanism but it's not the same drug. Probably the receptor repertoire from one guy to the other is a bit different. We haven't talked about epigenetics and we know very well from Bruce McEwen and a number of other people that there are modifications depending on your experience.[333] Post-traumatic stress disorder (PTSD), where you have been undergoing mistreatment and all kinds of traumas in your youth, will change your way of reacting to compounds and some depressed people will react to SSRIs, while others will not. We haven't talked about neurogenesis. Half of the population will believe in neurogenesis; the other half will say that it is bad science and it is never going to happen, because 20 years ago we said there was no neurogenesis in the brain. Now we know that there is neurogenesis and we know that 5-HT and some treatment in the hippocampus will induce neurogenesis and it has to do with BDNF etc.[334] But we don't have the right tools to work on BDNF for the time being so this is all up in the air. The Human Genome Project that was supposed to solve everything when it was published in 2001 has actually created an awful mess and I'm not talking about the epigenome. Was 5-HT the right example to be followed by people in the industry and academe for the next targets to come? I think it was the right example at the right time, but things have changed. Now everyone needs biologics and things like this, and you cannot get excited by the next small molecule, although I still believe that there's mileage in these as well. But with biologics you can ask $400 000 a year to extend your life for about six months or something like that, which you cannot do with a simple low molecular weight anti-hypertensive. So this is one of the major issues we are facing; Wall Street is still trying to dictate what people are doing and what big Pharma is doing. This is wrong, and one has to react at some point, because

[333] McEwen and Getz (2013).

[334] Quesseveur *et al.* (2013).

the whole mess that has been created in the last five or ten years is because of analysts, Wall Street and the bankers. The bankers have shown us that they are totally incompetent to start with, so what are we talking about?

Flower: Thought for the day.

Sanger: Gerald will probably be more sensible than I am. I can't add to what Danny said because he went through a *tour de force* beautifully. I was simply going to react to my own area, where I look at IBS, and one of the biggest drugs that's prescribed there is a proton pump inhibitor (PPI) that inhibits gastric acid.[335] I have a relative with slow transit constipation, who was prescribed a PPI. It's crazy, absolutely irrational, but that's the logic of prescription because there is nothing else and poor understanding of that syndrome. I think you just have to be so careful with these patients. But I agree with everything else everybody said.

Blackburn: These 5-HT drugs are out there in the clinic, whether their efficacy is 30 per cent of the population or 50 per cent of the population. But these drugs do show efficacy in patient populations.

Sanger: Perhaps marketing would say that the area is saturated?

Blackburn: Yes, and one could argue, and argue justifiably, that the SSRIs were a huge marketing success and rightly so. But at the end of the day they are efficacious and if you've sat at FDA meetings and listened to some of the patient groups, yes, they do work, however not for everyone.

Curzon: One of the things we were asked to address was the general question of tensions and collaborations between scientists and industry. I have had a quite long and sometimes tense collaboration with Servier, the only drug company that I've had much of an involvement with. When I began this about 20 years ago, they seemed to tie me up with a formidable legal document but what can they do to me now anyway?

They developed a novel antidepressant, tianeptine. What was novel about it was, unlike conventional antidepressants, *in vitro* studies suggested it didn't increase extracellular 5-HT but decreased it. I said this seemed unlikely and furthermore that the new technique of *in vivo* dialysis could show whether they

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[335] Omeprazole.

were right or wrong. They offered a grant to study the question. It did indeed turn out that it decreased *in vivo* dialysate 5-HT, which pleased Servier, and a number of useful research grants followed, which was very nice for me.[336]

There was also something else that, as a laboratory scientist previously supported by public bodies, I'd never had generous travel expenses. I know clinicians are spoilt for choice in this kind of thing but that was not my situation. They gave me a list of the following year's international meetings and told me to pick and choose whatever I wanted.[337] As it says in the Bible: 'The devil had taken me up to a high place and showed me all the kingdoms of the world.' I am a glutton for travel but I couldn't help feeling a bit uneasy.

The next thing was that Servier rang and asked me to speak at a series of meetings in Pakistan, a country I'd never been to: Karachi and Lahore, Multan. I hadn't even heard of Multan. Also Peshawar, up on the North West Frontier. The meetings were to be entitled 'Tianeptine: a new powerful antidepressant and anxiolytic drug.' I said that I'd love to go to those far-away places, but I couldn't accept because the evidence was against tianeptine being a powerful anxiolytic. 'Oh, that's alright,' they said, 'We won't say anything about anxiety.'

However, at Karachi, I found myself standing in front of a big banner claiming tianeptine was a powerful anxiolytic, although this was not the case. Somewhat to my surprise, Servier still kept giving me research grants. A few weeks later the French licensing authorities told Servier they must no longer claim tianeptine was anxiolytic. I got a letter from a personal contact at Servier, whose name I've forgotten, with the words: 'Strictly private and personal' on the envelope saying, 'Unfortunately we are in the hands of our sales department.'

My other drug industry experience was also with Servier. Some 15 years ago they were supporting our work on the appetite suppressant d-fenfluramine, then thought to act by increasing extracellular 5-HT. However, while it certainly did increase it, as indicated by *in vivo* dialysis, its effect on feeding was the same in normal rats and rats previously treated with large doses of an inhibitor of 5-HT synthesis. This indicated its effect on feeding must be due to some other mechanism. I thought this was rather exciting, as it suggested the conventional wisdom was wrong, which is always interesting for a scientist. But Servier's people could not have been less interested. They said the important

[336] Whitton *et al.* (1991).

[337] Professor Gerald Curzon wrote: 'They also paid for my wife's travel expenses (more than the MRC ever did).' Note on draft transcript, 22 January 2013.

thing was that d-fenfluramine had been given to many thousands of patients for many years and it did decrease feeding. It was as if Servier was one of those big battleships that took a long time to change its course. Anyway d-fenfluramine was soon withdrawn because its administration was reported 'in a few patients' to be followed by evidence of a defect of heart muscle. 'A few patients': was this sufficient evidence to totally withdraw an apparently successful drug?[338] Both tianeptine and d-fenfluramine are now (as far as I know) therapeutic dead ends. However they did provide quite a bit of interesting work for my lab. I have no idea what's happening with them at the moment.

Hoyer: I can answer this one: it was not a few patients.[339] I think thousands of patients eventually had valvulopathies with d-fenfluramine and also with one of the follow-up compounds by the same company. It's too long to go into details, but this is mediated by 5-HT_{2B} receptors, and has been perfectly well described and we have known this for about 15 years at least. It should have been stopped at the time.

Curzon: Why did it take so long, so many thousands of patients were given this drug and they never reported it?

Hoyer: It's not up to Servier to report it. Pharmacovigilance is implemented everywhere. The issue is that in France there are ways to manipulate things, as shown more recently; in other countries this has stopped, and very early on. D-fenfluramine was marketed by American Home Products in the United States; this was American Home's end, the company got involved in thousands of lawsuits and that was it.[340] So, it was reported very early on but depending on the country and depending on the company, it has had more or less effect. Servier was very resistant, we had a meeting in New York in 1989 and we were trying to make a point about the toxicity of 5-HT releasers and Servier had sent a whole range of competent medics and marketers there to tell us that this was no issue.[341] Excuse me!

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[338] For a review of fenfluramine, see Curzon and Gibson (1999).

[339] Figures cited in SoRelle (1999) suggest that the drug was withdrawn after 177 patients reported valvular abnormalities. However compensation was paid to many thousands of patients who had been prescribed the drug.

