PHARMACOLOGY & DRUG DISCOVERY

Compilation of edited interviews conducted by the
History of Modern Biomedicine Research Group,
Queen Mary University of London

Edited by E M Tansey and A Zarros

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CONTENTS

THE HISTORY OF MODERN BIOMEDICINE INTERVIEWS (DIGITAL COLLECTION) AND THE CURRENT VOLUME

The History of Modern Biomedicine Research Group originated in 1990 as the Wellcome Trust's History of Twentieth Century Medicine Group, which in October 2000 became a part of the Wellcome Trust's Centre for the History of Medicine at UCL. From October 2010 until June 2017 it was a part of the School of History, Queen Mary University of London, principally funded by a Strategic Award from the Wellcome Trust.

Throughout that period, the remit of the Group has been to develop and strengthen links between medical historians, and medical scientists, and practitioners, and to stimulate and expedite the historical study of contemporary biomedicine, especially by creating material resources to inform such studies. These have included the famous Witness Seminar series, widely available freely online and in print,[1] and more recently a series of in-depth individual interviews.

The History of Modern Biomedicine Interviews (Digital Collection), curated by Professor Tilli Tansey, Mr Adam Wilkinson, Mr Alan Yabsley, and Dr Apostolos Zarros, comprises these interviews.[2] The Collection has been deposited in Queen Mary Research Online (QMRO), the online repository of Queen Mary University of London.[3] The material has been linked to Digital Object Identifiers (DOIs) and can be cited.

The History of Modern Biomedicine Interviews (Digital Collection) contains approximately 700 items including audio and video interview transcripts (as .pdf files), and video interview media files (as .mp4 files; video clips corresponding to the video interview transcripts archived). In addition, each interview entry includes a 'How to cite' file (.docx file) that acts as a guide on how to cite each item.

Readers should note that video interview transcripts deposited there are edited for clarity and factual accuracy, following the principles of oral history methodology. However, the Collection's audio interview transcripts are in most

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[1] See http://www.histmodbiomed.org/article/wellcome-witnesses-volumes (accessed 28 March 2017).

[2] Tansey E M, Wilkinson A, Yabsley A, Zarros A. (curators) *History of Modern Biomedicine Interviews (Digital Collection)*. Queen Mary Research Online. Queen Mary University of London, London, 2016–2017; https://qmro.qmul.ac.uk/xmlui/handle/123456789/12359 (accessed 28 March 2017).

[3] For more details, visit the QMRO website at https://qmro.qmul.ac.uk/xmlui/ (accessed 28 March 2017).

cases subject to enrichment by the interviewee and further editing. Related material has been deposited in the Wellcome Library.

We now present a further edited selection from that Collection. This, the third of a three volume series of 'Voices of Modern Biomedicine', focusses on pharmacology and drug discovery. Sections have been selected and edited to highlight the broad features of each interviewee's career and contributions, and much detail has been omitted. Readers wanting to learn more are encouraged to read the full interview and other material listed in the 'Related resources' section at the end of the volume. Moreover, we should note that some readers might consider that the interview of Josephine Arendt is of less relevance to the thematic core of drug discovery and pharmacology; we, the editors, do not share this view. We believe that her work and her experiences – as highlighted within the included edited interview – offer an interesting account of the discoveries that led to the understanding of the crucial role that melatonin and other metabolites play in the regulation of circadian rhythmicity, which is a major (patho)physiological regulator in health and disease.

ACKNOWLEDGEMENTS

We are grateful to Professor David Webb for writing an introduction to this volume, and also to the Wellcome Library, London, for permission to use photographs.

We would like to thank Ms Lynda Finn for conducting a number of these interviews; Ms Emma M Jones, Ms Caroline Overy, Mrs Sarah Beanland, and Ms Fiona Plowman for their editorial assistance; Mr Alan Yabsley for his editorial and technical support (including filming and production of several of the original interviews); and Mr Adam Wilkinson for his excellent project management. We are grateful to Mr Jeremey Claridge, Dr Stephen Welburn, and Mrs Sarah Molloy for their time and assistance in setting up the History of Modern Biomedicine Interviews (Digital Collection), assigning DOIs to the interview transcripts, and making sure this Digital Collection is well integrated in QMRO. We are also grateful to Mr Akio Morishima for the design and production of this volume; the indexer Ms Cath Topliff; and Mrs Debra Gee for transcribing the original interviews. Finally, we thank the Wellcome Trust for their financial support.

ILLUSTRATIONS AND CREDITS*

* All photographs were taken by Thomas Farnetti, Wellcome Trust, and reproduced courtesy of the Wellcome Library, London.

ABBREVIATIONS

5-HT	5-hydroxytryptamine; serotonin
6-keto-PGF1α	6-keto-prostaglandin F1 alpha
AFRC	Agricultural and Food Research Council
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
BAP	British Association of Psychopharmacology
BBSRC	Biotechnology and Biological Sciences Research Council
B J Clin Pharm	*British Journal of Clinical Pharmacology*
BJP	*British Journal of Pharmacology*
BMJ	*British Medical Journal*
BNA	British Neuroscience Association
BPS	British Pharmacological Society; Pharm Soc
BRA	Brain Research Association
CASE	Collaborative Awards in Science and Engineering
CNS	central nervous system
COMT	catechol-O-methyltransferase
CWC	Chemical Weapons Convention
DMU	De Montfort University
DMPK	drug metabolism and pharmacokinetics
ECT	electroconvulsive therapy
EEG	electroencephalography
FDA	Food and Drug Administration (US)
fMRI	functional MRI
GABA	gamma aminobutyric acid
GI	gastrointestinal
GM	gastric motility
GP	General Practitioner
GSK	GlaxoSmithKline

HPLC	high pressure liquid chromatography
IBS	irritable bowel syndrome
ICI	ICI Pharmaceuticals
IUPHAR	International Union of Pharmacology
J Physiol	*The Journal of Physiology*
KCL	King's College London
MAO	monoamine oxidase
MDMA	3,4-methylenedioxy-methamphetamine
MIMS	*Monthly Index of Medical Specialities*
MRC	Medical Research Council
MRI	magnetic resonance imaging
Na^+,K^+-ATPase	sodium/potassium ATPase
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NHS	National Health Service
OUP	Oxford University Press
Pharm Soc	British Pharmacological Society; BPS
Phys Soc	The Physiological Society
PTSD	post-traumatic stress disorder
QMUL	Queen Mary University of London
R&D	Research and Development
RCS	Royal College of Surgeons
RS	Royal Society
SAD	Seasonal Affective Disorder
SB	SmithKline Beecham
SHO	Senior House Officer
SSRI	selective serotonin reuptake inhibitor
SWOT	Strengths, Weaknesses, Opportunities, Threats (analysis)
TAT	Therapeutic Area Team

INTRODUCTION

The science of pharmacology has made outstanding contributions to the discovery and development of medicines over the last 50 years, and at the same time supported the health and wealth of the United Kingdom. This fascinating volume, which complements the highly successful Witness Seminar programme, brings together edited interviews with a range of individuals with different fields of expertise and perspectives. It takes us through the careers and life journeys of eminent pharmacologists, and reminds us how research completed in academic institutions, the pharmaceutical industry and the National Health Service has had major effects to extend life, and improve the quality of life, in those of us born in recent times.

The pharmacologists and clinical pharmacologists who have contributed first-hand accounts are highly-regarded for the leading roles that they have played in advancing our vibrant field of science. We must be grateful to the participants for the generosity with which they have given their time to this project, and for their openness in discussion. We all gain from 'standing on the shoulders of giants' and it is essential that future generations of pharmacologists – and other medical scientists and practitioners – can learn from the successes and disappointments recounted here. Knowing something of our past is important for the vibrant good health of our discipline, to remain at the cutting edge of research, and continue to enhance health and wellbeing.

Several of these individuals have been leading figures in the British Pharmacological Society (BPS), and as its current President, I would like to thank them for supporting the Society in so many ways. Most of them speak with affection of the important role the BPS played in their own scientific development and career trajectories, and in turn also describe the leadership roles they too assumed within the Society in time.

I am aware that this volume, and the complementary Witness Seminars, represent only some of the key achievements in 20th century pharmacology. I would very much hope that these reminiscences and memories will encourage others to record and understand the stories of our recent past.

Professor David Webb
Clinical Pharmacology Unit, BHF Centre of Research Excellence
University of Edinburgh

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Figure 1: Professor Josephine Arendt

Professor Josephine Arendt (b. 1941) is Emeritus Professor of Endocrinology in the University of Surrey. Trained as a biochemist, she is a specialist on biological rhythms and has pioneered the field of chronobiology. She has researched biological rhythms and their mechanisms widely in animals and humans, including studies on jet lag, sleep disorders in the blind, shift work, and devised techniques to measure melatonin and its metabolites. In this interview and associated material, she describes her career and discusses many of these fascinating aspects of her work.

1 Arendt, Josephine*

Tilli Tansey: Thanks very much for coming, Jo. Could I ask you about how you first got interested in science and in developing a professional career in science?

Josephine Arendt: I emerged from University College London in 1962 with a degree in biochemistry and was looking for a PhD place. I ended up in the lab of Professor Merton Sandler at Queen Charlotte's Hospital in Goldhawk Road, working on tryptophan and its metabolism to 5-hydroxytryptamine (5-HT) or serotonin, which wasn't then known to be a neurotransmitter. I managed to separate out the D- and L-isomers of commercially available tryptophan; my first ever publication and the only one I've ever had in *Nature.* The L form of tryptophan – which is the precursor of 5-HT – was quite important from the point of view of metabolic studies. A chap called Aaron Lerner discovered a new hormone (by processing about 350,000 pineal glands), which he called melatonin (chemically, *N*-acetyl-5-methoxytryptamine). Julie Axelrod at National Institutes of Health (NIH) found that melatonin was derived from 5-HT, which was my Thesis subject. A very fascinating molecule because it causes frogs' skin to blanch by constricting cells called melanophores; exactly the opposite of what melanocyte-stimulating hormone does, and that was its only known function at the time. In fact, the pineal itself was considered to be a rudimentary vestige. It was a jolly good neuroradiological marker because it calcifies in most people early in life, and that was about all it was useful for. The discovery of this hormone was really fascinating, and because it was derived from 5-HT, I looked for a grant to work on it.

We liked Switzerland, and we both got jobs in Geneva. My husband got a job at the Cyanamide European Research Institute and I just went for whatever was going, and initially there was a research job in biochemistry at the École de Chimie. Then I applied to the Paediatric Clinic in Geneva to see if I could do some neuroscience work related to melatonin. Pineal tumours were associated with precocious puberty, and Virginia Fiske had shown that the pineal appeared

* Edited passages from the interview conducted by Professor Tilli Tansey, 17 March 2015, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

to be influenced by light and light affected the ovaries and might influence this hormone melatonin. So to connect endocrinology with my indole expertise was this little loop: 5-HT, melatonin, possible light effects, reproduction, puberty, and I got a grant to develop a measurement system for melatonin. The only way of measuring it at that time was by dripping it onto frog/toad melanophores, and a very tedious procedure it was. I had a whole breeding system for *Xenopus laevis* – the African clawed toad – in the lab and initially used the tadpole melanophore reaction to melatonin as a bioassay. Each point on the calibration curve required looking at 30 tadpoles separately under the microscope. But it was very sensitive, down to 10^{-12} pg/ml. It was quite hard to get the money.

TT: Where was the grant from and how did you get that?

JA: I applied to the Fonds National Suisse de la Recherche Scientifique [Swiss National Science Foundation] and their first answer was 'No.' Someone said, 'The reasons were that I was foreign, I was female, and I had a family.' Wouldn't be allowed these days.

TT: The "three Fs".

JA: I protested and they sent me to see Professor Alfred Pletscher, who was Head of Research at Hoffmann La Roche, and then Head of the Fonds National Suisse. I must have convinced him that it was worth supporting me, because I got the grant and set off to measure this difficult hormone. The Department of Paediatric Endocrinology were experts in radioimmunoassay; this was the standard technique at the time to measure steroid hormones, and Berson and Yalow had got the Nobel Prize for developing this technique.

I went for the most sensitive technique and we were lucky. It just so happened that in Geneva at that time there was a little lab called Plan who made *N*-acetyl-5-methoxytryptophan which is melatonin with a carboxyl group attached to it. And we were able to link through that with a peptide bond to a large antigenic protein, and we got antibodies to melatonin. And then Radioimmunoassay works on the principle of a radioactive label (that is we had to make melatonin itself radioactive), and the measurement is the displacement of the radioactive melatonin bound to an antibody by whatever melatonin is present in the tissue or fluid that you're measuring.

So we had to make a radioactive label and I managed to make the first tritiated melatonin with tritiated acetyl-CoA, which was highly radioactive. I'll never forget this moment actually when we had one of these old-fashioned radiation

counters called a Tricarb, and it counted β-radiation and γ-radiation. There was a little switch which changed the counting from one to the other. After working away at this synthesis and getting a minute amount of what I thought might be the right thing, I put it into the counter, turned it on and there was nothing there. And then I suddenly realised I'd got it on γradiation, and switched it over to beta and there it was. It was as radioactive as it was possible to be at the time. This was 1973.

TT: You were at the cutting edge, developing that radioimmunoassay?

JA: Pretty pioneering, yes. This was long before Al Lewy produced his GCMS [gas chromatography-mass spectrometry] method, his was published in about 1978? I started work in 1972, it worked in 1973 and was published in 1975.

TT: How influential was it at the time? Did lots of people then pick up on that, pick up on your techniques for developing other assays?

JA: It's a very niche area, the pineal gland. There's a whole school and vast numbers of publications on melatonin, but the pineal is still pretty much a niche area although we know now what it's most important function is. Once we had a measurement system going it just opened all the doors. People like Fred Turek who was interested in the endocrinology of melatonin; and people like Lennart Wetterberg, who was interested in Seasonal Affective Disorder (SAD). Wetterberg was interested in depression generally, he was Head of the St Joran's Hospital a psychiatric hospital at the Karolinska Institute. He phoned me up the day after the paper was published, and said 'I would like to measure melatonin. What can you do for me?' He had lots of strings he could pull, and one was a company called KABI, a Swedish company which makes reagents and they also made an antibody.

It turned out it was somewhat better than my first one, but mine was still the first! We collaborated with Wetterberg because he had access to clinical samples. Once this assay was up and running, almost the first proper experiment I did was to get all the lab to sit in darkness up to midnight, and take blood samples before and at the end of darkness; and then on another occasion, sit them in room light, up to midnight, and take blood samples before and at the end of light, to see if light affected human melatonin. And because it was room light, it wasn't strong enough.

The light connection was there because we knew from Wilbur Quay's work and also from Helena Illnerova that there was a strong rhythm in the pineal, of 5-HT that it went down during the night and up during the day. And from the work especially of David Klein and Helena Illnerova that *N*-acetyl-transferase the rate limiting enzyme in melatonin production had a high amplitude rhythm in the pineal – the opposite to that of 5-HT, and was suppressed by light. This is all in rats. We knew that 5-HT was the precursor of melatonin and we expected melatonin to be made at night in people. In our first radioimmunoassay paper in 1975 we looked at night and day melatonin in people and it was higher at night. So we knew there was a rhythm, and because it was night-related, we expected light to be important.

My remit, because I was in a Paediatric Endocrinology Unit, was to see if it had a role in puberty. We did a lot of careful work looking at pubertal samples, but they were never done properly by frequent sampling throughout the night in very dim light. It's jolly hard to get clinicians to take samples in the middle of the night. We, at that time, never found a difference. We now know it does go down in children before puberty, and it certainly does help to time puberty in animals. This is where the light comes in again because we knew from early pioneers that duration of the day governed the timing of seasonal reproduction in what are called photoperiodic species, including sheep, hamsters, mink, horses – vast numbers of animals govern their reproduction by the day length.

When we found nothing of any real interest in human puberty at that time, it was important to work on something which clearly responded to light. At that point we moved back to England. Now there's other stuff in-between times. There was, in the mid-1970s, well actually 1972, Joe Herbert in England, in Cambridge, and Klaus Hoffman in Munich, at the Max Planck, were both involved in showing that the pineal was involved in the timing of seasonal reproduction in ferrets and hamsters. They didn't know for sure that it was melatonin, but did know it was the pineal. So we have day length, melatonin being made at night in the dark phase therefore probably associated with photoperiod: photoperiod times reproduction.

In 1974, Dave Klein, Joan Weller, and Robert Moore, published a series of papers showing that the rhythm of the melatonin pineal production was governed by the suprachiasmatic nucleus, the central clock so-called, or pacemaker in rats. In 1977 we looked at pineal synthesis of melatonin, we looked at the enzyme in the pineal, the hormone in the pineal and the hormone in the blood simultaneously in rats, through 24 hours, and that was a night to remember. They showed a

beautiful correlation: the synthesis going up, pineal melatonin going up, and blood melatonin going up. So we knew that whatever is going on in the pineal appears in the blood, and therefore because the suprachiasmatic nucleus – the clock – governs the pineal rhythm, that we have an external peripheral marker for the clock. This was way back in the mid-1970s. So that was pretty exciting.