[340] In 1999 American Home Products settled lawsuits for billions of dollars for thousands of people who had taken the combination drug diet pill Fen-phen (fenfluramine and phentermine).For a summary, see SoRelle. (1999).

[341] See Whitaker-Azmitia and Peroutka (eds) (1990) for the conference papers and discussions. The Institut de Recherches Internationales Servier is listed as one of the sponsors of this meeting.

Tyers: I've been involved in setting up clinical trials with ondansetron in anxiety, in depression and in schizophrenia, both in America and in Europe. What's apparent is that American psychiatrists have different diagnostic criteria for each of these three conditions compared with the other countries, including the UK. It makes it very difficult and extremely expensive doing meaningful comparisons and complicates clinical trial criteria.[342]

Dourish: I can expand on what Danny was saying on the d-fenfluramine issue. The main reason it didn't get withdrawn sooner is that it never had been marketed in the US, which is clearly the biggest market for obesity. Servier did a deal with Wyeth, at the time I think they were owned by American Home Products, and when the compound was launched, it was projected to be a $1 billion-seller, so the sales within the first six months were way beyond anything that had been seen in Europe, where it was marketed in a limited number of countries. As a result, there were thousands and thousands more people exposed to the drug and therefore this huge increase in valvulopathy, which then led the FDA to withdraw the compound. After that Servier continued to market the drug in Europe for several months until eventually it was withdrawn worldwide.[343]

Hoyer: The successor compound [Mediator], with the same mechanism of action, kept being prescribed until four years ago, when it had been stopped in all other countries. In 1997, the French Medicine Authority allowed two generics of the compound to be marketed at the time everyone knew that it was toxic.

Dourish: It's probably also significant that, in the last year, Servier's management has been in court, including Jacques Servier, the owner. This is due to withdrawal of the obesity and diabetes compound, Mediator, and they're being charged with withholding of information about the drug from the regulatory authorities. So, there's an alleged scandal around what Servier have done.[344]

Blackburn: The interesting thing for me, after that New York Academy of Sciences meeting in 1989, where Servier were really pushing the compound, it was offered to SmithKline Beecham as an in-licensing opportunity. I was one of

[342] Dr Tyers wrote: 'In fact it took Upjohn 11 clinical trials with Prozac to get the two positive trial results that were sufficient for FDA approval.' Note on draft transcript, 20 December 2012.

[343] D-fenfluramine was withdrawn worldwide in 1997.

[344] Mediator was prescribed to up to 5 million patients between 1976 and 2009. It was withdrawn in Spain and Italy five years earlier and was never prescribed in the UK or US. It is believed to have caused between 500 and 2000 deaths. See Mullard (2011).

the people involved in the due diligence on the compound who turned it down. However, at the time the pressure from marketing people was intense with regard to in-licensing the compound, but thankfully we turned it down, largely based on the evidence presented at that New York Academy meeting, which showed neurodegeneration associated with the compound that was there for all to see, and which was completely ignored when the compound was eventually developed.

Sanger: Different countries do different things. Tegaserod was withdrawn worldwide some time ago, but a couple of weeks ago I talked to a German clinician whose patients were still getting tegaserod. They'd imported them from the Vatican [laughter], which is a separate state. So that led to a torrent of jokes about praying for safety and so on. [345] But you can get it anywhere.

Curzon: Something that I was rather uneasy about is the way Servier kept having clinical trials in exotic parts of the world. Were they deliberately choosing places where trial ethics were not as good as in Western Europe or the United States?

Hunter: I think I have to say something here. I can say this because I don't actually work for big Pharma now, but whatever was able to go on 15 or 20 years ago, there is no way these days that you would ever be able to run trials in that way, unless you were absolutely being completely and utterly illegal. In fact, what's recently happened is that ten companies have come together to form a company called TransCelerate, which is trying to get common clinical standards across companies, in terms of clinical site approval and standards of trial conduction.[346] So, I was a bit uncomfortable that it sounded like we were going down a 'Pharma is being completely unethical' route. Whatever happened

[345] The Vatican pharmacy, open to the public, '…is one of the only places people can buy – with a proper medical prescription – obscure, foreign or just-released pharmaceuticals that haven't yet hit Italian drugstores. Brother Kattackal said Italian bureaucracy can hold up approval for a drug's sale in Italy for months, or even years. But Vatican City State can purchase straight from international manufacturers drugs that have passed other nations' standards and approval, he said, without dealing with Italian red tape.' See www.catholicnews.com/data/stories/cns/0802820.htm (visited 9 July 2013).

[346] TransCelerate Biopharma was founded in September 2012 as a non-profit making organization, whose aims are to 'advance innovation in research and development (R&D), identify and solve common R&D challenges and further improve patient safety, with the goal of delivering more high quality medicines to patients. TransCelerate will seek to accomplish these objectives through its focus on identifying and capturing efficiencies in the clinical trial process, which will reduce costs, increase speed to market, and enhance quality, innovation and patient safety.' See http://transceleratebiopharmainc.com (visited 11 September 2013). The ten founder companies are: Abbvie, AstraZeneca, Boehringer Ingelheim, Bristol–Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Johnson and Johnson, Pfizer, Roche and Sanofi.

20 years ago in the industry, and there may have been things, and you've seen there have certainly been issues in terms of selling and some marketing, I wouldn't like to give the impression that Pharma companies can really get away with doing anything like that these days. It's very, very heavily regulated and watched. So, for example, when you are doing a clinical trial in Brazil, you have to be doing your clinical trials in the sponsor country as well.[347] They won't let you just run clinical trials in Brazil.

Flower: We wandered off message there but I think it was a very valid point. I am going to say a few words in summing up, but I just wondered if there's anything else anyone urgently wants to say about the 5-HT area before we wind up.

Aronson: I have one comment about a clinical aspect of 5-HT that I don't think we've discussed, and surprisingly it involves antipsychotic drugs. Many years ago, David Grahame-Smith was interested in the action of 5-HT in altering platelet aggregation *in vitro*. If you add 5-HT to a suspension of platelets they aggregate, but it's transient in 90 per cent of cases. In a few cases it's irreversible but most of the time it's transient, whereas if you add ADP or other aggregating substances, it's irreversible. What was reported was that chlorpromazine inhibited this aggregation *in vitro*.[348] At that time, David was interested in finding markers for pharmacological actions that could be used to monitor progress in clinical conditions, and schizophrenia was clearly a difficult condition to monitor. He thought that this action of chlorpromazine might be helpful as an indicator of efficacy, and so he got a load of patients who had been given chlorpromazine and studied the platelet aggregation *in vitro* using their own plasma.[349] Lo and behold, the aggregation was not reduced but it was markedly increased, for reasons that I think never really became clear, although presumably metabolites were involved. Whatever the reasons, that was the outcome and there's more to say about it. Some years later Hershel Jick from the Boston Collaborative Surveillance Program published a paper in the *Lancet*

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[347] The WHO International Clinical Trials Registry Platform was developed to 'to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.' See www.who.int/ictrp/en (visited 30 April 2013). Clinical trials sponsored by organizations such as the MRC and the Wellcome Trust are required to register on the metaRegister of the International Standard Randomised Controlled Trial Number Register.

[348] Boullin *et al.* (1975a).

[349] Boullin *et al.* (1975b).

showing that there is an increased risk of thromboembolism in patients taking classical phenothiazines.[350] We did wonder whether this aggregatory effect of chlorpromazine on platelets, perhaps through 5-HT, was the mechanism.