TT: You came back to the UK in 1977?

JA: We left in 1977. We came back mostly because of children's education and elderly parents. We both looked for jobs. My husband found a job in the Paint Research Institute in Teddington, and the University of Surrey had a big radioimmunoassay group under Prof. Vincent Marks, who you have probably come across? The Swiss let me take the technicians and quite a bit of the grant. And so I was welcomed with open arms. I was given lab space and it so happened that Vincent was very entrepreneurial. He used an Occupational Therapy Unit to make antibodies at Hurstwood Park Mental Hospital. The reagents that came out of it were supplied to the NHS (National Health Service). So I sent over my melatonin antigen and when I arrived in Surrey, we had a new antibody on the way which we are still using. I then acquired a whole batch of new antibody; this is now the third anti-melatonin antibody we used. One was the original one in Geneva; then there was the one in Stockholm, KABI, of which I had a free supply; and finally, the Guildford antibody. Vincent had set up a company to sell off any antibodies surplus to NHS requirements. So I set up my own company.

TT: This is Stockgrand?

JA: It's an off-the-shelf, £250 company, all set up in 24 hours. This was in 1988 and it has been enormously important, because it provides bridging funds. It has in fact supported wholly some PhD-students and partly many more – 18 I believe – it enables us to go to conferences and things like that.

And now, this starts relating to SAD. When I moved to England somebody told the Maudsley there was now a melatonin assay in England. There weren't many around at that time and Stuart Checkley got in touch. I knew Anna Wirz very well, she was in Switzerland at the Basel Psychiatric Clinic, and she'd gone to work at NIH with Tom Wehr and Norm[an] Rosenthal. And I'd met them all at conferences. Stuart wanted to collaborate, looking at his psychiatric patients, under different treatment regimes with light, and under different anti-depressants. Stockgrand, in addition to selling the reagents, offered an assay

service. After a bit I thought, 'This is not doing my academic career a lot of good. It's not my work, it's their work'. Mine was the Antarctic, and the sheep side, the melatonin chronobiotics. I'll have to backtrack on that, won't I?

TT: Yes, we want to go into that.

JA: I thought, 'Well, why don't we just do assays for money, and I'll employ somebody to do it,' which we've done ever since.

TT: Did you have a formal academic appointment at this point?

JA: I had a grant to pay my salary from the Medical Research Council (MRC).

TT: Did you apply for your own salary, or did Vincent Marks?

JA: He didn't have a job for me then. The Swiss I think paid me while I got going, and then I put in a grant to do further radioimmunoassay development of the major melatonin metabolite, and another one called 5-methoxytryptophol, all related to melatonin. The melatonin metabolite was really successful, it was a terrific project and that assay's gone all over that world. That enabled me to take on Debra Skene, then a post-doc, to develop the 5-methoxytryptophol assay. She took over most of my group when I officially retired, and we worked together from 1984. Other people have developed these assays since, but we did it first. I have to blow my own trumpet otherwise you just get lost in the literature. Students don't cite anything that's older than ten years these days. And if somebody writes a review, they don't bother to refer to the original literature. And I think, 'God, look at all that work we did.'

TT: That is one of the reasons we do these interviews and the Witness Seminars, to try and record the actual work that people do.

JA: It's great, and it's digitised, it's modern, it's accessible. It's terrific!

TT: Then had an MRC grant that was paying your salary?

JA: Yes. At some point, about 1980, Vincent found a job called 'Experimental Officer'. Then the Wellcome Trust stepped in at one point, they paid my salary for several years on condition that the University took it over.

About 1986ish I published the first treatment of jet lag with melatonin. Nobody believed it. Now half the world uses it. I applied to the Wellcome for a project grant, to see what melatonin might potentially do to circadian rhythms, for the therapeutic possibilities. I didn't get it, but the Wellcome Trustee Stan Peart

wrote me a really nice letter saying 'You'll get it one of these days'. In other words, he was favourable, but the prevailing opinion was that melatonin was a waste of time. I also applied to the MRC for a programme grant which in the end was not successful. People used to say things like, 'Circadian rhythms? That old chestnut.' It's funny, isn't it how things change?

TT: Could you say a little bit more about the jet lag study?

JA: Let me tell you how I got into it. In 1980 I developed breast cancer. I had a full mastectomy and felt dreadful afterwards – I couldn't sleep. We knew that melatonin had possibly some anti-cancer effects and I knew that it would shift rhythms in sheep, and so I thought, 'I'll take some melatonin.' And I did. And it worked, n=1, but there's lots more evidence these days. It made me sleep when I wanted to go to sleep, which it does for delayed phase sleep syndrome. Whether it did anything for the cancer, I don't know, but I went 28 years without any recurrence. Then, without any money really, I said, 'Well, I'm going to do a proper clinical trial, because if it shifts rhythms it has potential therapeutic value.' I'm talking now 1982. I recruited 12 of my colleagues at Surrey, I'm not sure I had ethical permission for it, to take 2 mg every evening, and we didn't know how long to take it for before it had an effect but we knew that it took at least a month to have an effect on sheep's reproductive rhythm timing. So we thought we'd better give it them for a month every evening [laughs]. I was very lucky to get all these volunteers; I don't think they'd do it these days. In fact, someone wrote an anonymous review in *The Lancet* about melatonin saying it shrank hamsters' gonads and was probably not a good idea for people. So the first proper study we did was to see if it really works on more than one person, two in fact. Does it have any nasty side effects? We didn't know how long we'd have to take it for, but they took it for a month and it was a double blind, randomised placebo controlled trial. It made people feel sleepy earlier in the evening, but most importantly, when we could distinguish the endogenous melatonin rhythm, from the exogenous, it shifted the endogenous rhythm; it advanced it. You couldn't see it in everybody because of variable metabolic clearance rates, but you could see it in five of our 12 volunteers: a clear advanced circadian rhythm shift. And at this point, I applied to do a CIBA Foundation Symposium on the subject of photoperiodism, melatonin and the pineal. The Symposium was in 1984, it was published in 1985. Then, having personally been convinced that melatonin could shift rhythms the next thing was, wouldn't it be fun to do a jet lag study?

Again, Vincent was helpful. He had a contact on the *Financial Times*, I think, and they put a little thing in the paper: 'The University of Surrey wants to do a jet lag study and is looking for sponsorship.' Through that, I got free flights from British Caledonian airways, some free hotels, including the Mark Hopkins Intercontinental, which is one of the poshest ones in San Francisco, several other small sponsors especially Horner Ltd Montreal – Dennis Jones – and no shortage of volunteers. We had enough money to send 17 people to San Francisco, and made them stay there a fortnight to adapt to West Coast time. We did the study on the return journey, so we could do all the measures in Guildford. It was really good fun doing this. Alex Borbely in Zurich lent me the very first actigraphs, small wrist monitors which measure activity and rest moments and tell people how they sleep. They're extensively used by sleep labs now to see how interrupted people's sleep is.

We had the actigraphs to get an objective measure of sleep, we got them to collect their urine every four hours during the day and overnight, so they walked around the west coast of California carrying bags of pee. They did that for several days before they left so we had a baseline to see if they were entrained to California time, and then sequentially for one week, and then 48 hours a week later, and 48 hours a week after that, when they got home. We collected urine because by then we'd developed a new assay for a melatonin metabolite which reflects melatonin beautifully, to decide if the treatment with melatonin or placebo retimed your clock to UK time coming back from San Francisco to London. Did it speed it up? And it did, just significantly. We published this in the *BMJ* (*British Medical Journal*) at which point all hell was let loose. The media just went absolutely bananas, and I was a sort of bad smell as far as the field were concerned – complete crap, no proper controls, etc. [laughter]. However, there has been a meta-analysis, several in fact, which says it works and there have been a lot of studies since then. You've got to get the timing right and then it really does work.

TT: I do want to talk about comparative aspects. There is a whole other group of people working on photoperiodism and circadian rhythms, the zoologists and the animal behaviour people.

JA: This is the real function of the pineal gland. When I arrived in Surrey there was a sheep reproduction expert there – Andy Symons – and he was only too happy to set up a joint grant because we knew that sheep bred according to the length of the day. The idea was to look at melatonin in sheep to see if it changes with the length of the day, and we had an AFRC [Agricultural and

Food Research Council] grant and we did at least ten years' worth of sheep and could show very clearly the change in duration of melatonin throughout 24 hours in the course of the seasons – a longer profile in winter. The next idea was, if we give them a winter melatonin profile in the summer – sheep breed in the winter – will they come into season? And they did. In other words, if you keep sheep in summer day length for long enough, even if they never see a winter day, they will come into season anyway because they've become refractory to summer day length. And, likewise, if you keep them in winter day length or if you like, winter melatonin, long enough, they'll become refractory to that and go out of season.

TT: So it overrides it.

JA: Yes. This was of academic interest, but also of commercial interest because you get better prices for early lamb than for late lamb.

At this time I was contacted by Prof. Isabel Forsyth from the AFRC Institute in Shinfield, Reading. She was interested in the neuroendocrine control of reproductive function in goats, and with AFRC funding we investigated the roles of photoperiod, temperature and melatonin in reproduction and coat growth in dairy goats during the 1990s. A goat's response is similar to that of sheep – photoperiod was modulated by temperature. But probably the most interesting observation was that we could demonstrate that pre-natal photoperiod dictates the timing of puberty postnatally. Thus, maternal perception of photoperiod was transmitted to the foetus.

The main thrust was the physiological role and therapeutic potential of melatonin. But it was a bit opportunistic as well, having assays means you can do all sorts of things. It was a good position to be in. It was hard to find funding, but the whole field was wide open and there was the SAD business going on, there were rhythms going on all over the place, there was the connection to NIH, the connection to the Maudsley... It was a busy time. What was difficult, but no longer is, was to do our own proper human experiments. We didn't have any proper human clinical research facilities except when on two occasions we could use a hospital ward. At one point I bought in six Z-beds, and put them in a very small room in order to give people light treatment in the middle of the night. That was our clinical research facility.

People were very interested to collaborate on the clinical front at the time, and particularly the NIH connection, because Tom Wehr, a really wonderful guy, kept people, not sheep, in 14 hours of solid darkness a day, for two months, and

then two months of ten hours solid darkness. He showed that people do what sheep do with melatonin: they have longer profiles in shorter days. That was all done through our company, the assays were done by Stockgrand.

TT: This NIH connection is through Anna Wirz?

JA: In 1977 Anna and I gave two related presentations, at one of the first ever chronobiology conferences in Pavia in Italy, and at that conference was Dan Kripke and Tom Wehr; both are psychiatrists interested in rhythms. Anna went to work with Tom and took the idea of measuring melatonin, although at this point Al Lewy went off to develop the mass spectrometry assay for melatonin at NIH. I had the only assay available at the time, so did quite a lot with them.

Anna and Tom got the Santa Monica Prize for looking at depression in a new way. They had sleep-deprived a depressive and completely remitted their depression more or less instantly. Rhythms were very strongly connected to psychiatry, and this is simultaneous with us working on sheep in Surrey. I took the sheep duration and breeding season change to a Gordon Research Conference in New Hampshire and I there also met Al and Norm.

At that point the British Antarctic Survey had asked me if I would like to give the Base medic a research project in Antarctica, because he hadn't got anything to do. So I knew about the SAD story. Al, Norm and I sat down on the beach, and I said, 'Look, I've got this wonderful opportunity to do a project in Antarctica. It doesn't get much darker than that. I assume that they get depressed in the winter and I'm going to give them some light treatment. What do you recommend? How long should I give it for?' They said, 'We don't know, try giving it for six weeks,' as we knew this would change the seasonal status of sheep. So I did. You can't get fit, healthy, young men to sit down for three hours in front of a bright light in the morning and the evening, as they did in treating the first SAD patients. I did an hour morning and evening, and we used the amount that Al said completely suppressed melatonin. It was of such interest that a chap called Luke Thorington, who was Director of a light manufacturing company, Full Spectrum Lighting, donated the lights to take to Antarctica and paid for them to get there.

We got the best possible advice, we got the lights, and we were allowed to take blood samples in Antarctica, and so that's what I did. What we showed was a very clear circadian rhythm shift with light treatment.

TT: Can I ask you a little bit more about SAD? You know Anna and Tom very well, you've met Al and Norm. How does this take off, and what are you views about some of the things that were going on generally?

JA: I had a problem with the phase delay theory about at that time, which I think was published in 1987. We'd done our first Antarctic work, and seen a major phase delay in the Antarctic winter. But they don't get SAD on the whole. If you look at it from that point of view, lots of people get phase delayed in winter, particularly in our climate, we have these miserable, dark days. And not everybody gets SAD. One is not a condition for the other to develop. There has to be something more than that, to my mind. Phase delay, and, of course, as Al says, phase advance in some cases plus what? Al has published in, I think, the *Annals of the New York Academy of Sciences* that there's a kind of sweet spot whereby people's circadian phase and their sleep has to be just right for them not to get SAD. It's quite complicated.

Also in Iceland, there's not very much SAD. You'd expect them to get loads of it, wouldn't you? And there is a publication that Icelanders who move to Canada don't get much SAD either. There's a lot of interest in the genetic side of it. But I also think that like a lot of these things including delayed sleep phase syndrome, there's a huge behavioural component.

I'm not sure how this fits in with SAD, but you'll have heard about teenagers not being able to get up in the morning and how they're going to start school later? I think that's behavioural. That's a self-induced delay by evening behaviour. Blue light in the evenings on the computer screen, no morning light, dopey in the mornings, etc. I'm sure many SAD patients have got a terrible problem, if it's not properly treated with light, and that their circadian systems might really not be completely balanced. The behavioural correction is exposure to the morning light, preferably morning light which is immediately alerting. And you don't shift phase immediately. There are things called 'transients', so that there are both immediate and delayed effects of light.

There's a lot more to it than phase shifting, there's a lot more to it than being delayed in the first place and the fact they put quite good films on telly late at night, and a lot of people work shifts and have their circadian rhythms disrupted frequently. A lot of people fly around different time zones. We probably do real damage to our inside timing mechanisms and what that has in the way of psychiatric effects, well, who knows? It is something that has been known for a very long time in the culture of particularly northern countries before the 24-

hour society. Although it's not common in Iceland, it is common in Sweden. It seems to me there's genetics, there's behaviour, possibly compounded by this sort of hyperphagia that they do tend to have, overeating, put on too much weight, look at yourself in the mirror and think, 'Oops.' Hard to get up in the morning, not much exercise. If you don't have to get up over the weekend, you can easily lose three or four hours, you know, and be very delayed on Monday morning. There's huge amounts of things all combined, I'm sure.

TT: By the late 1980s, you've got fingers in lots of different research fields but there are common themes. Is it chronobiology?

JA: Basically the circadian system. Chronobiology refers to biological rhythms of any periodicity. Photoperiodism is based on the circadian system as well because it has to generate the 24-hour photo period changes inside you, as well as the 24-hour clock system. I don't think humans are really different from other animals.

TT: It would be harder to explain if humans were very different from other animals; much harder to explain.

JA: Yes, but Al doesn't accept this, and one of the things that I am convinced of – remember it's really esoteric, I'm afraid, perhaps from your point of view – concerns these two oscillators: the so-called "dawn and dusk oscillators" in animals; they're all over the place. In fruit flies even. Helena Illnerova, brilliant lady and a good friend, so you know I'm biased, but she has shown a clear two oscillator structure of the circadian system generating the melatonin rhythm in rats. And that you can modify it so there's a rise of melatonin, and there's the middle bit, and then there's the fall, and theoretically the rise is controlled by the evening oscillator and the fall by the morning oscillator. And you can adjust them differently from each other so that, for instance, if you give bright light in the early morning it cuts off the melatonin secretion and produces a phase advance of the morning oscillator which is bigger than the phase advance of the evening one, and the same applies in the opposite sense. So you can affect them differently. Both effects temporarily shorten the duration of the melatonin profile. And when I went on about duration of melatonin in humans probably being important, we don't really know too much about it with respect to SAD, because everybody uses the dim light melatonin onset now which is the circadian marker that Al proposed, and it's been very important, no doubt about that. He says he doesn't believe duration of melatonin has got anything to do with it, and that there's no evidence for two oscillators in humans, but there

is in fact. And it may be the coupling strength of these two oscillators which is one of the features of this illness that we really don't know anything about, because it hasn't been properly studied, I think. But this is just me holding forth, I'm afraid.

TT: That's fine.

JA: I have got very nice pictures of human beings with double peaks in melatonin, strongly suggesting two oscillators. Most of them in fact come from Antarctica in semi-natural field conditions with hourly blood sampling for 24 hours. And our sheep clearly had two peaks in the winter, when the night is long enough. In the summer the profile coalesces into one peak.

TT: If we come back to the late 1980s, early 1990s, are all of these things still going on, Jo?