Blackburn: I did a clinical study with the compound ICI 170,809 on platelet response and showed a very marked antagonist activity on platelet aggregation.[351] At that time we were thinking it was through the S2 (5-HT_{2A}) receptor. Sitting here and thinking of people like Jimmy Black, who worked on 5-HT for a while, it would be interesting to have heard some of his comments on the complexity of this area with his background in H_1, H_2, β1, β2 receptors.[352] Also we just touched a little on the work of John Vane, who made a major contribution with the bioassay system.[353] These are contributions where it would have been nice to hear the thoughts from some of these guys.

Marsden: At the beginning of this discussion we talked a lot about Maurice Rapport, who was essential in the elucidation of what 5-HT. He died fairly recently and his family have, through the Serotonin Club, asked us to look after his papers related to this period of his research. The suggestion is that they should be lodged with the Wellcome Library. I would hope that that could be arranged through this event.

Bakhle: Is plasma 5-HT increased in people who take SSRIs?

Cowen: I don't think there's much 5-HT in the plasma, so what you get with SSRIs is a profound lowering of platelet 5-HT and some people think that could tie in with a possible protective effect of SSRIs against myocardial infarction. Also there is more bleeding during surgical operations. If you have an operation and take SSRIs, you're more likely to need a blood transfusion.

Bakhle: But why does the platelet 5-HT fall if you block uptake because you've got no metabolism in there, have you? There isn't a metabolizing enzyme, MAO within the platelet.

Marsden: We actually did this with paroxetine in one of the very initial clinical trials and looked at platelet 5-HT, which drops very rapidly on the start of

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[350] Zornberg and Jick (2000).

[351] Blackburn *et al.* (1990).

[352] Black, Fisher and Smith (1958).

[353] John Vane developed the technique of cascade superfusion bioassay; Vane (1964). For Vane's work, see also note 9.

treatment. The reason is because all the 5-HT in the platelets gets there through the uptake site. The platelets can't make 5-HT. So if you block uptake, you don't get any 5-HT in there and so it can't be stored there.[354]

Flower: Well, it's been a terrific day. One of the good things about these meetings is that it's like travelling through the entire history of a discipline by time machine. We started off this morning talking about substances of unknown structure found in clotted blood and we finished tonight with SSRIs, triptans and a whole swathe of 5-HT_3 antagonists, all of which are very useful medicines. Along the way we've learnt how important those defining meetings, such as the 'Birmingham meeting', were, and the significance of the Serotonin Club, and also the role of the BPS in fostering a sense of community between people working in this field. We've heard several times today how nice you all are – and I'm sure it's not just that – but for whatever reason, this field seems to have come together very well in terms of industry–academia collaborations. The fact that you're all so 'nice' may be that you've been brought up in a culture that encourages collegial collaborations and I think that's one thing that groups like the Serotonin Club and the BPS try to encourage. So an important lesson for all collaborations is that you need to have this sense of community. We also have heard how molecular biology had both a positive and a negative effect on drug development and also the importance of discussions with our clinical colleagues to discover what they know about diseases. We didn't really touch upon things like different disease pathotypes, which we could have discussed for a long time. We then wandered into rather philosophical territory when we tried to put the world to rights by identifying what was wrong with drug discovery today. Well, I've been to several of these meetings, and we always wind up at that point and that's one of the reasons why I thought it might be a good time to stop. You've been a terrific audience and a terrific group to work with.

Tansey: Thanks very much, Rod. I would like to add my thanks to you all for coming and sharing your experiences. I'm a lapsed neuroscientist and I did my PhD on catecholamine and 5-HT distribution in *Octopus* brain and I still remember the excitement of looking at that yellow fluorescence down the microscope, so it's been particularly nice to hear some of the stories about people whose papers I quoted so long ago. When I decided several years later to become an historian, I did a PhD on Henry Dale and his work, so again there's been a lot of resonance this afternoon and I'm delighted to have learnt so much about the continuation of some of that work. Obviously I'd like to

[354] Marsden *et al.* (1987).

Figure 25: Participants at the Witness Seminar.

follow up the point that Charles made about the Rapport papers and also the Serotonin Club papers. I think these would fit in very clearly with the Wellcome Library's collection strategy at the moment, which is emphasizing neuroscience and genetics. The archives of the Wellcome Library include the BPS archives and papers of people such as Marthe Vogt, Edith Bülbring and Bill Paton. So there is already a very good pharmacological collection in the Wellcome Library and I am sure they would fit very well. I'd like to say a particular thank you to Rod for chairing this meeting so ably. This is the third meeting that he's chaired and I'm delighted he allowed me to persuade him to chair this one. So, Rod, thank you very much indeed.

Appendix 1[255]

Pioneering research by SmithKline Beecham: 5-HT_3 receptor antagonism and anti-emetic activity, by Professor Gareth Sanger[256]

Our dissection of the different pharmacological properties of metoclopramide laid the foundation for the characterization of the 'prokinetic' 5-HT_4 receptor and identified a relationship between the relatively low affinity of metoclopramide for the 5-HT_3 receptor and the need to use high doses of the drug to prevent cytotoxic-evoked emesis. After successfully testing our pioneering analysis, we identified, developed and now market granisetron as the first 5-HT_3 receptor antagonist designed as an anti-emetic drug. We also patented the use of 5-HT_3 receptor antagonists for the control of emesis. Included in the patent was the world's first data on the anti-emetic properties of ondansetron, a compound identified by Glaxo for the treatment of schizophrenia and anxiety. Our discovery dominates the early 5-HT_3/emesis scientific literature.

Kytril: The link between the 5-HT_3 receptor and the mechanisms of emesis: significant publication history.

Prior to publishing in peer-review journals, we introduced the novel concept that high-dose metoclopramide might not prevent emesis via antagonism at the dopamine receptor.

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[255] SmithKline Beecham was formed in 1989 from the merger of SmithKline Beckman and the Beecham Group. Several of the pharmaceutical companies mentioned in the text have merged, and briefly these changes were: Allen and Hanburys research laboratories at Ware were absorbed into Glaxo (1958); SmithKline and French merged with Beckman Inc to become SmithKline Beckman (1982); SmithKline Beckman and the Beecham Group merged to form SmithKline Beecham (1989); Glaxo and Wellcome merged to form Glaxo Wellcome (1995); Glaxo Wellcome and SmithKline Beecham merged to form GlaxoSmithKline (2000).

[256] Professor Gareth Sanger wrote: 'This was prepared as an internal document (SmithKline Beecham) to support our successful patent claim over the use of the Glaxo drug ondansetron (Zofran) for anti-emetic control, and then subsequently in 1998, to support the PhARMA award. It emphasizes the fact that in the discovery of the involvement of the 5-HT_3 receptor in the mechanisms of nausea and vomiting, our research led the way.' Email to Ms Caroline Overy, 7 August 2013. See also the discussion on pages 56–60 and note 190 by Professor Sanger.

In 1984 we concluded: 'However, additional factors may also be involved, since unlike other dopamine antagonists, high-dose intravenous metoclopramide successfully prevents emesis caused by strongly emetic cancer chemotherapeutic agents.' (McRitchie *et al.* (1984), page 297).

In 1986 we stated: 'The results with Domperidone and BRL 24924 suggest that dopamine antagonism is not essential for the inhibition of cisplatin emesis in the ferret. The efficacy of metoclopramide and BRL 24924 may therefore involve other properties, such as 5-HT M-receptor (5-HT_3) antagonism and/or effects on gut motility.' (Miner, Sanger and Turner (1986), page 374P).

In 1986 we also began to submit our work for peer review. Firstly we concluded that 5-HT_3 receptor antagonism prevented cytotoxic drug-evoked emesis. This appeared as a Rapid Communication in the *British Journal of Pharmacology* and has now received several hundred citations (Miner and Sanger (1986)).

In 1987 we developed our discovery by including a range of cytotoxic therapies. Significantly, we published in the *British Journal of Cancer* and thereby directly addressed the oncology community (Sanger, Miner and Turner (1987)).

In 1988 we again published in the *British Journal of Cancer*, describing the efficacy of the highly selective 5-HT_3 receptor antagonist BRL 43694, later known as granisetron or Kytril (Bermudez *et al.* (1988)).

The development of Kytril was a superb team effort within SmithKline Beecham. Its discovery was the product of a highly productive association between Medicinal Chemistry, led by Dr F King, and Discovery Biology. The discovery of the link between the 5-HT_3 receptor and the mechanism of emesis, primarily involved three people: Dr G J Sanger, the late Mrs Christine McClelland and Mr W D Miner.

Biographical notes*

Professor Paul Andrews

PhD (b.1953) studied physiology at undergraduate and postgraduate levels at the University of Sheffield prior to obtaining lectureships at the University of Edinburgh and St George's, University of London, where he is Emeritus Professor of Comparative Physiology. His research over the past 30 years has focused on the pre-clinical neuropharmacology of emesis, with particular emphasis on anti-cancer chemotherapy and the role of the vagus nerve. He has worked on the site(s) of action of 5-HT_3 and NK1 receptor antagonists in conjunction with colleagues in industry and is currently working on mechanisms of nausea and non-animal methodologies to investigate emetic liability of new drugs.

Dr Jeffrey Aronson

DPhil FRCP FBPharmacolS FFPM (b. 1947) trained in the University of Glasgow (1964–73) and the Medical Research Council Unit and University Department of Clinical Pharmacology, Oxford, under the late Professor David Grahame-Smith. He is currently Reader in Clinical Pharmacology at the University of Oxford and Honorary Consultant Physician in the Oxford University Hospitals Trust. He was President of the British Pharmacological Society (2008/9) and is now Emeritus President. He was Vice-chairman of the Medicines Commission (2002–2005) and Editor-in-chief of the *British Journal of Clinical Pharmacology* (2003–07). He has been Chairman of the British Pharmacopoeia Commission's Expert Advisory Group on Nomenclature since 2006. He was a member of the Formulary Committees of the British National Formulary from 2006 and the British National Formulary for Children from 2003, and is now a member of the Advisory Board of the British National Formulary. For further details, see www.phc.ox.ac.uk/jeffrey-aronson (visited 9 September 2013).

Dr Julius Axelrod

PhD (1912–2004) obtained a degree in chemistry and biology in 1933 at the City College of New York and an MSc in chemistry at New York University in 1941. After working as a laboratory assistant and a chemist, in 1949

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

he was appointed to the National Heart Institute, part of the NIH in Bethesda. There he worked with Bernard Brodie on anti-malarial drugs and their research into acetaminophen led to the development of the new pain relief drug, tylenol /paracetamol. In 1955 he completed his PhD and was appointed as head of the section of pharmacology in the Laboratory of Clinical Science at the National Institute of Mental Health, where he remained until his retirement in 1984. His research focused on the neurotransmission of catecholamine, adrenaline and noradrenaline. In 1970, he was jointly awarded (with Bernard Katz and Ulf von Euler) the Nobel Prize for Physiology or Medicine 'for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation.' For further biographical details and details of Axelrod's research, see Iversen (2006b) and his interview in Healy (1996), pages 29–49.

Dr Y S (Mick) Bakhle

DPhil DSc (b. 1936) read chemistry, took chemical pharmacology as a supplementary subject and went on to do his DPhil in the Department of Pharmacology at Oxford; in 1993 he received a DSc. After two post-doctoral years as a Fulbright Fellow at Yale, he joined the Department of Pharmacology at the Royal College of Surgeons (RCS) in London in 1965, working with John Vane and was appointed Reader in Biochemical Pharmacology in 1980. After nearly 30 years at the RCS, he moved to the National Heart and Lung Institute at Imperial College, where he is a Senior Research Fellow. For five years (2001-2006), he was a senior editor of the *British Journal of Pharmacology* and has been Press Editor for the last six years.

Professor Sir James Black

Kt OM FRCP FRS (1924–2010) was Professor and Head of the Department of Pharmacology, University College London, (1973–1977), Director of Therapeutic Research at Wellcome Research Laboratories (1978–1984); and Professor of Analytical Pharmacology at King's College Hospital Medical School, London (1984–1993). He was chancellor of Dundee University (1992–1996). He shared the 1988 Nobel Prize for Physiology or Medicine (with George Hitchings and Gertrude Elion) for 'discoveries of important principles for drug treatment'. He was knighted in 1981 and appointed to the Order of Merit in 2000. See the special issue of

the *British Journal of Pharmacology* celebrating his life and work (McGrath, Bond and MacKie (eds) (2010)).

Dr Tom Blackburn

MPhil PhD DSc FBPharmacolS (b. 1949) received his degrees from Nottingham and Manchester Universities. He has held C-level executive and senior management positions at ICI Pharmaceuticals PLC, Beecham Pharmaceuticals PLC and SmithKline Beecham in the UK and with two biotech companies in the US, Synaptic Pharmaceutical Corporation and Helicon Therapeutics Inc. He has led companies, departments, and project teams that identified and developed novel therapeutics, including several 5-HT receptor subtype antagonists (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} & 5-HT_{3}), Galanin R3 and the SSRI antidepressant, Seroxat/Paxil. His passion, based on an extensive knowledge of pre-clinical and clinical drug development and marketing is helping to define strategies and positioning of pharmaceutical products for biotech startup companies. He has authored over 100 peer-reviewed scientific papers, review articles and book chapters and is an inventor on 22 patents. He is President Emeritus of the British Pharmacological Society and a member of the American College of Neuropsychopharmacology. He is also a non-executive Director for Motac Neuroscience Ltd., a neuroscience biotechnology company specializing in Parkinson's disease and neurodegenerative disorders.

Professor Bernard Brodie

PhD (1907–1989) graduated from McGill University in 1931. He was awarded his PhD in organic chemistry in 1935 from New York University and was then appointed Associate Professor in the Physiology Department. After carrying out research into anti-malarial therapy at the Goldwater Research Service at NY University from 1941 until 1949, he moved to the National Heart Institute in Bethesda, MD, where he headed the Laboratory of Chemical Pharmacology until his retirement in 1970. His research pioneered developments in drug metabolism, neuropsychopharmacology and toxicology. See Bickel (1989); Costa *et al.* (1989).

Professor David Clarke

PhD FBPharmacolS (b. 1936) obtained his undergraduate degree at the University of London and his PhD at the University of Bradford, where he was an Assistant Lecturer and then Lecturer in Pharmacology (1961–1969). He was Associate

Professor of Pharmacology, University of Pittsburgh (1969–1973); Professor and Chairman of the Department of Pharmacology, University of Houston (1973–1989); Distinguished Scientist at Syntex, and later Roche, Palo Alto, CA (1989–1996). Subsequently, he has worked as a freelance consultant for pre-clinical and clinical drug discovery and development, while serving on the Board of Pharmovation Ltd. Currently, he is engaged as the Principal Consultant for Recordati (Milan, Italy) and Afferent Pharmaceuticals (San Mateo, CA. USA).