JA: Another aspect of melatonin's chronobiotic activities is the possibility of helping night shift workers to sleep during the day. As a result of the jet lag publicity the Guildford Police approached me to see if we were interested in doing a study on their sleep and alertness. I asked Simon Folkard to help as he is an expert on shift work, and we carefully timed melatonin in a comparison with baseline and placebo, to delay their circadian system in order to improve daytime sleep. We were lucky with the schedule timing, as their sleep did improve. On other schedules results have been mixed, and a lot depends on bright light exposure at times which conflict with the circadian shift. Nevertheless, I think that some shift workers do use it if they have access to it and they find it helps. Simon also stimulating a collaboration with Rutger Wever at the Max Planck Institute in Munich, where I also learnt a lot about the circadian system.

Possibly the most successful therapeutic use of melatonin to date is the treatment of delayed sleep phase, when an individual cannot sleep before the early hours of the morning and cannot get up at a reasonable time. Professor David Parkes from KCL [King's College London] rang up about this time, late 1980s, to propose a collaborative study on his delayed sleep phase patients. This was a timed treatment with melatonin *versus* placebo and was carried out at KCL with some success, and appeared in *The Lancet* in 1990 – another first. Quite recently a meta-analysis of all the delayed sleep phase studies with melatonin concluded that there is good evidence for efficacy.

TT: You're still involved with clinical work, with human experiments, with the sheep work, and you're involved still with the Antarctic?

JA: All the way through. There were years when I didn't do it, but most years from 1984 to 2012, I gave the base doctor a project. And I went there twice.

TT: Did you actually do field work yourself when you went out there?

JA: I was the Medical Research Supervisor. I also did a bit of psychological questioning on request, the British Antarctic Survey wanted to see who would cope best with the situation. They called it SOAP, Selection of Antarctic Personnel – it went on for several years. And they asked me if I would do the questionnaire with all the various people at Halley that year. Mostly it was very important for me to appreciate the actual conditions down there, and how we could change the light conditions for the better as this was to be the focus of the future projects. I also took these potential UV [ultraviolet] monitors out with me, because I had this silly thought about personal monitoring of exposure to different spectra of light. We'd been involved in the effects on melatonin of different spectral composition of light. Jim Horne, a sleep researcher from Loughborough, and I published some effects of green light as compared to white light in the mid-1990s. My colleague Debra Skene had looked at colour-blind people and the effects of light on their melatonin, to see if we could pick anything out of the spectrum there. And then Russell Foster came into the picture.

He and I and some others from Europe put in for a European programme grant to look at an action spectrum of light on melatonin suppression in humans as well as what Russell was doing in his retinally degenerate rats and mice. This was 1999, it was a big grant, and we got it. Russell in the meantime had two *Science* papers in 1999 showing that, even without a functioning retina, mice could respond by circadian shifts to light and by melatonin suppression. That was the intrinsically light sensitive retinal ganglion cells and the melanopsin photoreceptor, so important for resetting the circadian clock, underlining the importance of blue light at *ca* 480 nm. We were all involved in this together.

My first thought was, 'They have delayed sleep in Antarctica in the winter and they have low mood. They don't have SAD, but they do have low mood, and we should do something about their light conditions to correct circadian phase, improve sleep, and improve mood.' On this occasion Phillips lighting were very helpful, because the first year we did it, they supplied 35 light boxes giving 10,000 Kelvin blue enriched light, and paid to ship them there. And then they

upped the Kelvin to 17,000, which was much brighter and bluer, and we did a second experiment. I went down South again for both those projects, and also to do a sleep study on the ship's crew.

What I did was to design the protocol with the base doctor, mostly by e-mail on both occasions. It has been said to me, 'This is all nonsense, isn't it, this light treatment of people for SAD?' I said, 'Delayed phase and poor sleep is not SAD, but it's related' We did a particular protocol right through six months with a month's blue light, a month's white light, a month's blue, a month's white, a month's blue, a month's white. And it was symmetrical so we got the same photoperiods with blue and with white. And the first lot of blue light – 10,000 K – was not very effective.

The maximum lux with the existing base lighting we could measure down there, in 1985 and in 2000 was about 500 lux. If we sat by your window today, we'd probably get 1,000 or so. It's standard indoor lighting, but of course, there's no outdoor sunshine in the winter to back it up. With the first 1985 study, we made sure they got 2,000 lux for an hour, morning and evening. Trying out the blue-enriched *versus* white light, we decided it was easier for them to put the lights all-round the base, have one by each bedside and in the work rooms and in the garage, and Phillips supplied us enough lights to be able to do that, and for us to have them on all day. So they got pretty much a full photoperiod, 10 to 12 hours' worth say, and we told them to turn them off at six o'clock in the evening. We could see on the records actually, because the actigraphs measure light exposure as well as activity and sleep – they can measure lots of other things as well. When they experienced up to 1,000 lux in 24 hours, and it could be any time during the 24 hours, it had a minor effect on sleep efficiency. And it had a minor effect on shifting the delayed phase to a slightly earlier time. But the second study with blue-enriched *versus* white light, they had 17,000 K blue light, which Phillips call ActiViva Active, and this time we had highly significant improvements in sleep timing, in sleep efficiency and a significant advance shift in circadian phase.

On that occasion they got 2,000 lux maximum similar for both types of light. And there was very little difference between the treatment of the blue enriched and the white light. Now if you were to say, as I believe Harvard have done, if you just take the blue wavelengths in that blue light and give them just the blue, you wouldn't need anything like so much light. And that's quite possible, and so when I say that the blue was no more effective than the white, I'm meaning blue mixed with white, and not corrected for wavelength energy, because there's

more energy in blue light. But it was significantly better, both blue and white were significantly better at improving sleep, improving circadian phase, etc. But nobody yet has shown convincingly in SAD that one is better than the other, I'm afraid. One of the things we did with Stuart Checkley at the Maudsley a long time ago, was to look at the effect of three hours of light *versus* one hour of light, morning and evening on melatonin, and there was no difference really in the effect on melatonin. Chris Thompson found some evidence for changes in sensitivity to light in SAD as is discussed in your text [reference to the Witness Seminar transcript; see Related Resources].

TT: Throughout this period, Jo, what is your job situation? You were an experimental officer in the late 1970s, early 1980s.

JA: Very early 1980s. Then I had this op and was off for about six months. I said, 'I want to come back, Vincent.' He had a part-time Senior Lecturer leave at that time, and that post became available, and I got it with a full board interview, as part-time. I was told, 'You don't need a full-time job, you've got a husband.'

TT: Been there, yes, had that myself.

JA: The kids these days, they can't believe it. That was when the Wellcome Trust must have taken over to give me a decent salary because I think it was two fifths, the Senior Lectureship. They gave me a salary for several years on condition the University gave me a full-time job at the end of it, which actually they never did. I never had a full-time job there ever since. I did a fair bit of teaching as well. I set up and ran final year modules in Biological Rhythms and in Neuroendocrinology. Stockgrand Ltd, the company I set up in 1988, would take on selling reagents, doing the assays for money – "three Fs" – and every so often we would do a pharmaceutical company project, we'd make a profit and we'd use the profit for research support.

TT: When you were talking about Geneva, you mentioned those, the foreign female with family. Do you think that if you had been a man you would have been supported more? Would you have had a full-time job?

JA: Very likely, yes. I gave a talk to the European Sleep Research Society in Lisbon a few of years ago on women's experiences in sleep research. I found the most extraordinary figures from UNESCO. The figures for women entering,

say, science and technology and medicine, they are more than 50% for university entry level. And at the other end of the scale, at Chair and better than Chair level, it's less than 10%. Not fair.

TT: And that's an improvement from what it used to be. I want to ask you about influences in your career.

JA: I have greatly admired Joe Herbert in Cambridge. Lovely man. I admire the way he thinks. And I have enormous admiration for Gerald Lincoln. He's a real gentleman, and just to listen to him talk about science is a pleasure. He's terrific.

TT: And why, what is it? Is it the breadth, the depth?

JA: The depth and the sort of comprehensive understanding of the entire subject. In fact, Gerald was one of our entries into sheep photoperiodism because in 1979ish he worked on Soay sheep, which come from the island of Soay, and he took away the pineal principal innervation by superior cervical ganglionectomy, and wanted to know if they produced any melatonin after that. He got in touch with me and I measured melatonin in his Soay sheep, and the melatonin profiles were flat, no rhythm at all in the ganglionectomised sheep. It was another very nice, sort of validation of our assay as well.

TT: What about meetings, conferences you've mentioned a few. What was the most important society or did it change through your career?

JA: The Gordon Research Conference introduction was enormously important. I've been to every pineal Gordon Conference bar one, and they've just stopped having pineal Gordon Conferences, which shows you that the pineal is still very much a niche, but not melatonin. The Endocrine Society was very important. And Brian Pickering – former Deputy Vice-Chancellor of the University of Bristol – introduced me to the Society for the Study of Fertility. But the one which is closest to my heart, although perhaps not so much these days, started off as the European Pineal Study Group in 1977. It's called the "European Biological Rhythm Society" now.

TT: You were a Founder Member? What was your purpose in starting that?

JA: I was certainly a Founding Member. The actual Founders were Professor Johannes Ariens Kappers, Head of the Brain Research Institute in Amsterdam, who found the sympathetic innervation of the pineal, and his student, now Professor Paul Pevet in Strasbourg, France. Kappers and Paul wrote to all the people they knew who were interested in the pineal and we met in 1977 in

Jerusalem and they asked if there was interest in forming a society to study the pineal gland. I was President for three years, and it has been very important to anybody involved with the pineal, and with melatonin for a while, for a long while in fact. But when it became obvious that the importance of melatonin is to do with the whole circadian system, it evolved.

TT: Would you like to talk about shift work and some of the other human studies?

JA: I was rung up, about 1995, by the occupational health doctor of a large oil company, who said, 'I'm a bit worried about accidents on the night shift, would you like to do some investigations?'. It's not often that a project falls into your lap like that, so we collected samples of pee and records of sleep and photo period on the Shell rigs to which we had access. This is a very particular situation, because they have no social life. Once they finish work they can watch a film, go to bed; there's no alcohol, it's all men, although I think some of the cleaners might be women. We wanted to know if the circadian system adapts to nightshifts in these circumstances; sometimes they're there for three weeks. If you're not adapted, you are working under par in a relatively dangerous environment, you are trying to sleep at your most alert phase, and trying to work at your least alert phase.

TT: Can you say something about how that was all negotiated and set up? Your student arrives there with lots of canisters, plastic bags, access to deep freezers? Was it already explained to all the participants, or did your student have to start negotiating individually?

JA: The rig paramedics helped explain why they should volunteer. You only need somebody to measure the urine volume each time they pee, and they're perfectly capable of doing that themselves. If they're compliant, they record volume and the time and keep a tiny little bit in a pre-labelled tube – we don't need very much, and it goes into a deep freeze. The metabolite we measured, 6-sulphatoxymelatonin is rather robust. Later we persuaded many blind people to do sequential urine collections using speaking scales for urine volume, and Braille-labelled tubes for sample storage and audio tapes for keeping volume, time, *etc*, records. I've also done this on ships' crew working shifts sometimes in a force ten gale, and the crew are perfectly capable of doing that as well.

TT: So somebody was out on a rig for how long?

JA: Initially to set up and explain how to do it and how it was important. The paramedics were very helpful. Urine and records were sent back to Guildford. The first experiments were simply collecting urine and recording the timing of sleep, and the photo period. We showed very clearly that certain schedules, like working six in the evening to six in the morning, that's the 18:00 to 06:00 night schedule, most people adapt. The whole circadian rhythm shifts by nearly 12 hours to be in the right phase to be working at night and being awake during the day. This is almost completely unknown in shift work on shore. Even permanent nightshift workers hardly ever completely adapt. But if you were on the schedule which runs from midnight, 24:00 to 12:00 – nightshift – and 12:00 to 24:00 – day shift – you don't adapt. And this is to do with the way that they are exposed to light on this particular timing at a time, which stops the circadian system adapting. It's absolutely crystal clear how this works.

We also looked at the circadian status of rollover shifts that's seven nights' shift then seven days' shift – 18:00 to 06:00, 06:00 to 18:00 – which is the worst of all from a circadian point of view, absolutely horrendous. In a week most of them will adapt to nights and then they've got to go back to days. So they spend the whole time out there on the rigs desynchronised.

TT: What was the impact of that work? Did it alter the work schedules?

JA: Well, there's a little intermediate story to tell in between, because somehow the rumour grew that Shell were feeding their oil rig workers melatonin to make them more productive. They instantly stopped the project, and employed a Professor of Risk Assessment to see if our little project was a major problem for this gigantic, multinational oil company. Then the Health and Safety Executive heard about it and said, 'We'll fund it from now on.' And they did. We had the best part of ten years funding from them, and based on the fact that people are theoretically healthier and sleeping well when they fully adapt, it was recommended that people work the adapted schedules.

TT: I know you're now retired, but like most academics you're still busy working. Thank you so very much, Jo. This has been a great pleasure and a privilege.

Figure 2: Dr Jeffrey Aronson

Dr Jeffrey Aronson DPhil FRCP HonFBPhS HonFFPM (b. 1947) trained in the University of Glasgow (1964–1973) and the MRC Unit and University Department of Clinical Pharmacology, Oxford, under the late Professor David Grahame-Smith. He was Reader in Clinical Pharmacology at the University of Oxford, and Honorary Consultant Physician in the Oxford University Hospitals Trust until 2014, since when he has held honorary contracts as a Consultant Physician and Clinical Pharmacologist in Oxford. He was President of the British Pharmacological Society (BPS) (2008–2009) 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* (2003–2007). 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*.

2 Aronson, Jeffrey*

Tilli Tansey: Could you say, to begin with, a little bit about your family background and your early education? Where did your interest in science and medicine come from?

Jeffrey Aronson: I was born in Glasgow in 1947, an only child, and in my father's family (they mostly lived in Glasgow) there was no science whatsoever. My father, aged about 13 or 14, had to leave school and earn a living, there were nine children in the family and there was no opportunity for them to be better educated. My mother came from Liverpool and her twin brother was a General Practitioner (GP) in Liverpool, as was his wife. I think the stimulus to me to become a doctor came from my mother. In fact, I do not remember a time when I did not want to be a doctor. I went to the Glasgow High School, which was the equivalent of an English direct grant school. I had a very good, broad education there, so when I sat the Scottish equivalent of A levels – the Highers – I took six subjects: three sciences, Maths, Physics, and Chemistry; and three arts' subjects, English, Latin, and Greek. I was 17 when I went into Glasgow Medical School. I went through the university course without any great upsets, and emerged in 1970 as a qualified doctor. In those days you did pre-registration house jobs; I did my surgery with a very good general surgeon called Mr Hugh McKay, at the Victoria Infirmary, and I did my medicine with an equally good physician called Sam Lazarus at the Southern General Hospital. I then decided that I wanted to be a Clinical Pharmacologist. That was very unusual at that time, I decided early on, and it happened because I came home from the university one afternoon just after our final results, and a neighbour of ours, Jake Davidson who was a Radiologist at the Western Infirmary, came across to congratulate me. So he said, 'What are you going to do?' I said, 'Well, I haven't really thought about it.' And then he asked me, I think, a very important question: 'What was your best subject?' That was quite clear, it was what we called "*materia medica*", which was a very ancient subject in Scotland. It was the study of medicines and their actions and it went back at least over 100 years, or

* Edited passages from the interview conducted by Professor Tilli Tansey, 25 April 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

150 years, and it's what we now call 'clinical pharmacology'. I said, 'Well, that's my best subject, *materia medica*. I got a distinction in the exam and it was very interesting.' I did find that very interesting, although I find all of medicine very interesting, actually, and I could have chosen anything really. He said, 'Well, that's a big subject at the moment. You should go and read the editorials in the journals.' So I looked at the *BMJ*, I looked at *The Lancet*, and sure enough there were editorials about clinical pharmacology as an up and coming subject. I then found that the Royal College of Physicians in 1969, just the year before, had set up a working group under the chairmanship of Cyril Clarke, who later became President of the College. They had produced a report on the future of clinical pharmacology. And in 1970 the World Health Organization produced a report on the future of clinical pharmacology. So I got hold of these reports and read them and thought, 'Yes, that's it. That's what I want to do.' It was quite clear.

TT: Can I just go back a little bit, Jeff, and ask you about your schooling? You have an interesting mix throughout your career of arts and writing, as well as the sciences. You didn't do Biology?

JA: Biology wasn't a subject available to us in those days; the sciences were Physics and Chemistry, and of course Mathematics. I didn't have any inspirational science teachers. They were all rather dull. Well, not all of them. There was one teacher who was very ebullient who taught us Chemistry but he was amusing and entertaining, not really inspirational. Our Physics teacher was deadly dull and it wasn't until I took an extra subject at O level, which was called 'Applied Mathematics' that I started to understand Physics. Inspirational teachers, if there were any, came on the arts side actually, people who taught us Latin and Greek and English were really quite inspirational and very interesting. I guess that I was already set on a scientific course and I didn't need inspirational teachers in the sciences, whereas having inspirational teachers in the arts was very helpful.