Dr Alec Coppen

DSc FRCP FRCPsych (b. 1923) trained in medicine at Bristol University after military service during the Second World War. He went on to the Institute of Psychiatry and the Maudsley Hospital and in 1960 became Clinical Director of the MRC's Neuropsychiatric Research Institute and was Head of the WHO-designated Centre for Biological Psychiatry in the UK. His research focused on 5-HT and mood disorders and was the first to propose a 5-HT theory for depression. For a discussion of his research, see his interview in Healy (1996), pages 265–86.

Professor Brenda Costall

PhD DSc (b. 1947) worked at the University of Bradford as Lecturer in Pharmacology (1973–1979), Senior Lecturer in Pharmacology (1979–1983), Reader in Neuropharmacology (1983–1985), and Professor of Neuropharmacology since 1985 and Head of the School of Pharmacy (1998–2004). She retired in 2007.

Professor Philip Cowen

MD FRCPsych (b. 1951) trained in medicine at University College Hospital, London, and then in psychiatry at King's College Hospital, London. He went to Oxford to work in the MRC Unit of Clinical Pharmacology under David Grahame-Smith and Richard Green. Since 1983 he has been an MRC Clinical Scientist and Honorary Consultant Psychiatrist in the Department of Psychiatry in Oxford. He was elected to a personal chair in Psychopharmacology in the University of Oxford in 1997 and the Academy of Medical Sciences in 2001. His main interests are in the biochemistry and treatment of mood disorders, particularly the pharmacological management of resistant depression.

Professor Helen Cox

PhD (b. 1957) completed her PhD at University of Southampton and post-doctoral research at University of Cambridge, and has been interested in peptide receptor signalling. Her current research focuses on how the intestine senses nutrients and signals their presence locally to alter gut function, and acts as an interface that regulates energy homeostasis. 5-HT has a role in these sensing mechanisms. She has been Professor of Pharmacology at King's College London since 2004 and has served on an IUPHAR subcommittee for nomenclature of NPY receptors, on the editorial board of the *British Journal of Pharmacology* and other pharmacological journals, on the British Pharmacological Society Council, as well as the finance and executive committees.

Professor Gerald Curzon

PhD DSc (b. 1928) was educated in Leeds at state schools and Leeds University (BSc Chemistry, PhD Biochemistry.) He spent most of his career at the Institute of Neurology, University College, London, and received a DSc in neurochemistry. He has broad historical interests and spent a period of time as historian and archivist of the International Society for Neurochemistry.

Dr Colin Dourish

PhD DSc (b. 1955) received a BSc in Psychology (1977) and a PhD (1980) and DSc (1993) in psychopharmacology from Queen's University, Belfast and carried out post-doctoral research at the University of Saskatchewan in Canada and at the Institute of Neurology, London. He is Chief Executive Officer of the clinical research organization P1vital Limited. Prior to co-founding P1vital, he was Senior Vice President Research and CSO of Vernalis Group plc, Research Director and co-founder of Cerebrus Limited, Director of Neuropharmacology at Wyeth Research and Section Head at Merck & Co. He is an Honorary Fellow of the Department of Psychiatry at the University of Oxford and formerly a William Pitt Fellow of Pembroke College, Cambridge, Visiting Professor of Psychopharmacology at the University of Durham and Visiting Professor of Neuroscience and Psychological Medicine at Imperial College of Science, Technology and Medicine, London.

Professor Vittorio Erspamer

(1909–1999) graduated in medicine and surgery in 1935 and after a short appointment as Assistant Professor of Anatomy and Physiology at the University

of Pavia, he went to the Institute of Pharmacology at the University of Berlin. In 1939 he became Professor of Pharmacology in Rome and in 1947, Professor of Pharmacology at the University of Bari, a post that he held until 1955 when he moved to the University of Parma. Much of his research focused on marine organisms and amphibians, isolating and identifying more than 60 new chemical compounds; later in his career he concentrated on peptides. In 1935 he identified an extract from the enterochromaffin cells contained an amine, which he named 'enteramine', which was later shown to be the same as 5-HT.

Professor Roderick Flower

PhD DSc FMedSci FRS (b. 1945) trained as a physiologist at Sheffield University, subsequently receiving a PhD in experimental pharmacology from the University of London and a DSc in 1985. After 12 years working in industry at the Wellcome Foundation, he left to take the Chair of Pharmacology at the University of Bath in 1985. In 1990 he returned to London to establish a new unit at the William Harvey Research Institute, Barts and The London School of Medicine and Dentistry. During this time he was Head, on a part-time basis, of the Clinical Pharmacology Department, and was President of the British Pharmacological Society (2000–2003).

Dr John Fozard

PhD, studied pharmacy at the University of London and received his PhD in Pharmacology from the University of Bradford in 1968. After a lectureship and senior lectureship at the University of Manchester and a year at the University of Mainz, he was appointed Head of Pharmacology at the Merrell-Dow Research Institute in Strasbourg France in 1977 where he remained for ten years. He was subsequently Head of Hypertension Research and then Head of Asthma Research at Sandoz in Basle. In 1996 he became Head of Respiratory Disease Research at Novartis and after three years a Novartis Distinguished Scientist in the Respiratory Disease Research section of the Novartis Institutes for BioMedical Research. He retired in 2005. See the biographical information submitted by Professor Daniel Hoyer to the Serotonin Club Newsletter, Autumn 2005 to mark Fozard's retirement, at http://serotoninclub.org/newsletters/Nwsltr66.pdf (visited 15 July 2013).

Dr Ray Fuller

PhD (1935–1996) studied at Southern Illinois University, graduating in chemistry in 1957 and gaining a Master's degree in microbiology in 1958. He went on to receive a PhD in biochemistry from Purdue University in 1961. In 1963 he was appointed a Senior Pharmacologist at the pharmaceutical company Eli Lilly and Co. in Indianapolis. His research with David Wong and Bryan Molloy on antidepressants led to their discovery of fluoxetine, the first SSRI, which from 1988 was marketed as 'Prozac'.

Professor Sir John Gaddum

Kt FRS FRSE (1900–65) went to Trinity College Cambridge in 1919 on an entrance scholarship for mathematics and in 1922 became a medical student at University College Hospital, London. He worked at the Wellcome Physiological Research Laboratories, London, in 1925; at the National Institute for Medical Research, London (1928–1934); and was Professor of Pharmacology at the University of Cairo (1934). In 1935 he was appointed Professor of Pharmacology at University College, London and in 1938 took the Chair at the School of Pharmacy, University of London. During the Second World War he worked at the Chemical Defence Research Station, Porton, and in 1942 was appointed Professor of Materia Medica at Edinburgh University. In 1958 he became Director of the Institute of Animal Physiology, Babraham, Cambridge. See Feldberg (1967).

Professor David Grahame-Smith

CBE FRCP (1933–2011) was Rhodes Professor of Clinical Pharmacology, University of Oxford (1972–2000), Honorary Director of the MRC Clinical Pharmacology Unit, Oxford (1972–1992), Honorary Director of the Oxford University SmithKline Beecham Centre for Applied Neuropsychobiology (1989–1999), and Honorary Consultant in Clinical Pharmacology and General Internal Medicine to the Oxford Radcliffe Hospitals (1972–2000). See Aronson (2011b).

Dr Arda Green

MD (1999–1958) studied chemistry and philosophy at the University of California, Berkeley, and went on to receive an MD from Johns Hopkins School of Medicine in 1927. Following research at Harvard Medical School and Radcliffe College she went to Washington University as Research Associate and Assistant Professor and worked with Carl and Gerty Cori, who went on to be jointly awarded the 1947 Nobel Prize

in Physiology or Medicine. In 1945, Green was invited to join the research staff at the Cleveland Clinic, where she worked with Irvine Page and Maurice Rapport on 5-HT. She remained there until 1953 when she was appointed to the McCollum-Pratt Institute of Johns Hopkins, where her research focused on biolumiscence. See Colowick (1958).

Professor Richard Green

PhD DSc (b 1944) completed his PhD (1969) with Gerald Curzon and following two years at National Institute of Mental Health (NIMH), Washington, DC, with Erminio Costa, he joined David Grahame-Smith at the MRC Clinical Pharmacology Unit in Oxford becoming Assistant Unit Director in 1981. In 1986 he was appointed Director of the new Astra Neuroscience Research Unit in London. In 1996 he was appointed Director, Global Discovery CNS & Pain Control, for Astra. After retiring from AstraZeneca in 2007 he has continued psychopharmacology research in Nottingham, and is currently Honorary Professor of Neuropharmacology at Nottingham University. He was awarded the DSc by London University in 1988 and in 2010 was given the Lifetime Achievement Award by the British Association for Psychopharmacology. He is a President Emeritus of the BPS and a former President of the Serotonin Club.

Professor Daniel Hoyer

PhD DSc FBPharmacolS (b. 1954) received his PhD in Pharmacology (1981 Strasbourg) DSc (1986 Strasbourg), was a post-doctoral fellow (University of Pennsylvania, Philadelphia), Cardiovascular Research Sandoz (Basel, 1983), and Neuroscience Research (1989-2012, Sandoz/ Novartis). He worked on catecholamine, serotonin, neuropeptide receptors and ligand-gated channels; genomics of depression and schizophrenia; epilepsy, sleep disorders, RNAi and epigenetics of neuropsychiatric disorders, and published more than 300 papers/articles. He is a member of the British and German Pharmacological Societies, European College of Neuropsychopharmacology, Society for Neurosciences, scientific council of the Institut Pasteur, Council/ Director of the BPS. He is past editor of *European Journal of Pharmacology*, *Neuropharmacology*, *Current Opinions in Pharmacology*, *Current Drugs*, *Drug Discovery Today*, *Journal of Receptors and Signal Transduction*, *Pharmacology and Therapeutics*, and is currently a senior editor of *Psychopharmacology*,

Naunyn Schmiedeberg's Archives of Pharmacology, *Encyclopedia of Psychopharmacology* and *British Journal of Pharmacology*. He chaired the Serotonin and the Somatostatin Receptor Nomenclature subcommittees (NC IUPHAR), and was President of the Serotonin Club and the European Neuropeptide Club. He was Novartis Leading Scientist (1998), Professor adjunct, MIND, the Scripps Research Institute, La Jolla, CA (2004), Fellow of the BPS (2005); he was in the top ten most cited researchers in pharmacology (see www.in-cites.com/scientists/pha-10-aug2003.html, visited 9 September 2013), with to date more than 22,000 citations and an H index of 75. He is Professor, Chair and Head, Department of Pharmacology, School of Medicine, University of Melbourne (December 2012), and Honorary Professorial Fellow, Florey Institute, Melbourne (March 2013).

Dr Patrick Humphrey

OBE DSc PhD FBPharmacolS (Hon) (b. 1946) was born in South Africa and graduated from the School of Pharmacy, University of London, in 1968, with a strong interest in drug receptor theory. After obtaining a PhD in pharmacology at St Mary's Hospital Medical School and briefly working as a Lecturer in the Department of Physiology, he joined Allen & Hanburys at Ware to initiate a project on migraine. His work on cerebrovascular pharmacology led directly to the development of sumatriptan, the prototype of a new drug class (the triptans) for the treatment of migraine. During this time, he became the overall Director of the Glaxo Division of Pharmacology that was not only instrumental in the discovery of sumatriptan, but also naratriptan, alosetron, ondansetron, vapiprost and salmeterol, covering a broad spectrum of therapeutic areas. He has received many important academic honours, including an honorary Professorship from the University of Cambridge, as well as the Royal Society's Mullard medal. In 1999, he was awarded the OBE for 'services to migraine research'. He maintains a passion for research aimed at drug discovery and was latterly the successful Head of Research and Executive Vice President at Theravance in San Francisco, CA, from 2001 to 2008. He has over 300 published scientific papers and book chapters to his name and was ranked fourth in the list of total literature citations in Pharmacology and Toxicology from 1994 to 2004. He is currently consulting for a number of new, innovative pharmaceutical

companies and is a non-executive Director on the board of Verona Pharma plc.

Dr Jackie Hunter

PhD FBPharmacolS gained a BSc in physiology and psychology in 1977 and a PhD in animal behaviour at the University of London in 1980. Subsequently she undertook a Wellcome Trust post-doctoral fellowship at St George's Hospital Medical School, London, in behavioural pharmacology. She has been a senior leader in the pharmaceutical industry for over 25 years and more recently has become widely recognized as an expert in the application of open innovation in healthcare. In terms of research and development, she was responsible for both clinical and non-clinical portfolios at GlaxoSmithKline (GSK), primarily within the neuroscience therapeutic area, taking compounds from early research to late phase development. She was also a non-Executive director for Proximagen plc, a neuroscience biotechnology company, prior to its acquisition by Upshire Smith in 2012. She has extensive international experience in industry and academic collaborations and alliances and has served on the boards of large public private initiatives such as the Innovative Medicines Initiative. She has also held numerous other positions on academic and industry advisory boards as well as committees for funding bodies and charities. After leaving GSK, she formed OI Pharma Partners Ltd, which helps companies and institutions across the life sciences apply open innovation principles effectively within their businesses. She has received several awards including Women of Achievement in Science, Engineering and Technology and a CBE for Services to the Pharmaceutical Industry. In 2013 she was appointed the new CEO for the Biotechnology and Biological Sciences Research Council.

Professor Leslie Iversen

CBE PhD FRS (b.1937) studied biochemistry and pharmacology at Trinity College, Cambridge. After post-doctoral fellowships at the NIH, Harvard Medical School and Trinity College, Cambridge, he became Locke Research Fellow of the Royal Society in the Department of Pharmacology, University of Cambridge in 1967. In 1971 he was appointed Director of the MRC Neurochemical Pharmacology Unit, Cambridge, until 1983, when he became Director of Merck, Sharp & Dohme Neuroscience Research Centre in Harlow. From 1995 he was visiting Professor of Pharmacology at Oxford University

was Professor of Pharmacology and Director of the Wolfson Centre for Age-related Diseases, Kings College, London, from 1999 to 2004 and has been Emeritus Professor of Pharmacology at the University of Oxford since 2007.