TT: At university, your best subject was *materia medica*: did you have any sense when you were a student, 'Oh wow, this is really exciting,' or was it later when looking at those reports?

JA: I don't recall a feeling of excitement. I was interested pretty much in everything in medicine. The whole broad sweep of medicine was interesting and that actually is important to being a Clinical Pharmacologist because you cover the waterfront of medicine, and if you're not interested in everything, you'll miss a lot of what is relevant. I just found that this whole subject was utterly fascinating. The textbook we had was *Dilling's Clinical Pharmacology*.

There were two clinical pharmacology textbooks: Lawrence's textbook was largely used by English students, but Scottish students were encouraged to buy Dilling's which was an Edinburgh textbook. And it was a pretty dull book actually. Lawrence's textbook was full of jokes, full of pictures, very lively. Dilling's textbook was solid text, fact after fact, no jokes, terribly dull. But I read it half a dozen times during the course and I just thought the subject was fascinating and I can't tell you why. Why is anybody turned on by anything? I don't know. But that's what really turned me on. And of course, as you imply, later on one does become excited, one learns about what goes into making these things, how drugs are made, how they act, what their targets are, and so on; you learn that there are things that aren't known. But as a medical student that didn't occur to me, and I suspect it's true of many medical students, you don't understand that what you've being taught is not dogma, that there is still a lot to learn, a lot that's unknown.

TT: Did you particularly select house jobs and positions with the idea of becoming a Clinical Pharmacologist?

JA: You got what job you could. Most of my colleagues had arranged their house jobs in their fourth year. I hadn't done anything about it until the final year. I'd been a student on Sam Lazarus' firm and he'd given me the top certificate among the students at that time. I asked him if he had a job and he said, 'Oh no, we're full up. All the jobs are taken. I'll put you on the waiting list but it's unlikely.' A week later he said he had a job, so I guess he bumped me up to the top of the list. I then met one of my colleagues, he said, 'What are you doing for surgery?' I said, 'I don't have a job.' He said, 'There is a spare place in Hugh McKay's unit.' So I went and spoke to McKay and he said, 'That's fine.' House jobs were not regarded as being important from the point of view of one's career, you just had to do the preregistration job and get it over with. I was very lucky because I fell into these two jobs which were really excellent, with good colleagues and enjoyable surroundings. Luck plays a huge part in everybody's career and people don't always acknowledge it, but I was exceptionally lucky with those house jobs.

After that I started thinking about clinical pharmacology and I went to see Abe Goldberg, Professor of *Materia Medica* in Glasgow by that time. I'd known him already from being a student on his firm and I said I wanted to be a Clinical Pharmacologist. I also went to see people at the Middlesex Hospital in London. I had a link there because in my final year the Nuffield Foundation had offered Glasgow students bursaries to go and study at the Middlesex Hospital and I

went and studied surgery there. I got to know the staff there, particularly the Dean of the Medical School, and when I graduated I wrote to him telling him that I'd passed, that I was on my way through London, and that I'd call in and see him. So I did and he introduced me to the Professor of Pharmacology, a man called Franz Hobbiger, a specialist in cholinergic pharmacology of the parasympathetic nervous system. I met Hobbiger and he offered me the chance to do a PhD with him. The only disadvantage of that was that it paid a non-clinical salary, but I didn't mind that; I thought it was important to get some proper training.

I went back to Glasgow and spoke to Abe again and he said, 'That sounds like a good idea.' So I was about to write to the Middlesex and tell them that I was interested in doing a PhD with Hobbiger, when the postal strike happened. Tom Jackson and his Union went on strike. There was no e-mail, there were no faxes; there was telephone but it had to be a written application and so I had to delay sending my letter. In the meantime, Abe said 'I've been thinking about this. I think you'd be much better advised to get a general medical job, do your postgraduate training for Membership of the Royal College of Physicians before you consider specialising.' I was very disappointed at that, because I had my heart set on going down to London. Having spent 25 years of my life in Glasgow, I thought it was time to branch out and see what the rest of the world did. So I was very, very disappointed in this advice, but I could see that he was absolutely right.

When the strike was lifted I wrote to Middlesex saying I was sorry, I decided that I wouldn't come and I applied for a job as a Senior House Officer (SHO) in Stobhill Hospital, which is where Abe was working, and they interviewed me, and it's the only interview I've ever had for a job, and I got the post. That was a three-year appointment: two years as an SHO and the third year as a Registrar provided you'd passed the Membership. The two years as an SHO were in four-month chunks, doing various medical specialties and subspecialties like dermatology and psychiatry. Before the two years were up I passed the Membership and decided to look for jobs in clinical pharmacology. I was still keen to go to London. And so I went down and had a look around. Simultaneously, an old school friend of mine, Murray Macbeth, had come down to Oxford to read for a DPhil in Philosophy, and I'd come down to visit him. And I thought, 'Wow, this is a fantastic place. Afternoon tea on the lawn, punting on the river, studying in an Oxford college. What a marvellous place.' Murray said, 'Well, why don't you come too?' I said, 'Oh, don't be silly.' I said, 'There's no way that

the Medical School will take me here.' He said, 'Why don't you go and have a look?' So I made an appointment to see the Nuffield Professor of Medicine, Paul Beeson, an American physician. Lovely man, very good scholar in the old American tradition. I told him I wanted to be a Clinical Pharmacologist, and did he have a job as an SHO? He said, 'Do you have your Membership?' I said, 'No.' He said, 'We don't have SHO jobs for people who don't have their Membership. But the MRC is going to fund a Unit of Clinical Pharmacology in a year or two. Get your Membership and write to me again.'

I kept Oxford open as an option, and also London. In 1973 I saw the new Professor of Clinical Pharmacology at Oxford, David Grahame-Smith, in what was a joint arrangement between the MRC, the MRC Unit, and the University Department of Clinical Pharmacology. The MRC funded 90% of everything, the Rhodes Trust funded David's Chair, and the University gave us premises. I'd just got the Membership and I told David that I wanted to be a Clinical Pharmacologist and he discussed the work going on in his department. And he said, 'Well now, it's April. It's too late for you to apply to the MRC for a Research Fellowship, but if you're willing to wait until next year we can apply in March for a Fellowship starting a year in September.'

I said, 'Well, I have a job and don't have to be in a rush so I'll let you know.' I was very interested in the particular work they were doing on a group of drugs called 'cardiac glycosides'. I'd worked with a man called Brian Whiting in Abe Goldberg's unit, who was working on cardiac glycosides but I didn't think he really got to the heart of the problem, although I didn't know what the way to go was. To put it in technical terms, Brian had been taking a pharmacokinetic approach and David took a pharmacodynamic approach. Rather than looking at where the drug was, David was looking at what it was actually doing and choosing a surrogate marker of action. That seemed very exciting. That was the first thing that really excited me. I went back to Glasgow and within six or eight weeks I got a letter from him saying, 'If you'd like to start in September, I've got a place for you.' Again, it shows how lucky you have to be, because a man doing the work on cardiac glycosides had decided that he wanted to give up academic medicine and become a GP. So David offered me his post, to start in September as a member of the clinical scientific staff of the MRC.

TT: Were you still thinking of doing your DPhil? There's your clinical career here, and this underlying tension almost scientific training.

JA: When I came back to doing clinical medicine after a three- or four-year break to do basic science, the main thing that had changed was the drug therapy. So by virtue of being trained as a Clinical Pharmacologist, I had kept up-to-date with the therapeutics, and that was the thing that had changed most in the time that I was away from clinical medicine. I didn't suffer any difficulty in catching up, I was already up to speed because that was my specialty. General medicine, on the whole, the changes were not as dramatic as the changes in drug therapy, which I had kept up with. All the time I was keen to get both the clinical and scientific training, because I thought that was hugely important. You had to understand both sides in order to work effectively as a Clinical Pharmacologist, I recognized that from the reports that I had read about how clinical pharmacology was developing. Clinical and research activities went hand in hand. So it was clear to me that that was important, that I ought to do both and be trained as a scientist as well as a clinician. I don't think I could have found anyone better to train me than David Grahame-Smith. He was a biochemist in effect. He had done his MD Thesis on a very, very basic piece of biochemistry, describing the existence of an enzyme that nobody had described before, tryptophan hydroxylase. His biochemistry background and his training in science was very useful in training me to be a pharmacologist in the clinical setting.

TT: When you got the opportunity to work with David Grahame-Smith, what were your responsibilities? Did you have clinical responsibilities or was it purely a lab job?

JA: It was purely a lab job to start with. But I was attached to one of the three clinical firms that were in Oxford at that time. I used to go twice a week to do ward rounds with them, to advise supposedly on the drug therapy, wet behind the ears though I was. But that was very good training; doing ward rounds with those physicians was really very informative and very helpful. From time to time I did have a chance to do practical clinical medicine, but most of the time, up to 1980 when I became a Consultant, I was doing research in the laboratory.

TT: Could you say something about the research, Jeff? This was all on the cardiac glycosides?

JA: It developed into more physiological research eventually. The main cardiac glycoside that was used in those days was a drug called 'digoxin'. In 1785 a Birmingham physician called William Withering had described how he used foxglove, which is where digoxin is found, to treat what he called "dropsies", namely 'collections of fluid in the body', some of which would have been due

to cardiac problems. John McMichael, when he was Professor of Medicine at the Hammersmith in the 1930s, showed that digoxin was also useful in the management of heart failure and so, for many years, digoxin and other cardiac glycosides in this country had been used to treat both atrial fibrillation and heart failure. A major problem was that it was difficult to use because a dose very slightly more than effective was toxic. So the balance between finding an effectively therapeutic dose and avoiding toxicity was very, very narrow. It was a tightrope. Furthermore, the drug was eliminated by the kidneys, and as you get older your kidney function deteriorates, and it could be quite difficult to use as your kidney function deteriorated. The third problem was that the drug was often used with diuretics – drugs used to get rid of fluid from the body and they would do this by getting rid of sodium and potassium at the same time – and losing potassium made you more sensitive to digoxin.

So there were real problems with this drug, but it was the only drug available for treating atrial fibrillation, and to some extent heart failure. What David Grahame-Smith was doing, was to measure the action of the drug rather than just the amount.

Ideally you'd want to measure its action in the heart itself but that's difficult and you couldn't do it non-invasively with any great ease. David had developed a method based on the mode of action of cardiac glycosides which work by inhibiting an enzyme in cell membranes called the sodium/potassium ATPase [Na^+,K^+-ATPase; ATPase: adenosine triphosphatase]. This enzyme is responsible for transporting sodium out of the cell and potassium into the cell. By measuring the rate of transport of potassium into cells you can measure how well the drug is working, what it's actually doing at its site of action, at its target. There is an easily obtained source of the enzyme and that is red cells, erythrocytes. David was taking patients' erythrocytes and looking at how much ATPase function there was. We did a lot of work on studying the ATPase, first of all in red cells and later in other cells such white blood cells, and then in experimental animals as well. We discovered what nobody had described before, which was really exciting, was that when you gave digoxin long-term, you saw it inhibiting the pump, the ATPase, to start with, but then after a week or two the ATPase function would start to recover even though the drug was still there. Then there would be a struggle between the drug and the ATPase and there would be fluctuation in the ATPase activity as it tried to recover and the drug kept on trying to pull it back down There will be fluctuation of this sort until after a few weeks and then the pump, the ATPase, would win and ATPase function would return to

what it had been before you introduced the drug, even though the drug was still there in the same amounts that it had been from the start. This observation was a central interest of David's, not only in relation to cardiac glycosides but to all other pharmacological, adaptive responses to treatment. We went on to study the mechanisms whereby these adaptive responses occurred, and so from being a pharmacologist I became a physiologist studying the function of Na^+,K^+-ATPase in cell membranes, and we did quite a lot of experiments looking at stimuli that alter the function of the ATPase and thereby cause it to up-regulate in response to stimuli that alter its function. We did all that work in various ways, looking at mechanisms of adaptation of, in my case the Na^+,K^+-ATPase and in David's case, other functions in the brain relating to 5-HT and other neurotransmitters.

TT: Did you have much involvement with other people in the Unit, the 5-HT people and the psychopharmacologists?

JA: Yes, particularly with Richard Green, with whom I shared an office for many years. He was interested in 5-HT, it's synthesis, it's action, and how it was abnormal in mental illness and how drugs used to treat mental illness, for example antidepressants, might affect its function. I did some work with Richard bringing my clinical pharmacology background to bear on his pharmacological interests for example, looking at the pharmacokinetics of tryptophan. Tryptophan is a precursor of 5-HT and you can measure its plasma concentrations after oral therapy, and by measuring how the plasma concentrations change with time, you can model the distribution and elimination of the drug from the body, and make conclusions about where it's going and what's happening to it. And you can then use drugs that interfere with that disposition and make conclusions about what's happening. We published several papers on tryptophan kinetics, making conclusions about the metabolism of tryptophan in relation to 5-HT and its action in mental illness.

TT: You were a member of staff of the MRC Unit. Did you have interactions with University Departments, say Physiology or Pharmacology?

JA: We didn't have much interaction with Pharmacology. They were two separate Departments, Pharmacology and Clinical Pharmacology. We used to run joint seminars, and those were very useful, and I met people like Hugh Blaschko, who although he was retired by then, used to come to all the seminars and always had something interesting to contribute. We had almost no connection with

Physiology, except occasionally with Clive Ellory who was Reader in Physiology at that time and was interested in the physiology of Na^+,K^+-ATPase, and so it was natural that I should go and discuss the work with him.

We did however have a lot of connections with clinical Departments. I did a lot of collaborative work with Peter Sleight and his colleagues in the Department of Cardiovascular Medicine. David did a lot of collaborative work with the Department of Psychiatry, with Professor Michael Gelder. We did some collaborative work with the Department of Neurology and particularly Neurosurgery, because we were interested in the pharmacology of subarachnoid haemorrhage. I also did some collaboration with the nephrologists because I was interested in Na^+,K^+-ATPase function in renal impairment, The way those collaborations occurred was generally by importing Registrars who wanted to do further research, usually for an MD degree, and who would come to our Department research drug therapy that was relevant to their specialty.

We had psychiatrists coming to the Department because of David's and Richard Green's interest in 5-HT, and I worked with the psychiatrists as well because there was a story at one time that Na^+,K^+-ATPase might be abnormal in depression. We had a lot of collaborations.

One day a man called Azad Khan came to the Department. He worked with one of the senior gastroenterologists, Sidney Truelove, who was very well known in Oxford. Sidney invented what was known as the "Five Day Regimen" for treating acute severe ulcerative colitis, a very effective method. Sidney was interested in the aminosalicylates, which are very effective in the management of ulcerative colitis, and he sent Azad Khan along, a Bangladeshi doctor who had come to work with him and was doing research, to ask my advice on how to design a pharmacokinetic study. We went on to study the pharmacokinetics of sulfasalazine, and later of another aminosalicylate called "olsalazine". Nowadays these drugs, particularly mesalazine, are mainstays in the management of ulcerative colitis, and we did the very early work on the pharmacokinetics of those compounds. There were lots of opportunities for collaboration with other clinical departments, much more so than with the preclinical departments, because we were known in the Clinical School as clinicians going on ward rounds, teaching the medical students, taking part in the grand rounds, and also, well, the science area was geographically away from where we were, so there were fewer opportunities to meet and collaborate.

TT: This seems an incredibly fertile period. You also did your DPhil?

JA: Yes. I enrolled as a graduate student in Corpus Christi College and being a member of a College at that time was a great opportunity to meet other people, not just scientists, but people from the humanities. I enrolled in Corpus as a graduate student and wrote up the early cardiac glycoside work as a DPhil Thesis in 1977.

TT: Towards the end of 1980, you moved from the MRC Unit to become an NHS Consultant. Was that associated with the University?

JA: Well, it is and it isn't. I came to Oxford in 1973 on a three-year contract, and then the MRC renewed it, which gave me six years. And at that point it would have been normal MRC practice to appoint me to a tenured post. Basic scientists after six years pretty much got tenured posts without any fuss at all. But there was I, six years as a clinical scientist. I'd spent 10 years of my life training to be a doctor, wasted as far as the scientists were concerned. Perhaps that's a bit unkind [laughs]. I was 16 years on: I had six years medical training where a scientist would have had three years, so that's an extra three years "wasted", if you like. And then four years clinical training, quite a long time, that scientists would have been working hard at the science, which I did not have. So my six years of training as a scientist were not regarded as being sufficient qualification for a tenured post, which is not unreasonable. But the MRC were very generous and they said, 'We'll give you another three years and at the end of that period we'll see what's happened, where you are, and if you are ready for a tenured post with the MRC.' So that took me to 1979, when the Wellcome Trust announced its Senior Lectureship scheme. I think it was Peter Williams' idea. It was a time of retrenchment and financial difficulty in universities, and the Trust was willing to fund posts that would not otherwise be available, for five years in the first instance, on the understanding that the university would take over the post at the end of that time. I think we were a very unusual group of individuals, but then we were chosen by the Trust because, I suspect, we were unusual in that way or in some ways. So I applied for one of these posts and was awarded it. Actually the story of how that happened is quite interesting, I think.