Sir David Jack

KT CBE PhD FRS FRSE (1924–2011) studied pharmacy and pharmacology at Glasgow University where he became Assistant Lecturer before National Service. After working in the pharmacy research department at Glaxo (Greenford) and at the pharmaceutical company Menley and James (later part of Smith Kline and French), completing a part-time PhD at London University, he was appointed Head of Research at Glaxo (Allen & Hanburys) at Ware in 1961, becoming Research and Development Director from 1978 to 1987 when he retired. He pioneered major developments in the treatment of asthma (salbutamol), gastric ulcers (ranitidine), migraine (sumatriptan) and cancer therapy-induced emesis (ondansetron) He was awarded the CBE in 1982 and knighted in 1993. For further details, see Watts (2012); Barnes and Breckenridge (2012).

Paul Janssen

(1926–2003) trained in medicine in Leuven and Ghent and after military service studied pharmacology and chemistry at Cologne University. After several years of teaching and study trips, he turned to independent research and founded his own research laboratory in 1953. In 1961 the company merged with the American company Johnson and Johnson, but retained its own identity and independence, and in 1964 the company was renamed Janssen Pharmaceutica N V (formerly N V Research Laboratorium C Janssen, after his father, Constant Janssen). By the time of his death, Paul Janssen held over 100 patents, had published more than 850 papers, and received numerous awards. See Watson (2003).

Professor Alberto Kaumann

MD (b. 1936) trained in medicine at the University of Buenos Aires, receiving his MD in 1961. He devoted his research to drug receptor pharmacology and cardiac arrhythmias. Between 1961 and 1965 he carried out research at the Centro de Investigaciones Cardiologicas in Buenos Aires, finding that the β-blocker sotalol prevented ventricular fibrillation and death after coronary artery ligation through a mechanism

independent of blockage of β-adrenoceptors. From 1966 to 1968 he was Instructor in Pharmacology at the Department of Pharmacology of Harvard University, discovering (with Camille Olson) that sotalol acted through a novel antiarrhythmic mechanism. From 1969 to 1971 he was a Fellow and Research Associate at the Mayo Clinic (US), uncovering atypical agonist properties of some β-blockers, which culminated with the concept of a low-affinity site of the β1-adrenoceptor in 1999. He was an Assistant in Physiology at the University of Dusseldorf (1975–1985), and obtained an MD and Professorship, describing (with Horst Lemoine) a selective coupling of β2-adrenoceptors to Gs protein. After 1985 he worked in the UK as a scientist at Imperial Chemical Industries (1985–1986), SmithKline Beecham (1987–1992), the Babraham Institute in Cambridge (1992–1999) and until 2012 in the Departments of Clinical Pharmacology and Physiology of the University of Cambridge.

Professor Charles Marsden

PhD DSc (b. 1943) read zoology at the University of London before going to Southampton University where he obtained an MSc in biochemical pharmacology (1967), a PhD in invertebrate neuropharmacology (1969) and a DSc in 1986. Following his PhD, he went to the University of Bergen (Norway) for three years (1969–1972) before going to the Institute of Neurology, London to work with Professor Gerald Curzon. In 1978 he moved to the Department of Physiology and Pharmacology at the University of Nottingham, where in 1981 he obtained a Wellcome Trust Senior Lectureship and subsequently a Professorship in Neuropharmacology (1986). From 2002 to 2008 he was co-director of the Institute of Neuroscience at Nottingham. During this time he was President of the British Association of Psychopharmacology (2000–2002) and of the Serotonin Club (2008). He was awarded the J R Vane medal by the British Pharmacological Society (2002) for his contribution to neuropharmacology. In 2012 he was made an honorary member of the Serotonin Club and in 2013 was given a Life Time Achievement Award by the British Association for Psychopharmacology.

Mr Wesley Miner

BSc (b. 1948) is a graduate in physiology from the University of Edinburgh. From 1982 to 1986 he worked at Beecham Pharmaceuticals (GlaxoSmithKline since 2000) with Gareth Sanger.

During this time, Miner and Sanger discovered, and were the first to publish that 5-HT_3 antagonists were extremely efficacious pharmacological agents for preventing and treating anti-cancer therapy (chemo and radiation) induced nausea and vomiting (Miner and Sanger (1986)). This seminal experimental work translated very well to the clinic when granisetron (Kytril) was shown to be highly efficacious in human patients (see Appendix 1). Importantly, this discovery became one of a very select few where research into 5-HT mechanisms actually culminated in a marketable drug that markedly improved the quality of life for patients. Following this groundbreaking research at Beecham, he relocated to another major international pharmaceutical company and became a key member of the biology team that discovered darifenacin (M3 selective antimuscarinic), which is now indicated and marketed for Over Active Bladder (OAB) and urinary incontinence.

Professor Robert Naylor

PhD DSc FRPharmS (b. 1943) graduated from Bradford in 1967 and undertook a doctoral neuropharmacology research programme under the supervision of J E Olley. With Brenda Costall, he subsequently established the Bradford Neuropharmacology Research Group, becoming Lecturer, Senior Lecturer, Reader and Professor of Pharmacology, with a Personal Chair in Neuropharmacology and Head of the School of Pharmacy at Bradford. He investigated the functional role of brain dopamine systems in motor control and the detection of atypical antipsychotic drug action, and anti-Parkinson treatments. Concomitant investigations of the role of 5-HT in central and peripheral systems revealed the anti-emetic actions of the 5-HT_3 receptor antagonists in animal models.

Dr Irvine Page

PhD (1901–1991) trained in medicine at Cornell University. After carrying out research in physical chemistry in New York and at the Kaiser Wilhelm Institute in Munich, between 1931 and 1937 he worked at the Rockefeller Institute in New York. In 1937 he was appointed Director of the Laboratory for Clinical Research at the Eli Lilly Research Unit at the City Hospital in Indianapolis, IN, and in 1945 established a new Research Division at the Cleveland Clinic. He remained chairman of the division until 1966 and Senior Consultant and Emeritus Consultant until 1978. As well

as his identification of 5-HT, he is remembered for his pioneering research into hypertension. See Gifford (1987); Frohlich, Dustan and Bumpus (1991).

Professor Maurice Rapport

PhD (1919–2011), studied chemistry at City College, New York and received his PhD in organic chemistry from California Institute of Technology in 1946. He then went to work with Irvine Page at the Cleveland Clinic. With Page and Arda Green, in 1948 he isolated 5-HT and in 1949, determined its structure. Following research in Rome, Columbia, the Sloan-Ketting Institute for Cancer Research, New York, and the Albert Einstein College of Medicine, New York, in 1968 he was appointed to the New York Psychiatric Institute as Chief of Pharmacy and Professor of Biochemistry, and in 1969 established the division of neuroscience. He remained there until 1985 when he moved to the Albert Einstein College of Medicine, and retired in 1986. His research led to major contributions in cardiovascular disease, connective tissue diseases, cancer and demyelinating diseases. For further details, see his obituary in the *New York Times*, available online at www.nytimes.com/2011/09/03/health/03rapport.html (visited 16 July 2013).

Professor Gavin Reynolds

PhD (b. 1952) studied chemistry at the University of York and received a PhD in biochemistry from the University of London. His post-doctoral work in London and Vienna established his long-standing interests in the neurochemistry and pharmacology of schizophrenia and other neuropsychiatric disorders. He developed these research interests further while 'brain-banking' with the MRC in Cambridge and following an appointment in 1985 as Wellcome Lecturer at the University of Nottingham. In 1990 he moved to the University of Sheffield and in 2004 took up the Chair of Neuroscience at Queen's University Belfast. He is now Honorary Professor in the Biomedical Research Centre at Sheffield Hallam University and Professor Emeritus at Queen's University Belfast. He was President of the British Association for Psychopharmacology (2008-2010).