TT: Please tell me.

JA: I applied for one of these Wellcome Trust Senior Lectureships. They had appointed six the previous year, and this was the second round and I don't know how many applicants. I came up to the Wellcome Trust to be interviewed. Bill Paton chaired the panel, and it was clear that he was the only one who knew what was going on as far as my work was concerned; the others didn't

understand the work. And from the start we got on to the wrong foot because, and I didn't appreciate this, Paton along with Humphrey Rang had invented the techniques that I was using. ATPase was not a usual type of receptor; it was very unusual in one particular regard, which was that it very specifically bound digoxin to almost the exclusion of everything else. Paton was used to systems which in which the nonspecific binding was very large. I didn't realise that, because to me the system I was using was pretty straightforward and I really thought this was old hat actually. I hadn't appreciated how very new it was. Anyway, Paton and I got onto the wrong foot because he thought there would be high non-specific binding and I knew that there wasn't, and we debated this for five minutes. I went back to Oxford and David said, 'How did you get on?' I said, 'David, it was absolutely terrible. It was really bad. I got on to the wrong footing with Bill Paton. He didn't understand what I was doing, I failed to explain it properly. I really made a total mess.' He said, 'Well, never mind. There'll be other opportunities.' So I went on holiday for a couple of weeks. And I'm sitting reading the newspaper one day and I look down the column "University News": *'The following have been awarded Wellcome Trust Senior Lectureships: J K Aronson …'*

I looked at it, 'My God! That's incredible.' I thought I'd totally, totally screwed it up. That was how I got the Wellcome Trust Senior Lectureship. That was for five years. The scheme in those days was to apply after three years for renewal, so you always had a two-year buffer; the first three-year review was just a written report and that went straight through and the lectureship was renewed. After another three years I was called up for another interview, and the same thing happened. It was a different panel, but it was clear they didn't understand what I was doing [laughs]. It was very bizarre. I went out feeling really quite annoyed actually. But they renewed the post and so I went for 13 years on a Wellcome Trust Senior Lectureship until the Wellcome Trust said, 'That's enough. We can't fund you forever. The university will have to take over.' At that point the University found funds and gave me a tenured post. I went for 20 years in Oxford with funding, from the MRC and then the Wellcome Trust.

TT: You also had clinical responsibilities.

JA: I had been doing clinical work from time to time on an *ad hoc* basis, so I'd done some Registrar work, I'd done some Senior Registrar work and I as employed by the University with an honorary contract from the NHS. And so

at some time or other, it must have been in the early 1990s, I became one of the on-take physicians and I did that from then until I stopped doing it about four or five years ago when I was about 65, I suppose.

TT: You had honorary positions whilst with the MRC?

JA: Yes, throughout my time in Oxford, David Grahame-Smith organized whenever he could for all the clinicians to have honorary positions in the NHS, so that they could go on ward rounds, advise, do clinics and do all the things that a clinician might want to do even while they are doing research. So I had an Honorary Registrar contract when I first came and then an Honorary Senior Registrar contract. And when I became a full-time Consultant, although I was employed by the University, my contract was an honorary contract with the NHS; what was then called the "Oxford Area Health Authority" and then later the "Oxford Radcliffe Hospitals Trust".

TT: When you moved from the MRC Unit, what were your research objectives?

JA: All that changed was the source of funding. I applied for the Wellcome Trust Senior Lectureship on the basis of the work that I had been doing with the MRC. I had laboratory facilities with David all the time that he was there, from 1973 until he retired in 2000. All the work I did in the laboratory was with him and with people as part of their attachments to the Department.

TT: Do any of those collaborators stand out in your memory or were a particularly enjoyable collaboration, or the converse?

JA: We had good relationships with all those with whom we worked. It was really a very productive and enjoyable time. I particularly enjoyed working with Peter Sleight. He had a very fresh approach to science, although not himself a scientific researcher. He was full of insight into physiological mechanisms, understanding of how science worked, even though he didn't do a great deal of scientific research, and he used to give us people to collaborate with. I enjoyed learning a lot from him about clinical medicine in general, and cardiology in particular. But we had good relationships with everyone.

TT: Did you find tensions between your clinical career and your lab career?

JA: I managed to make them meld, and again I've been very fortunate in that in those two separate careers neither made excessive demands on me. When I was doing my clinical work I was able to get on and do what I had to do, but at the same time take time off to go back to the lab and *vice versa*. I think that's very

important: that there is crosstalk between clinical work and laboratory work, which can – if you use it properly – feed your research and feed your clinical activities. I always found the two complementary, and it's important that anyone who is a clinical scientist should be active in clinical medicine, because you get so many ideas from seeing patients and their clinical problems. Your scientific expertise can bring information into the clinical sphere that allows you to deal with clinical problems better.

TT: That was always David Grahame-Smith's adage as well.

JA: Absolutely. There were times when I felt that David pushed it too far. For example, he gave up some very nice premises in the Radcliffe Infirmary that we could have had because he wanted his laboratory to be closer to the wards. Now I'm not criticising that, but that was the strength of his feeling that the two should be very close together, so much so that he wanted them to be geographically close, not just close intellectually. So that was something I learned from him very early on, that it was important to have the juxtaposition of those two things and crosstalk between them. I think that was an important lesson.

TT: What about the people in the Units who were not clinicians? Did they feel that somehow they were missing out, that they weren't really working on the same kinds of problems?

JA: I never had that feeling in our laboratory. I sometimes had the feeling that scientists elsewhere rather looked down on clinicians as being not very scientifically literate. I never had it in our Department and the main reason for that was that David was such a good scientist. It was clear to the clinicians, and to all of us in fact, that he understood science very deeply, his leadership really made that an important facet of the Department.

TT: You mentioned these two parts of your career, the lab scientist, the clinician, but that's just part of your career because you write a lot, you edit, you publish a wide variety of things, Jeff.

JA: Yes, very much so.

TT: When did that start? I take it that's always been an interest?

JA: I had always been interested in words, and my love of Latin and Greek reflects. I had for some time wanted to write about etymology and philology in relation to medicine, but I was put off by two things: one was that there was a

man called Bernard Freedman who used to write the most wonderful articles in the *BMJ* on medical philology, whom I admired enormously; and the other thing was that I felt that it wasn't my subject really. When Freedman stopped doing those articles, I started thinking that perhaps I might write an article or two on medical words. We were on a ward round one day, chatting to the students about a young man who came in with a subarachnoid haemorrhage and we did a spinal tap, and the fluid was yellow. Normally the spinal fluid is what people describe as gin-clear. But his fluid was yellow – this is a well-known phenomenon. If you bleed into the brain and the blood trickles out into the spinal fluid, it then breaks down and the haemoglobin turns the spinal fluid yellow. This is known as *xanthochromia* [ξανθοχρωμία], which in Greek means "yellow colour" literally. I said, 'What does *xanthochromia* mean?' and we talked *xanthelasmata* [ξανθελάσματα], which are little yellow coloured growths, around the eyes or elsewhere. And *xanthomata* [ξανθώματα] which you get over tendons, the Achilles tendon and the knee sometimes, and so on. We talked about *xanthines* [ξανθίνες], so that gave me a chance to discuss theophylline and the treatment of asthma, and the *xanthines* are so called because they form a yellow colour when you react them with nitric acid. This was very interesting and we were getting into all kinds of areas away from subarachnoid haemorrhage. Then I said, 'Any other words?' and one of the girls said, 'Ah yes! '*Chrysanthemum!*' [Laughs]. It was an interesting error that she'd made. Anyway I thought, 'That's a funny story, I'll write it up,' and I wrote it up as a filler in the *BMJ* and they accepted it without question. I called it *Curious, yellow* and I thought, 'Well, that was fun.'

TT: That was 1996?

JA: The other reason I'd held off was that I thought that by writing about such trivial matters it would somehow sully my scientific reputation. When I realised I didn't have a scientific reputation [laughs] I thought, 'It doesn't matter!' That was very liberating. I then wrote other things, and people started stopping me in the corridors saying, 'I did enjoy your article.' Nobody ever stopped me and said, 'I thought your piece in *The Lancet* on Na^+,K^+-ATPase in Alzheimer's disease was utterly fascinating!' But they did stop me and say, 'I enjoyed your piece on *chrysanthemums*.' I got a letter one day from a physician in Hungary: could he use my pieces as translation exercises? And I got letters saying, 'I enjoyed your piece on this, that and the next. When are you going to publish them in a book?' I suppose I've done about a hundred of them in the last 20 years or so. I've written some in the *Quarterly Journal of Medicine* which are 1,200 word

pieces, and occasionally I get invited by other journals to write articles. Now instead of writing occasional fillers in the *BMJ* I have a weekly blog, and I called it *When I Use a Word* which is taken out of *Through the Looking Glass*. It's been very fruitful and most enjoyable, very enjoyable.

TT: You had already published a little bit in medical humanities by that time?

JA: Yes, a little bit. When I was writing my DPhil Thesis on digoxin you always write a bit about the history of your subject to get it into context. I had to delve into the history of the cardiac glycosides over quite a long period of time and found myself researching 18th century medicine. I was very fortunate at that time to have met Charles Webster who was the Librarian Fellow at Corpus. I sent him the draft of my chapter, and he said, 'You ought to publish it.' I didn't think that it was my place to publish in a field in which I was not regarded as member of the profession, a card-carrying historian, if you like.

So I'd done my research, I published the chapter in the Thesis and that was 1977. 1985 was the 200th anniversary of the publication of Withering's original monograph in 1785, and I proposed to Oxford University Press (OUP) a book on the history of the foxglove from that time, for the last 200 years, because I'd done a lot of work by then on the development of cardiac glycosides. They accepted that proposal and as an afterthought I said, 'And we can publish an annotated facsimile of Withering's original,' because I thought that my own contribution wouldn't be big enough to fill a proper volume, and I thought it would be nice to annotate Withering's text. They accepted that, and I published *An Account of the Foxglove and its Medical Uses 1785–1985*, and it begins with an annotated edition, a facsimile with marginal annotations explaining all the terms, the use of the medicines and what they meant, who the people were to whom he was referring, all the botanists and herbalists and so on. Then that was followed by my own history of the foxglove and its development over the years.

The print run of that was something like 800 or so, it sold out and you can now buy it on Amazon for about £150 or more, some crazy price. It was translated into Spanish. A drug company, I think it was Boehringer Ingelheim or it may have been Boehringer Mannheim wanted to print 3,000 copies, and give it free all over South America and Spain. I said to OUP that I didn't want my name associated with a drug company's advertising campaign.' OUP came back to me and said, 'We've got an agreement that they won't put their logo on your book.' So they published a Spanish translation, and I've no idea what happened to it. I suppose there are people in South America who have copies of it.

It was on the strength of that book that I was later asked to join the Wellcome Trust's History of Medicine Units and Grants Panel, as it was then called. And I served on that for two three-year terms. The panel always wanted a token doctor and I enjoyed serving. I met a lot of historians of medicine through that, people like Roy Porter, Bill Bynum, yourself of course and others. It taught me a lot about the practice of history of medicine, the academic practice in the history of medicine and the scholarship and so on.

TT: Do you think that practising doctors, have a role to play in the history of medicine?

JA: I'm sure they do. Traditionally, of course, it's the retired doctor who takes up history of medicine as a hobby, and that's fine; there's nothing wrong with that. Although in recent years, the last 30 or 40 years, medical historians, have become much more interested in the social aspects of the history of medicine, whereas the retired doctor is more likely to write the biography of the famous man or woman. And that has been frowned upon by academic historians. But it's important that younger doctors should take an interest in the history of medicine, and I'm very keen that they should be taught about the history of medicine. Perhaps even undertake special study modules or maybe a bit of research, because it's not just that history of medicine supports the subject – which is important – but it gives them a different outlook on clinical practice and for example, ethics, the problem of uncertainly and how to deal with it in clinical practice. They should at least be exposed to it and whenever possible encouraged to do some of their own research, perhaps as students or even later if they want to take sabbatical leave to study the history of their own subject – I think that's very useful. But I don't discount the elderly retired physician who writes an adequate biography of some great figure in history. That's just as important, even though historians of medicine may have a different view.

TT: You've also been a very prolific editor of pharmacology *per se*. Not everybody gets involved in that kind of work.

JA: I am very interested in it partly because of my interest in language and the desire to see things well written, clearly written, because communication is important, and clear communication can only be achieved, or is greatly helped, if you understand how the language works. That doesn't mean avoiding split infinitives or all those rules that the prescriptive grammarians adopt. I mean writing clear prose that is instantly understandable by people reading it whether they are expert or not. That has to an extent fuelled my interest in editing,

because editing gives you a chance to produce text that is as clear as one can make it, from other people's text, which may not always be as clear, particularly if they are foreign-language contributors whose command of English may only be a little better than most English people. That's been part of my passion about editing.

I came into editing via *Meyler's Side Effects of Drugs*, which has been a major task over many years, from a very, very peculiar angle. It started with a publication called *MIMS Magazine*. Now *MIMS*, the *Monthly Index of Medical Specialities*, is a paperback book, which drug companies corporately issue and send around to all prescribing doctors. As a Clinical Pharmacologist I used to receive it every three months, but GPs would get it every month, and it contains a list of all proprietary formulations available in the UK. It's a massive advertisement for drug companies, in effect, but it's got a lot of useful information in it about the names of drugs and the doses and so on. Sometime in the 1970s, David Grahame-Smith received a phone call from somebody at *MIMS*, and he said, 'We're going to start *MIMS Magazine,* a little magazine that contains articles about the drugs. Would you and your colleagues like to contribute?' David said, 'Yes, we can do that' and he asked me to write an article on diuretics. It was organized according to the way *MIMS* was organized, so it wasn't just diuretics, I had to write about antidiuretics as well. I knew absolutely nothing about diuretics, but it was a good educational exercise, so I looked it all up, and I wrote my article. It was published, I didn't think any more about it.

A few months later I got a phone call from this chap who had been in touch with David to chat about the article. He said, 'We're having a lunch for our contributors, would you like to join us in London?' I thought, 'Oh, that's good, I'll swan off for a day and have lunch in a posh restaurant in London.' I can't remember where it was, it was in a basement somewhere in the West End, a very nice lunch. I found myself next to a clinical pharmacologist who introduced himself as Joe Collier. I didn't know Joe in those days. We got chatting and 'What are you doing?' he said, I said, 'I'm working on digoxin.' 'Oh, that's very interesting,' he said, 'What do you think about β-methyl digoxin?' This was a new drug, and again luck plays such an important part in all these stories, you can't manage your own life – I had been reading about β-methyl digoxin the day before. It was all fresh in my mind and so I gave him chapter and verse. 'Terrific,' he said, 'Will you do me an article for the *Drug and Therapeutics Bulletin*?' So I said, 'Yes, sure, delighted.'

I did the article and it was published in *Drug and Therapeutics Bulletin,* which was a very idiosyncratic publication. Somebody like me would be commissioned to write the article, but then it would be sent to all and sundry, 30 or 40 people maybe, all of whom would add their comments. It would then be edited so that by the time you got the thing back it was nothing like what you'd written in the first place, and it's anonymous, so my name isn't attached to it because it's a corporate venture. A year later, as a consequence, I got a letter asking me if I would contribute a chapter to the *Side Effects of Drugs Annual* on cardiac glycosides and antiarrhythmic drugs. I went on contributing an annual chapter to the *Side Effects of Drugs Annual* and then I was asked to be a co-editor, and later sole editor of the annual, and I then started editing the encyclopaedia that went along with it. All because, I think, I swanned off and had lunch at a fancy London restaurant one day, just for the hell of it. Last year, the latest edition of the encyclopaedia *Meyler's Side Effects of Drugs* is in seven volumes. It's something like 3.5 million words, 365,000 references, something like that; it's enormous.

TT: How many contributors?

JA: I do the whole work for the encyclopaedia based on what's published in the annuals. In the annuals we have 50 chapters, each with one, two or three authors, so there's upwards of 100 authors in each annual, and it changes over the years, and we've probably had about 200, maybe 250 authors.

TT: It seems to me to be an enormous job to take on.

JA: [Laughs]. For the 15th edition, which was only six volumes, I had part-time assistants, but I found it difficult to get funding from the publishers for that. They want to make money yesterday and aren't keen to cast their bread upon the waters. Latterly I was doing it all myself. It is a huge job, yes.

TT: You've been Managing Editor for other journals?

JA: I was Managing Editor of the *European Journal of Clinical Pharmacology* for some years, but there were four of us, and we shared the work. Although I did a lot of editing of manuscripts even then. Latterly I was Editor-in-Chief of the *B J Clin Pharm* (*British Journal of Clinical Pharmacology*), buthad a lot of help, and it's not very time consuming, I would say.

TT: Related to that is one obvious further question, that of learned societies – the BPS that owns *B J Clin Pharm*?

JA: Yes, indeed. One of the jobs that the Editor-in-Chief of the *B J Clin Pharm* has, and the Society now has three journals, the basic journal and the clinical journal and then an online journal, is to be a Member of Council of the Society. One day I came to the meeting of the Council, and the President asked me whether I would be interested in being President?' Well, I was stunned, I said, 'That's fantastic, I would be very keen to do that.' Because I saw it as an opportunity to promote clinical pharmacology. I was proposed, there were no counter-proposals and I became President-Elect. The first active clinician, I think. There must have been others who had clinical qualifications, but who hadn't practised. I'm not sure about that. But certainly I was the first active clinician to be asked to be President of the Society. The position was President-Elect for two years and then President for two years, so a four-year post.

For some years several of us had been concerned about the development of clinical pharmacology in the UK. The subject had really grown up during the 1960s and early 1970s. There weren't many of us, maybe 80 to 100 in all, but we were very active and very successful and some became Professors of Clinical Pharmacology went on to national roles. But in the 1990s, and I put this down largely to the advent of Research Assessment Exercises during which universities did not rank clinical pharmacology high on their list of subjects that would score highly, and the numbers of Clinical Pharmacologists declined. By the beginning of the 21st century, the number of Clinical Pharmacologists had declined markedly, and this was a matter of great concern for a lot of us. So when I was asked if I might be interested in being President of the Society, I saw this as an opportunity to do something to revitalise clinical pharmacology. Over the next four years I tried to take advantage of that position the developments during that time are far too many to discuss, I told the whole story of that period in the *B J Clin Pharm.* We – and I say 'we', other people did all the work here, I can't claim any credit – published studies on teaching of clinical pharmacology, we talked to the General Medical Council and persuaded them to include in the new version of *Tomorrow's Doctors* in 2012, two pages on skills and knowledge that young doctors ought to have in therapeutic. We talked to the press through the Science Media Centre, and we did a large number of things to get clinical pharmacology into the public eye, into the government's eye, into the eyes of regulatory bodies and so on. That work has been continued by my successors as Presidents of the Society and others who have been influential in maintaining the impetus of clinical pharmacology.

When I stepped down as President I organized a 'Meeting for an agenda in Clinical Pharmacology' in Oxford. From that three-day meeting, very lively, we published a special issue, of the journal in which we had papers on virtually every aspect of clinical pharmacology and its future. The VOICE paradigm emerged – 'Visibility, Outreach, Integration, Coverage, and Emissaries'. From that beginning when we were unhappy about the way in which clinical pharmacology was diminishing, we have started now to grow again.

TT: That was about that time we talked about doing a Witness Seminar.

JA: That's right, and you were very helpful. It was part of the whole business of promoting clinical pharmacology.

TT: Going back to the Society, when did you become a Member, and can you remember your first communication?

JA: Yes, I do remember my first communication [laughs]. I imagine everybody remembers their first communications. A bit like your first kiss. It's something you don't forget because it is a baptism of fire, at least it was then; I think it's less so now. I don't remember when I became a Member, it would be some time in the mid-1970s. I presented data on the work that we'd done on erythrocyte Na^+,K^+-ATPase activity during treatment with digoxin and it was very, very well-rehearsed; a 10 minute talk, eight slides only, very rigorously rehearsed in advance, timed to perfection because if you went over even one second the red lights would go on and you weren't allowed to go on any longer than that. Then there would be five minutes of questions, the first person to ask a question almost always was Colin Dollery. Colin asked me what sounded like a very straightforward question, but those questions were never straightforward, there was always something that you might not realise or appreciate at the time. I gave what I thought was a reasonably good answer and then there were one or two other questions and afterwards David Grahame-Smith said to me, 'Well done, Jeff; that was very good. The answer you gave to Colin was totally wrong but you handled it very well.' [Laughter]. I was very lucky again because I don't know if anybody realised apart from David that what I'd said was rubbish, but in those days a paper could very well be thrown out and not accepted for publication if it didn't meet rigorous standards, and so I think I was very lucky; I got away with it. I remember it vividly.

TT: Is the BPS the natural home for Clinical Pharmacologists? What about the Royal College of Physicians and its Faculty of Pharmaceutical Medicine?

JA: Yes. The natural home for Clinical Pharmacologists is the BPS, without doubt, for all Clinical Pharmacologists who are clinically-qualified. There has always been place for a clinical section in the Society and now we have alternate Presidents, clinically and non-clinically qualified, so I think it's the right place for Clinical Pharmacologists. Now there are other societies, you mentioned the Royal College of Physicians, which is a much bigger organization. It doesn't specialize in clinical pharmacology or pharmacology, it deals with medicine as a whole. There is a liaison committee between the College and the BPS and that is a very useful institution. Then the College, as you say, has the Faculty of Pharmaceutical Medicine, and they were very kind a few years ago to offer me Honorary Fellowship. That is primarily for physicians working in drug companies. They have their own examinations and their own diplomas and so on, and they are very active in pharmaceutical medicine within drug companies.

TT: I think at this point we must stop. Thank you so much Jeff.

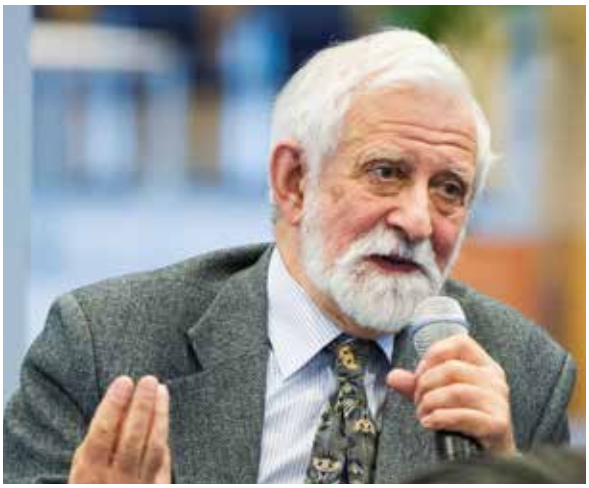

Figure 3: Dr Mick Bakhle

Dr Yeshwant Shriharsh (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* (*BJP*), and became Press Editor in 2006.

3 Bakhle, Mick*

Tilli Tansey: I'd like to ask you how you became a pharmacologist, and if you became interested in science as a boy? Was your family involved in science or medicine?

Mick Bakhle: My father and my grandfather were both army surgeons, so that I suppose, how it started. But it was the second form at school, a crazy time, to make decisions, but that was the way it was in those days. You had to decide whether to go on the science side or to do Latin and Greek. My Dad did medicine at Guy's, my uncle did mechanical engineering somewhere in London, and my youngest uncle went to Corpus to read Greats, and went into the Indian Civil Service, the ICS. So they said, 'Are you going to be like your uncle and do Greats? Or are you going to... etc., etc.?' For some reason I decided to go into science, but I didn't want to be a doctor. The only option really available was to do chemistry, and I have actually spent most of my time almost getting back into medicine [laughs].

TT: It sounds almost as if you became a scientist by accident?

MB: I certainly wasn't driven. I don't think I've ever been driven, which has been a failing for me as a scientist. One does need to be driven in some way or another. I think you get driven by ideas, a project gets hold of you and you eat, sleep and drink the project. But I was not a dedicated scientist, I didn't have an urge to find out how things were. I can't remember ever feeling like that.

TT: Where were you at school?

MB: Dulwich, where my Dad had been and his two brothers. It was very useful and odd. All through my career I've been lucky in the sense that, I've benefitted enormously from the Old Boy network or having what I call 'uncles' to see me through. When I came to this country, I could read and write, but not much else. And aged 12 I had to sit the entrance exam for Dulwich. I didn't understand what the questions were about. The English questions about

* Edited passages from the interview conducted by Professor Tilli Tansey, 10 August 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

language and reading, were OK, but there were these mathematical questions. I could add and subtract and divide, but that was about all. But despite that they gave me a place. I suspect it was 'He's the son of an Old Boy and those three brothers didn't do too badly so…'

TT: You came to this country aged 12, could you just say a little bit about your family background to put this in context?

MB: My grandpa came to France to look after the Indian soldiers in the First World War. For reasons best known to him – he put his wife and his three sons into South London, and put his three sons through Dulwich. My grandma, who had never been anywhere, suddenly found herself in South London with three sons, while her husband was in France. And so they went to school and she managed. The three boys went through Dulwich, and then one went to Guy's, so on and so forth, and then they all went back home.

TT: Home being?

MB: Home being, in India, wherever my dad was stationed. Most of the stations in my time, were in Northern India. He would have gone back, this was 1927/28 something like that.

My mother was English. She met my dad somewhere in the East End, during his time at Guy's, she was a sort of charity worker at Toynbee Hall. My dad went home and then some time later my mum went out and they got married. In 1948, with Partition and everything she said, 'This place is going to be in considerable upheaval, I want the kids to go to England and have a proper education.'

TT: You arrived aged 12 from an Indian childhood: that must have been quite a culture shock, an emotional shock? Or did you just adapt?

MB: I never felt like that. I knew there was turmoil out there. When I came here, the strongest emotional reaction that I can remember was that we landed off a troop ship in Southampton, and it was May, and it was raining, and I could not understand how it could rain in May.

TT: That wasn't monsoon season! [Laughs].

MB: I just couldn't understand that. The other thing that happened was that in India we had a servant, called a 'bearer', who had been always there. And when we came here, we had nothing, no nothing. My mother, for instance, hadn't

kept house for all the time she was in India; 20 years. It must have been quite difficult for her, as her only close relation, her sister, had died the year before. So there really was nobody here that was family. She had a hard time.

TT: You have two quite remarkable women in your background. Your paternal grandmother in South London in the First World War, and then your mother coming back after 20 years in India. Was it a shock for you being in England?

MB: People have said, 'Did you feel you were being discriminated against?', because I was clearly a different colour, and still I'm told people can hear an Indian accent in my speaking. It's worse when I've been drinking, I'm sure. [Laughs] But I was in this new school, and I don't think I had the wit nor appreciation of the difficulties I might have been in, or perhaps I was in.

TT: Perhaps that enabled you to move ahead in lots of ways, where lots of people might collapse? You had resilience?

MB: It's a lack of introspection. I don't have that inward analysis, it's the way I am.

TT: So home was London, or was your father moving around?

MB: In 1948, as you might imagine, it was almost impossible to find accommodation. We landed in May and I went to school in September. Eventually we moved to a place which was meant to be more convenient for my schooling, a flat in Crystal Palace, Upper Norwood.

TT: At school you go into sciences rather than the arts. How did you decide what A levels to do? Or was there a choice?

MB: Once you were in the science side, the only choice that you had in our school was to do biology, because you could become a doctor, or to do chemistry, physics and maths, because you're going to go into science. The chief master on the science side was called George Way, who was very, very organised. There was an end, and the end was passing the examination and gaining entry into a good university, and that was the whole purpose of this education. You were drilled to pass the exam and it worked.

TT: And University chemistry seemed the best option for you?

MB: Yes. I went to Oxford, to Corpus, I didn't even think about changing anything. It was only later that chemical pharmacology seemed so much more interesting. The chemistry course was four years – three years' book learning, and then a year in the lab. For Part 1, you took the special subject in the last year and I did chemical pharmacology.

TT: How had you got onto doing chemical pharmacology?

MB: It was a relatively odd thing to do. It wasn't the most popular special subject. The most popular special subject for chemists, was biochemistry.

TT: Was Krebs in office then?

MB: Yes, Krebs was there. Several of my fellow students did biochemistry as a special subject. Why didn't I? It's probably wanting to do something not the same as everybody else, and it just seemed to me to make so much more sense of the chemistry, because just doing pure chemistry for chemistry's sake, it didn't fire me in any sense.

TT: Who taught the pharmacology course?

MB: The chemical pharmacology course was run by a man who himself was an oddball, H R Ing, Harry Raymond Ing. Anyway, I managed to get a Distinction, and I am sure it helped me. Then I did my Part 2, with Raymond Ing.

TT: This was a research dissertation, a project?

MB: Yes. I worked on acetylenic bis-quaternary compounds, because Ing was very interested in quaternary compounds. At that stage they were probably the most instructive chemical compounds for studying structure-activity relationships. They were very simple and they had a wonderful range of activities. At that time there was a great mystery: why were bis-quaternary compounds physiological blocking agents, when the mono-quaternary compound was a stimulant? So that's why I did the acetylenic quaternary compounds for my Part 2. Then I stayed on to do a DPhil, and Ing was very good in that he said, 'You're going to have to do it with Edward Gill.' Edward had been through essentially what I'd been through. Edward was a chemist, he must have been at least five years, ahead of me. He'd also done chemical pharmacology and his Part 2 with Raymond, and then he'd done his DPhil on hexamethonium.

TT: What was the subject of your DPhil?

MB: I was making long chain fatty acid lactones with the lactone at one end and a water-soluble group at the far end. The idea was that was a model of digitalis. Nobody had much idea how digitalis worked, nor were there any substitutes. We knew how curare worked, and we had made decamethonium based on the structure of curare, although the effects of these compounds were different, and we thought we'd cracked it. But nobody had made a successful attempt at a synthetic digitalis. It was a pretty undistinguished DPhil Thesis, I tell you. It really wasn't at all mind-grabbing, because the compounds weren't particularly effective. The chemistry was interesting, but the biology wasn't really very interesting at all.

TT: Did you have any pharmacological or pharmaceutical objective? Burroughs, Wellcome were producing digoxin by this time.

MB: The initial driver was that there was no substitute for a herbal medicine which you still had to collect and purify. Here we were in the middle of the 20th century, 1960, and we were still extracting it, like morphine. Later on, I found out that Wellcome had fields of foxgloves just to produce digitalis. And there was nothing else which did anything like it. People recognised that digitalis was actually quite a toxic compound, but for those people it worked in, it absolutely changed their life. So the driver was to try and find out something more about digitalis which you could use to manipulate its activities and still, nobody has produced a synthetic digitalis.

TT: Even 20 years after you, people like Jeff Aronson and David Grahame-Smith were still looking, weren't they?

MB: The mechanism of digitalis, blocking ATPase, has too many side effects. Even now you have to be careful with digitalis, because the therapeutic window is really very narrow and you can get as sick with an overdose as you can with an underdose. But when it works, my goodness me, it works.

TT: What was the Department like?

MB: I certainly told everybody that I would go into the drug industry. But then, very odd things happen. It was at the Department in Oxford, which itself was a very curious social environment. I've never been in a place like that before, or again. We all had lunch together every day, a fairly basic lunch, but we all sat in the library and everybody had a plate of meat and two veg. In terms of food, disastrous, but in terms of the environment, fantastic, because you just sat down next to whoever else was on the table. Usually, you left the top space for Burn,

the Professor, and the next two spaces you left as well, because they were very often occupied by Edith Bülbring and some colleague of hers. Everybody else would fill up the spaces. So you have this great mix of people all sitting down at lunch and you talked about this and that, but also talked about science and bounced ideas and so on. Added to that you had coffee and tea in the library, where again it was expected that most people would organise their work so it would happen. But you absolutely had to come down to lunch. If necessary, if there was an animal on the experimental table and you wanted to keep it going, you'd take it in turns. It was a small Department; I suppose we were about 30-40 people so it was feasible, and the lunch persisted. I supposed Josh started it and it persisted when Bill Paton was there.

TT: I've never heard of a Department having lunch together. Tea and coffee; that is a common theme. Where did the lunch come from?

MB: Oh, there was a kitchen in the basement and we had a cook. At one end of the basement there was the kitchen and at the other end was the workshop. Actually, it was quite close to the animal house.

TT: When you say everyone ate together, was that secretaries, technicians?

MB: Students, faculty, secretary. Only the Chief Technician: Harold Ling, who had been with Burn since Pharmaceutical Society days, I think. He was the other constant figure. We also had a very good mechanical workshop, and latterly an electrical workshop in the basement. The man in charge of the mechanical workshop was a proper engineer, O B Saxby. Everybody, even the chemistry DPhil-students, had to go down to the workshop and learn how to use basic tools to make things. Depending upon your needs, you actually had to make your apparatus, especially for biological apparatus, clamps and electrode plus tissue holder devices, you had to make that yourself. It was a part of the DPhil process, you couldn't have it made, first of all you didn't have the money, and secondly Burn said, 'If you want this, you have to learn how to make it, because then you know how it works and you will know what to do when it doesn't quite work.' He was very authoritarian in many ways, and it was very sensible in those days.

TT: What were you thinking of doing as you were finishing your DPhil?

MB: The person who made the greatest impact on me was Blaschko. I was extremely impressed by him, and he was such a nice man, although I believe he was horrendous to work for. But as somebody who would talk to you in the

coffee room he was really good, encouraging and with enormous knowledge and his comments were always valuable. Anyway I applied to go for a post-doc to Yale. There was a shuttle which went between the Yale department and the Oxford department, and I should have gone to work with the chemist at Yale but his lab was full. Someone from the Department at Yale, who had been a year or so before in Blaschko's lab, was Bill Prusoff, who offered to take me. Bill was a straight biochemist, and the Department in Yale at that time was essentially a cancer chemotherapy department. Several people, all beavering away on different aspects of cancer, putting compounds into cancer and seeing what happened.