Professor Merton Sandler

MD FRCP FRCPath FRCPsych (b. 1926) trained in medicine at Manchester University, and held various house and registrar jobs leading to a Lectureship in Chemical Pathology at the Royal Free Hospital Medical School. He was Professor of Chemical

Pathology, University of London, from 1973 to 1991. He was President of the British Association for Psychopharmacology (1980–1982). He has received various international honours and awards, including the CINP (Collegium Internationale Neuro-Psychopharmacologicum) Lifetime Award for contribution to monoamine studies in human health and disease. For an interview with Merton Sandler, see Healy (1996), pages 381–400.

Professor Gareth Sanger

PhD DSc FBPharmacolS (b. 1953) received his BSc and PhD degrees in physiology from the Universities of Newcastle-upon-Tyne and Manchester (1974 and 1977), later returning to Manchester to be awarded his DSc in 1998. He worked as a post-doctoral fellow at King's College Hospital Medical School, London, where he was among the first to examine the functions of some of the newly discovered prostanoids on the human isolated gut. A move to industrial research led to his identification of a novel 5-HT receptor-mediated function in the gut, later named by others as the 5-HT_4 receptor. Parallel research led to the identification of the role of the 5-HT_3 receptor in the mechanisms of emesis and to new drugs to treat severe emesis, for which he was jointly awarded the 1998 Discoverers Award by the Pharmaceutical Research and Manufacturers of America (PhRMA). Within industry he then explored several research areas, helped place several novel compounds into development, published more than 110 original research papers, served on editorial boards and taught on MSc courses (Palliative Medicine, Gastroenterology). In 2008 he was elected Fellow of the British Pharmacology Society and in 2009 he joined Queen Mary, University of London as Professor of Neuropharmacology within the Neurogastroenterology Group. His current research focus is on the use of human gastrointestinal tissues to undertake translational neuropharmacology and investigate functional changes during advanced age and different conditions associated with gastrointestinal neurodegeneration. His first paper won a 'highly commended' award from NC3Rs for promoting a culture shift in the use of human tissues for functional research.

Professor Tilli Tansey

PhD PhD DSc HonMRCP HonFRCP FMedSci (b. 1953) graduated in zoology from the University of Sheffield in 1974, and obtained her PhD in *Octopus* neurochemistry in 1978. She

worked as a neuroscientist in the Stazione Zoologica Naples, the Marine Laboratory in Plymouth, the MRC Brain Metabolism Unit Edinburgh, and was a Multiple Sclerosis Society Research Fellow at St Thomas' Hospital, London (1983–1986). After a short sabbatical break at the Wellcome Institute for the History of Medicine (WIHM), she took a second PhD in medical history on the career of Sir Henry Dale, and became a member of the academic staff of the WIHM, later the Wellcome Trust Centre for the History of Medicine at UCL. She became Professor of the History of Modern Medical Sciences at UCL in 2007 and moved to Queen Mary, University of London (QMUL), with the same title, in 2010. With the late Sir Christopher Booth she created the History of Twentieth Century Medicine Group in the early 1990s, now the History of Modern Biomedicine Research Group at QMUL.

Dr Mike Tyers

PhD DSc (b. 1946) obtained his first degree in pharmacology at Chelsea College, London. His industrial career started at Allen & Hanburys Ltd, Ware, (now part of GlaxoSmithKline), where he undertook his PhD studies on nicotinic receptor blocking drugs under the supervision of the late Sir David Jack and Dr Roy Brittain. This early work included the discovery of fazadinium, a muscle relaxant that was used clinically for a few years. He later undertook research in the field of opioid, neurokinin and 5-HT receptors, aiming to identify novel analgesic drugs. After several senior roles in Glaxo, he became Director of Pharmacology at Ware in 1992. Moving to new laboratories in Stevenage in 1996, he then undertook a role as Group Director of Therapeutic Research, providing oversight of all therapeutic areas internationally. His greatest recognition came from the discovery of ondansetron, a 5-HT_3 receptor antagonist. His investigation of the functional role of 5-HT_3 receptors led to early clinical studies in migraine, and emesis associated with cancer chemotherapy. In 1990 ondansetron (Zofran) was launched as an anti-emetic And was awarded the European Prix Galien Award for best drug introduced that year, and in 1998, Mike was jointly awarded the Discoverers Award by the Pharmaceutical Research and Manufacturers of America (PhRMA)for his contribution to the launch of Zofran in the US. Also that year, together with colleagues, he was awarded the Royal Society Mullard Medal

in recognition of their work in the field of 5-HT therapeutics. He received a DSc in 1994 in recognition of his research into drug receptor subtypes.

Dr Sydney Udenfriend

PhD (1918–1999) graduated in chemistry at City College, New York, in 1939 and then went on to receive his Master's degree and his PhD in biochemistry from New York University in 1948. After post-doctoral studies, he joined Bernard Brodie at the National Heart Institute, Bethesda, in 1950, where he collaborated with Julius Axelrod and Al Sjoerdsma on malignant carcinoid. He set up a laboratory of clinical biochemistry focused on the biochemistry of 5-HT, biogenic amines and collagen biosynthesis. In 1968 he was appointed Founding Director of the Roche Institute of Molecular Biology, Nutley, New Jersey, where he developed a fluorescent technique for peptide and protein chemistry. He remained until the closure of the laboratory in 1996, afterwards becoming Director of the Charles A. Dana Research Institute for Scientists Emeriti at Drew University until 1999. For full details of his research, see Weissbach and Witkop (2003).

Professor Sir John Vane

Kt DPhil DSc FRS (1927–2004), pharmacologist, discovered the role of prostaglandins in the human body in response to illness and stress and later demonstrated aspirin's mechanism of action. He shared the 1982 Nobel Prize for Physiology or Medicine (with Sune Bergström and Bengt Samuelsson). A student in Professor J H Burn's laboratory at the University of Oxford, he gained a BSc in pharmacology in 1949, followed by a DPhil with Dr Geoffrey Dawes at the Nuffield Institute for Medical Research, Oxford, and later held the Royal Society's Stothert Research Fellowship. He was Assistant Professor of Pharmacology at Yale University, Newhaven, CT, from 1953 to 1955, moving to work with Professor Sir William Paton at the Royal College of Surgeons' Institute of Basic Medical Sciences, London, in 1955, first as Senior Lecturer, Reader and as Professor from 1966 to 1973. He became Group Research and Development Director at the Wellcome Foundation, Beckenham, Kent, from 1973 to 1985, moving to the William Harvey Research Institute as Director in 1986 and Chairman from 1990 until his death. He was also Professor of Pharmacology and Medicine at the New York Medical College

(1986–2004). See Moncada (2006). See also http://nobelprize.org/medicine/laureates/1982/vane-autobio.html (visited 24 July 2013).

Professor David Wallis

PhD HonFBPharmacolS (b. 1934) trained as a zoologist at the University of Cambridge, and was a Research Fellow at the University of Pennsylvania, Philadelphia (1959–1961) and in the department of Physiology, University of Aberdeen (1961–1967), working with Hans Kosterlitz and Gordon Lees. In 1967 he moved to Cardiff with main interests in neuropharmacology and neurophysiology. He was on the editorial board of the *British Journal of Pharmacology* (1982–1988) and was Chairman of the British Pharmacological Society committee. He is Emeritus Professor of Physiology at Cardiff University.

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