So I went to Yale on a Fulbright Fellowship and had a very good time, learning biochemistry essentially. I was fairly disappointing as a post-doc. I'm sure Bill Prusoff thought, 'My God what have I got here? Somebody who hasn't published a single paper, and I've taken him on as a post-doc.' One of the duties even then for a post-doc in US academic life, was to generate papers like a machine, both for himself and for his supervisor. He would have to teach me all the stuff that he wanted me to do. Years ago, he said, 'You were a dreadful, dreadful post-doc.' I said, 'I know, I'm sorry about that.' He said, 'But you were fun.' [Laughter] But we did have fun, and we got some work done and I have very pleasant memories of that whole event, those two years. But it sounds and looks on paper to be a brilliant career to begin with.

TT: Yes, at Yale you finally got a publication, a paper in *Nature*. Followed by papers in *Annals of the New York Academy of Sciences*, *Nature* again, *Science*. Really prestigious publications.

MB: It seemed not to be such a big deal. Now, of course it's quite a different thing. So that's what always happened to me. When you look at people's work, or what they are doing, now, I think you rate it according to present day standards. What you can't always do is to rate it at the time. It turned out to be a good experience, and we came back to the UK, and I spent the next year trying to find a job. We came back to Oxford, my wife's an Oxford girl. I had a year's fellowship at Oxford but I didn't really do very much scientific work, just chuntering around trying to find a job. There was a chance of getting another post-doc in London, in the Research Department that John Vane and Gus Born ran at the RCS. I took the path of least resistance, which was to come to London with a wife and young child and work in the Department in the RCS.

TT: You were on an MRC Fellowship – what were you doing?

MB: Trying to make slightly different analogues of my digitalis analogues. Instead of putting the quaternary group at the end I was trying to put glucose, make a glycoside. I did that for two or three years and it really didn't work.

TT: Were you on your own doing this?

MB: Yes. There were two of us up one end of the corridor [laughs]. Physically, the Department was along a corridor on the 6th floor, and one end of the corridor was Gus Born and a chemistry lab. At the other end of the corridor, beyond the coffee room, which in fact, worked as sort of dividing line was all John Vane's pharmacology, more like heavy duty biology, down that end. So I was at the Born end, which is where the chemistry laboratories were. There was me and another post-doc who had just returned from the States, and I bumbled around doing chemistry in a not very effective way for two or three years. Sometime in the last years that I got a message from a post-doc I had known at Yale, Alan Reynard, 'I think I need a sabbatical. Why don't I come over to London?' He was a good scientist, he was a biochemist, working on something to do with renin in Buffalo. John Vane said, 'What's Alan going to do? Why don't you have a look at this angiotensin converting enzyme.' I said, 'OK, why not.' He said, 'You'll have to sort out what he's going to do. Because he's going to come here and he'll have to come in and use a system which is working.' So I spent some time trying to get a system where you could measure angiotensin conversion in lung homogenates. Actually, we did some nice work together and we also had some perfused lungs working by that time. This must have been at the end of my MRC time, 1968, something like that?

TT: You published on the angiotensin converting enzyme in *Nature* 1969.

MB: That's right [laughs]! I remember I said to John 'This is presumably going to be Bakhle and Vane?' And he said, 'No, only your name's going to be on that paper.' That is an amazing thing for a Professor to say. I really didn't have any feelings one way or another, because to me it was natural that he should be on it. He'd actually told me more or less, 'You should do this.' I was reluctant to do the experiment, but he said, 'Go ahead!' But the thing about this converting enzyme project, it actually started to produce results, and as you know, there's nothing so seductive as results. Getting an experiment which actually gives you a clear answer one way or another, no matter what the answer is. It sucks you in, and I had three, four, five years of doing experiments which all worked and

got really involved. My wife was very upset with me [laughs]. She said, 'This is a hotel I'm running!' because I would get up early, go to work, and come home quite late. And the kids, both of them were small, hardly saw me.

It's only now that I think of it as a sort of heady time. We were almost like brigands. You'd go out and beat a path in the bushes of 'not knowledge', and drag out a result and take it home and analyse it, and then you'd come back and you'd drag out another. There was this same thing going with Gus Born's people. With that platelet system that he had going, the aggregometer, he was getting brand-new results with every experiment, because nobody had been able to do that before. Everything you did was new. You couldn't help being sucked into the fact that you were really doing new things all the time.

TT: It must have been so exciting.

MB: I think it was. It's only now that I realise that I used to spend so long in the lab, and I never stopped thinking about the project. As it happens until 1970, we lived behind the old Prudential building on High Holborn. So I used to walk to work, I couldn't really have been closer. It really was rewarding, because the experiments were working, and were all new. It was a great time.

TT: It's what people nowadays refer to as low-hanging fruit.

MB: Yes, that's what John Vane did. He went into an area, got quick results and then got out again. But it wasn't quite as cold-blooded as that. The thing was that he had a technique, which enabled things to be done. And the way you maximise that technique is by using a lot of substrates. Because if you use just one substrate and follow that the way through, what you have to do is you have to start getting new techniques as you're going through.

TT: That takes time.

MB: A member of the department said, 'Oh, he's a prisoner of his technique.' And I thought, 'Well, you're probably right.' But in fact, so was Gus Born. He happened to be at that time a one technique guy. But my goodness me they were generating results. John Vane took almost every transmitter you could think of and put it through his system. In a way that's what I tried to do, but was much less successful with the perfused lung, turning my mind to different substrates, and then to different pathologies.

TT: Was that the beginning of your interest in the lung?

MB: Yes, because in those days John was using the blood-bathed organ technique to look at the pulmonary pharmacokinetics of natural substrates. It was very interesting, because, for instance, at least 50% of noradrenaline was lost on a single passage through the pulmonary bed, but adrenaline survived. Histamine survived, but prostaglandins were almost totally entirely wiped out. I was very impressed, I kept thinking, 'How sensible of the dear Lord to organise it like that!' Because there are only two organs, as we know, in the body that receive the entire blood volume. One is the heart, and one is the lung. And the heart is volume without area, because it's a pump, whereas the lung is area without volume, because it's a thin smear, for gas exchange. In those days, heart and lung operations were, and they still are, a little bit dodgy, because you can get what is called 'post-pump syndrome'. People who had a very good operation, everything was fine, and you put everything back, reconnected them, and four or five hours later, they were not at all well. Nobody quite knew why.

My private opinion was that those membrane oxygenators and other devices were excellent at exchanging gas, but not biochemistry. All the biochemistry that had been in the lung just wasn't there during bypass. Essentially you had very dirty blood, you didn't have that general cleansing which went on in the pulmonary circulation. Because it was cleansed blood, which normally goes into the coronary circulation. When you plugged people back in again after the heart lung bypass, there was all this crummy blood which probably overwhelmed the first pass of the pulmonary circulation. So the coronary circulation got a lot of it, got all the rubbish. It was very difficult to get a handle on it and to devise a system which one could use practically.

TT: Let's go back to your work on angiotensin.

MB: We started it because of Alan Reynard's visit and it worked out so well; the success of those early experiments of converting enzymes, more of less coincided with the end of my MRC Fellowship. The fellowship ended in 1968 and I went to work for John and this was the start of the converting enzyme and the lungs business. I was on John Vane's programme grant and after that I became a University Senior Lecturer.

MB: I finished the converting enzyme business, and then I went on to do 5-HT, because Duncan Thomas had done the work *in vivo*, with John showing 5-HT clearance in the lung *in vivo*. What happened next was that John Vane got sucked into the prostaglandin-anaphylaxis area. He started to concentrate on that new area, so I did 5-HT, and then we did some work with Moussa Youdim

on monoamine oxidase (MAO) and 5-HT, and then we started branching out into different conditions; for instance, the oestrus cycle. Then I did some work with diabetes and the effects it had on the lung, because we know the vasculature goes bad during diabetes, type 1 diabetes. Type 2 wasn't really recognised in those days.

TT: And this was the rat model?

MB: Yes, mostly. We also were doing at this stage some human lung, because we managed to get some human lung samples, from operations. I was stuck in there, staying away from prostaglandins completely and looking at all these other natural substrates in the lung; how they were handled, the systems, how all the enzymes are arranged. And then going into certain conditions, and I had put out a couple of grant requests for doing this work in perfused heart, because nobody had ever looked at the effects of the coronary circulation, what happens to luminal transmitters in the coronary circulation? And the other thing was if you put especially high amounts of 5-HT, say a microgram per millilitre of 5-HT through the pulmonary circulation, all the 5-HT was mostly destroyed, but you got prostaglandins out at the far end, in the pulmonary vascular outflow. It was an injury type of reaction. I remember talking to Merton Sandler about this, and Merton said, 'I think that's got to do with migraine.' We tried a little bit, but we never got anywhere. We probably weren't doing the right sorts of experiments to analyse, organise, this release of prostaglandins, because it was prostaglandin-like materials from the lungs when they had a high dose of 5-HT. That project never got very far.

TT: When you went onto the University's books as a Senior Lecturer and then a Reader, did that involve you in teaching very much? It was an unusual set up at the RCS?

MB: Yes, the critical difference was we did not have any undergraduates. The College required us to teach pharmacology to surgeons and to dental surgeons, neither of whom really wanted to hear about it. We also taught pharmacology to anaesthetists, who were much more receptive and much more with it, and needed it much more, of course. Eventually, mid-1980s something like that, I was in charge of organising the whole of the pharmacology, and eventually the whole of the timetable for the Part 1 Fellowship course that the Institute (IBMS, Institute of Basic Medical Sciences), as it was called, put on for the anaesthetists.

TT: You were actually at the RCS for nearly 30 years?

MB: 28 yes, nearly 30 years. I moved several times, I moved down the corridor towards, but never got really into, the John Vane end. For a scientist, at times, he had the most subjective responses. A lot of what he did was trying to get to the other side of that barrier, sort of scientific snobbery barrier, the fact that he would frequently get into areas in which he had no background and make a good discovery and people would discount it really because he was a newcomer. 'Where does he come from?'

TT: So Gus left…

MB: Gus left and everybody said the RCS would advertise, because they had to, but then they really have to appoint John Vane. They never advertised and everybody thought the RCS were scoundrels. It was rumoured that the RCS couldn't stand the thought of a non-medically qualified person holding a Chair at the RCS. Gustav, the only clinical practice that he had, had been his House Officer years, but then he'd gone out on National Service, but I don't believe he'd ever seen another human patient after that.

TT: But it didn't matter, he'd got the right bit of paper.

MB: He'd got the right bits of paper. Humphrey Rang is another example of an excellent pharmacologist who was minimally medically-qualified; he didn't even do his house jobs. He told me one day that he actually hated the idea of patients. He just wasn't interested.

TT: What happened to Gus' Chair, with the Vandervell Chair?

MB: John must have been fairly fed up, because it was quite clear that the RCS would not give him official command of the Department, although he was running it because there was nobody but him. And it was booming. The aspirin papers were just published, and everything was up and running, and things were happening. Then he got offered the job at Wellcome, and he went. He was clearly going to be given *carte blanche* and he took Rod Flower and he took several technicians. And at that time Salvador Moncada had just arrived, and Sérgio Ferreira was there as well. They all went with John to Beckenham. They set up a Department of Prostaglandin Research, which did basic science, nothing to do with drug discovery necessarily. That was the Unit which eventually did the prostacyclin work, it was set up completely separately, because the Pharmacology Department of the Wellcome drug company was run separately from this private, Vane enclave. The first person in charge was Sérgio Ferreira, and then Rod was temporarily in charge for a short while. Then

Salvador came back from Honduras, he was there for at least two years, but it was impossible. So he wrote to John and said, 'Can I come back.' John said, 'Sure.' But I stayed at the RCS.

TT: What happened to those of you who were left, because suddenly you'd lost both the big chiefs?

MB: As soon as John said he was leaving, they advertised the post.

TT: The Vandervell Chair?

MB: Yes. And they appointed a non-medic. G P Lewis, Graham Lewis. But he came out of industry, what was then Ciba-Geigy at Horsham. It really was very clear that the RCS did not want John Vane. They couldn't have made it clearer. John was immensely loyal to the RCS in his own way. He called his mystery prostaglandin substance 'RCS', rabbit aorta contracting substance, but he chose the letters purposely.

TT: How did this affect you? Did you just carry on?

MB: I just carried on. I was more or less self-funding, and I became a Reader during his time. Graham wasn't a difficult boss, but he wasn't anywhere near as inspiring as the other people. He was very different. So I just kept on doing my bit, and he did his bit, and we just kept out of each other's way.

TT: How long was he there for?

MB: John went in 1973/74 to Wellcome, and Graham came very soon after that until 1990 or so. He had two heart attacks and decided to retire. College were looking to close the entire Institute down from end to end.

TT: How many of you were in the Department then?

MB: Probably about 20 people. I was still a Reader, and it became clear that the College were going to close the Institute. At this time (circa 1993), Tim Williams had come down from Northwick Park and the CRC [Clinical Research Centre], and was at the National Heart and Lung [Institute] as Professor of Pharmacology there, said to me, 'Why don't you come and spend some time with us? I can give you an honorary appointment.' I didn't have any research money and I talked to John Vane, and he said, 'See what you can do and also come along and be a consultant for three days a week.'

TT: At the William Harvey Institute?

MB: Yes, that's what I did for four to five years, and I was two to three days at Tim's Department at the National Heart and Lung Institute. In both places I helped out, teaching, editing people's manuscripts, trying to make sense out of them. I also joined a rather curious group of external consultants, headed by a chap who had been many a physiologist, but had translated himself into a 'medical educationist' – somebody who essentially worked for drug companies, producing reports and analyses and sometimes arranging meeting. It was mostly science input; he wasn't really into the PR [public relations] side of it so much, although that of course happened.

TT: What was his name?

MB: Jim Nurse, and he said what he found particularly difficult, so many bioscientists come to the age of 65 and they're just finished. He said, 'All that knowledge, all that experience, and nothing happens with it. Just at the age of 65 it disappears. It's not accessible to anybody because there's no way to access it. It's gone. I like to employ people as they're about to retire, because they have all this information there, they know how to write a report and things like that, and they very often have the time to do that. They've been teaching so they know how to explain things. There are lots of reasons to use all that resource.' I did that for quite a few years.

TT: You had what nowadays is called a 'portfolio career'?

MB: Yes, a portfolio career from 1993 onwards. One by one my portfolios closed up; Jim Nurse's contacts became old and it was difficult to get contracts. John Vane's arrangement came to an end after four to five years. I appreciated very much the fact that he had done it to begin with, because in 1993 I was mentally fairly, not disturbed, but depressed, because being made redundant academically is a fairly unpleasant experience.

TT: It's facing me in six months' time; it is most depressing.

MB: I've retained a title at Imperial and a share in a desk and a chair, and most of the work I do now is for the journal (*BJP*). And that occupies me adequately. Apart from the actual physical editing of manuscripts, it's also about trying to change perceptions of what and how to write a paper.

There are also the collaborations that I have in Brazil, I have input from them about ideas and the experiments that they do. And I say, 'Hang on, that's an interesting experiment, but have you tried this or something else like that,' and then we argue about what to do next.

I saw a paper in the *BJP*, this is in the days when it was all printed, it turned out to be quite interesting because it was about bradykinin metabolism. And they came to the same conclusion that I had come to 15 years earlier. I had written just a short communication in the *BJP* about the metabolism of bradykinin saying that there were effects of the potentiating agents was not entirely due to effects on metabolism. This paper, 15 years later, turned out to be one chapter of a PhD Thesis. I knew one of the co-authors – Pramod Saxena – so I wrote to him and 'I don't wish to be bitchy about this, but you might just remind the author, that I'm very glad that you came to the same conclusion as I did, 15 years later, with a different approach and using different compounds.' Pramod got his own back on me. He said, 'Right, I've told the author about this. By the way, would you like to be examiner of his PhD Thesis?' [Laughter]

TT: On that note, Mick, we have to finish. Thank you so much.

Figure 4: Dr Tom Blackburn

Dr Tom Blackburn CBiol MIBiol MPhil PhD DSc HonFBPhS (b. 1949) received his degrees from Nottingham and Manchester Universities. He has held C-level executive and senior management positions at ICI Pharmaceuticals plc (ICI), Beecham Pharmaceuticals plc and SmithKline Beecham (SB) 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} and 5-HT_{3}), galanin receptor 3 antagonist and the selective serotonin reuptake inhibitor (SSRI) antidepressant, Seroxat/Paxil. His passion, based on an extensive knowledge of pre-clinical/clinical drug development and marketing, helps to define strategies and positioning of pharmaceutical products for biotech startup companies. He is currently Founder and CEO of TPBioVentures LLC, a "virtual" drug development and consultancy company in the US and UK. 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 BPS 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 cognitive and neurodegenerative disorders.

4 Blackburn, Tom*

Tilli Tansey: Tom, to begin with, when and where you were born, and how did you get interested in science?

Tom Blackburn: I was born in Liverpool, where my education was somewhat compromised; like many children at the time, I was a 'latchkey kid'. I have two younger sisters and my time in school meant going home after school while my mother went out to work. So I couldn't do the after school activities I wanted to do, whether they were academic pursuits, athletics, football training or whatever. I didn't pass my 11+, but did pass my 13+ exam. I had a fascination with history, geography and biology. I used to help Mr Harold, who was the Biology teacher, look after the greenhouse plants and the animals I left school with a few O levels at 16, and got my first job at Evans Medical, where I worked on bronchitis vaccine for hens, because once hens caught bronchitis, their egg production went down. I stayed for about a year, when a friend told me of a job in the Physiology Department at Liverpool University. I went along and got the job as a laboratory technician. I'd been going to night school to finish off my A levels, in chemistry, biology and physics, and later I obtained a City & Guilds qualification, Advanced Laboratory Technician's qualification in Physiology and Pharmacology Techniques. I was passionate on driving myself forward, wanting to educate myself in science.

At Liverpool University, I worked for Professor R A Gregory, famous for studying gastrointestinal (GI) secretion and the isolation of the stomach hormone gastrin, and to earn extra money to finance my studies, I used to go in on Saturday and Sunday morning to help clean out the dog kennels. Towards the end of the 1960s, I saw a job at ICI and was interviewed by Dr Mike Barrett and got a job as senior lab technician in Dr Dave Greenwood's and Dr Brian Leonard's lab in the central nervous system (CNS) group.

TT: Can we just step back a bit to the Liverpool days?

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* Edited passages from the interview conducted by Professor Tilli Tansey, 22 February 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

TB: Yes, I worked for Dr R A Gregory, who was a tough taskmaster. I learnt all sorts of lab skills, handling data and many experimental techniques, I was well schooled. Gregory was extremely demanding, but a brilliant scientist. He always used to have these big blocks of chocolate in his desk drawer and I think only once in the three or four years did I get a piece of chocolate. Hilda Tracy was in the lab then, she was lovely, and she used to sneak me a piece or two occasionally [laughs].

TT: Was the purpose of the chocolate to reward good boys and girls?

TB: No, it was his energy source. He'd run up and down the spiral staircase, from one floor to the other in the physiology building, where he had his experiments. He used to pound up and down them every day and weekends. I also remember it was the first time I met Sir James (Jimmy) Black when he visited Gregory's lab, when I was there in the 1960s. As we know, he was very interested in gastric secretion, and later went on to discover the histamine (H_2) receptor antagonist, cimetidine (Tagamet®). Those times with R A Gregory taught me a lot about designing experiments, working in a lab, and he taught me about drugs, dose response curves and anaesthetics.

TT: You probably had better training than most postgraduates at that time.

TB: Yes, I think so. Towards the end of my time in Liverpool, I was getting restless to further my education. The ICI days were great days too. There was a tremendous buzz about the place with regard to drug development. The labs near me were where the β-blocker heart drug propranolol (Inderal®) and tamoxifen (Nolvadex®) for breast cancer, were developed. My main job at the time with Dave Greenwood was developing *in vivo* assays and biochemical assays to look at anti-depressant anxiolytic-like activity in animals. They were really fun times, full of good science, but hard work holding down a full-time job and part-time further education. I'd just turned 21, I'd passed my Higher National Certificate in Applied Biology/Microbiology, and I went to Stockport College and did a MIBiol. I got my MIBiol, this must have been about 1976. And I asked ICI, 'Could I do an MPhil course?' They were very good with me at ICI, Drs Barry Cox and Mike Turnbull sponsored me to go on the MPhil CNAA [Council for National Academic Awards] course at Nottingham University. That was with Professor Charles Marsden on my life-long passion, 5-HT receptor subtypes.

TT: You were working in Alderley Edge and studying at Nottingham?

TB: Yes, it was a busy time, bringing up a young family, doing a full-time job and then studying all hours for an MPhil. I eventually gained my MPhil after being examined on my Thesis by Professors Richard Green, Gerald Curzon and Charles Marsden, at ICI, and Richard Green will tell you the story of how I wined and dined them, and that was the only way I got the qualification!

TT: Let's have it on record. You bribed your way to an MPhil [laughs]?

TB: The restaurants at ICI Alderley Park were some of the best in Cheshire. The manager, Trevor Stone had trained at the Savoy and he was my centre half in the ICI football team, and a good friend. My examiners got a good meal! Charles is one of my all-time heroes. Richard and Gerald gave me a tough time and in my Thesis I'd developed a number of models. People have said since, that it was like two or three PhDs, because it wasn't just one *in vivo* model I'd developed to characterize 5-HT receptor subtypes, but three or four.

TT: Can you say a little bit more about what you did at ICI?

TB: I was working with Dave Greenwood trying to identify new novel anti-depressants. This is the late 1970s. We'd identified and were developing Vivalan® (viloxazine); a selective noradrenaline reuptake inhibitor and 5-HT releaser. Unfortunately, one of the side effects was that it caused nausea and emesis in about 25% of the population. In 1979, Peroutka and Snyder published a *Nature* paper on S_1 and S_2 5-HT receptors subtypes, and we were particularly interested in 5-HT at that time. I was also working on propranolol because it was widely reported in those days for its "anti-anxiety-like" activity by snooker players, jockeys, and for public speaking. That may be related to anxiolytic-like activity. So I worked on and developed a number of *in vivo* and *in vitro* models to look at this activity. In particular, I developed a model to test for 5-HT antagonists, at what was later found to be the 5-HT_{2A} receptor, using a compound called fenfluramine, a 5-HT-releasing agent, and the one I subsequently worked on and developed for the ICI compounds.

So using this 5-HT_{2A} receptor *in vivo* model, I measured the temperature of the animals pre-treated with 5-HT_{2A} antagonists and then given a standard dose of fenfluramine to induce a hyperthermic effect. Using a series of classical 5-HT antagonists at the time, I produced beautiful dose response curves to these mixed 5-HT/dopamine antagonist, and the medicinal chemists at ICI started to synthesize novel 5-HT antagonists to test in this and in other 5-HT models I developed.

TT: Would you go next door to the guy in the chemistry lab and say, 'I've got this, it looks very interesting;' did you have not only the intellectual freedom, but also the operational freedom to go and do that?

TB: Yes, I went upstairs to them and we worked together on identify new pharmacological tools. A bit like the way Jimmy Black worked with his chemists. They were very much part of a team in understanding the biology, just as much as you understood the biology. They got you to understand the chemistry just as much as them, and so that was one of the best relationships with chemists I had in my ICI days. From this work, two compounds out of quite a number of compounds, ICI 169369 and ICI 170809, were identified as development candidates. With other selective 5-HT compounds, I started to build up the compound data bank of 5-HT receptor subtypes and selective compounds. By this time I'd become laboratory head for all the CNS testing at ICI. So I would get compounds from all over the place in ICI to test, whether paraquat from the agricultural side or paint constituents. I also profiled all the therapeutic area development compounds that were going in for clinical testing, so I learnt a lot about drug development from sitting in on therapeutic teams, and also various other compounds and drugs in the organization.

TT: For your MPhil, and later your PhD, did you get support from ICI, like day release or something like that?

TB: I got a lot support from ICI management with regard to time off in Nottingham. But, like my PhD later, a lot of it was my holidays, which didn't always go terribly well with my wife and family. I used to take time off for a week or so, to finish off experiments or at weekends. ICI were very gracious in allowing me to do experiments that contributed to my MPhil, and were a great organization to work for. They were also very supportive with some of the 5-HT tests I was developing. I always challenge the dogma in science and, this got me into a couple of situations where I was going against current research with my data. It wasn't corresponding to what others were saying and basically I got a lot of support from senior management.

TT: Were many people that ICI supported to do their qualifications?

TB: Yes, there were some who stayed with the organization and achieved very high positions. And, a number of them had come through MIBiol at Stockport College, which was a very good course. That really laid the foundation for me in pharmacology to go onto the MPhil, PhD, and then DSc.

TT: So you get your MPhil. That was published in a series of papers. And you continue with Charles Marsden to do a PhD?

TB: No, I didn't because there's always management changes, and people coming in, and the focus of the organization changed. But we had a lot of internal changes in those days and Dr Mike Rance came in, very much an opioid man. So I ended up developing tests then for opioid analgesic efficacy and side effects, but 5-HT was still there in the background. I was stuck in the middle of trying to continue the development of 5-HT compounds, yet build an opioid background. This is the thing about what you see in industry, or what it used to be like, or perhaps it's still like to day, is that people in academia can stay with a project forever as long as the grants come along and they can build that academic research profile, which is great because that's what you need to make breakthroughs: time. But in industry you're constantly, and more so now, chopping and changing. I was trying to link opioid receptor subtypes (μ, κ, δ and σ receptors) and we developed a δ-opioid antagonist which didn't seem to do very much. It was sent all around the world to look for efficacy in different test systems, essentially with little result. But, the κ opoid receptor really piqued my scientific interest, and one of the actions was diuresis associated with κ stimulation. I developed a system/model to test these compounds, whether they were acting centrally or whether they were acting peripherally, and I got to know this guy in Manchester, Professor Richard Balment in the Physiology Department. I worked with Richard on κ-opioid receptors and diuresis. I think it was my idea from reading the literature, which suggested that the adrenal medulla may be important in diuretic-like effects of κ-agonists. With Richard's help, I de-medullated rats' adrenals and we tested them for their diuretic response to κ-agonists. And, surprise, surprise, you lost the κ-induced diuresis in saline-loaded animals, but produced antinatriuresis. So here was a way of looking at peripheral κ-opioid receptors. So I developed this *in vivo* model at ICI. I asked ICI if I could I do a PhD based on this model, and thankfully Mike Rance supported me. So I began my PhD in 1986 and finished it in 1989, again taking some time off in Manchester, working weekends, taking holidays, all to get my PhD.

TT: Can I just ask you about the ICI work and your drug development work – were you taking these drugs into man? What was your involvement in that?

TB: Like with the chemists, I worked very closely with the medics. I used to spend my time going into the clinical unit and developing tests like pupillary diameter measurements. Again, I'd researched the literature, brought it to the clinicians'

attention; 'Here's a physiological response, can we look at this in the clinic to see if there are any effects?' This was the time that EEG [electroencephalography] was starting to become more quantitative rather than qualitative, and we set up a small unit to look at EEG changes, because with a lot of the antidepressants like viloxazine, we saw an arousal-like effect. So here were two translational clinical pharmacology models, we using in the 70s, which became part of the clinical trials and I have used those tests in subsequent studies as well. I was always getting involved with the clinical people and safety people. It was known that I used to go into the safety and medicines department to see why my compound wasn't showing any plasma levels. And, basically being told that, 'Oh, it's not getting into the system.' So I would go along and you watch the technician dose it and you see that the rat spits it out straight away because of the bad taste.

TT: So do you get involved in formulations as well?

TB: Yes, I would always get involved in formulations, sometimes upsetting senior managers in the safety of medicines department. To get back to the ICI compounds, unfortunately they lost their way and I'd been offered a couple of jobs in the States, and I was also interviewed for a job at Beecham. This is 1988/1989. And the ICI compounds were still hanging in there, just, but it looked like the Americans wanted to do it their way. Barry Cox and myself actually went over to the States and showed them some of our data with regard to them eventually developing the mixed 5-HT_{2A}/D_2 compound, quetiapine (Seroquel®), which made a fortune for AstraZeneca.

TT: When you say you went to the States to show 'them', who are 'they'?

TB: Their senior research people, because they had a number of primate models and I was trying to show them that 5-HT was important in modulating dopamine release and vice versa. I don't know why I wasn't asked to go over there and become part of their CNS team, but it didn't happen. I was approached by Beecham and because ICI's CNS at Alderley Park was closing down, I joined Beecham Pharmaceuticals. I really wanted to pursue the depression/anxiety area. By then I'd really got to grips with understanding the depression/anxiety area. This takes me right back to my mother. Her house was blitzed in May 1941 in Liverpool. She was nearly killed next to her mother; her mother was killed. Panic disorder and post-traumatic stress disorder (PTSD) were very much part of my mother's life. Later on in my career I started to understand a

bit more about panic disorders and PTSD, and other problems associated with mental health in later life. That drove me even more to be looking for novel antidepressants, anxiolytic agents.

So Beecham approached me, to join as a Director of the Anxiolytic Programme at Harlow. I was just finishing my PhD then, so this was 1989. They offered me a section head job to look at potassium channel openers, which Beecham were heavily involved in. I was tempted to stay at ICI because the site at Alderley Park was absolutely beautiful, and a great place to work. It had all kinds of wonderful memories for me there. But I accepted the Beecham job and I moved down south, much to the disgust of my daughters. The fact that it was a bigger, better job, was something teenage girls did not understand. I enjoyed Beecham very much, because of the responsibility and freedom I was given. I was heading up a team of 40 people and I had my own chemistry team, I had my own formulation drug metabolism and pharmacokinetics (DMPK) people, I had clinicians, and we were a really good and productive team. In fact, we were so good, we were invited across to Merck at Terlings Park. My Head Chemist (Merv Thompson) and myself, were invited across to Merck by Drs Les Iversen and Geoff Woodruff to tell them why we had better compounds than them. We developed compounds, based on anticonvulsant models, SB 204269 (Carabersat®) and another compound SB 220453 (Tonabersat®), which eventually went into man. If more time had been spent with these compounds internally, I think we would have got somewhere. But management changes happened and we didn't have a mechanism of action, we didn't know how they were working. New management came into what was now SB and Dr Peter Goodfellow and others, saying we couldn't move forward with these compounds because we didn't know their molecular mechanism of action. The compounds seemed to lose their way a bit because of management changes and the need to know what the molecular mechanism was. The Therapeutic Area Team (TAT) had dismissed further development of the compounds. Later, when the head of the CNS TAT left SB, he took the compounds with him to form his own company.

TT: Was that allowable? How was that negotiated?

TB: I've seen quite a lot development people walk away with compounds and set up their own company. Sadly, that is one piece of my drug development life which I would have liked to have seen develop into a novel antiepileptic - something with a better efficacy than some of the standard anticonvulsant

agents, or perhaps effective in a subset of refractory patients. So that was one, if you like to call it a failure, I don't know? The team and I won the SB "Simply The Best" award in 1993 for the novel anticonvulsant programme.

TT: This was a different team? You were running a number of different teams?

TB: Yes, I was running the $GABA_A$ [gamma aminobutyric acid A receptor] team anxiolytic programme, which we had very good subunit selective compounds. I was also responsible for the CNS $5HT_3$ receptor antagonist programme and the lead compound BRL 46470, which came from Dr Gareth Sanger's labs at Beecham.

TT: So that's three teams you've mentioned.

TB: Yes. And there were others. One of my favourites, was the 5-HT_{2C} receptor. The 5-HT_{2B} receptor goes back to my ICI days, before the subtypes were identified. I was seeing a difference between non-competitive and competitive 5-HT antagonists in that rat stomach fundus preparation at ICI. I was saying, 'It's not 5-HT_{2A}, it's a 5-HT_2-like receptor. There must be another receptor there.' When I went to Beecham, a young guy and his wife, Gordon Baxter and Carol Routledge, were working in Syntex in California, and they approached me for a job. So I brought Gordon in and Carol to Beechams, and Gordon eventually found what was called the 5-HT_{2B} receptor. We synthesized a selective antagonist for the 5-HT_{2B} receptor and then a French scientist, Luc Maroteaux, showed that this particular 5-HT_{2B} was found in the heart and may be an issue with regard to cardiac valve atrophy. And SB decided not to pursue this compound. Gordon left the company not long after.

However, the compound was an important pharmacological tool, and really helped us in many ways to tease out which of the 5-HT receptors were important. This was just before and after the Beecham/SB merger 1989 to '91.

TT: The merger with SmithKline?

TB: SB already had the antidepressant paroxetine, and for 10 years, between 1989 and 1999, when I left, I was the front person for paroxetine at Beecham and SB. Not only were we doing bench/preclinical work, it was during this period I actually presented the compound to visiting clinicians, neurologists, scientific advisory board members from the UK, Europe, and America. I then fed the clinical observations from them back to my team, as we were trying to understand why a lot of antidepressants had to be titrated to the patient, and on the spectrum of anxiety and depression you had disorders like panic

attacks. Why were patients given 60 mg of paroxetine for panic attacks, and 10 or 20 mg for depression? Is there some pathophysiology/neuroanatomical difference in these disorders, is the circuitry somewhat different between these brain areas, what receptors were the side-effects due to? So we developed one protocol where we were chronic-dosing for two weeks with paroxetine in a rat model that basically gave us an anxiolytic-like effect, and we repeated that in non-human primates as well. I think that data helped the clinicians rationalise this difference and downstream Paxil® (Seroxat®) into the anxiety disorders.

TT: Can I just ask: what was the status of Seroxat at that stage? It wasn't yet on the market and this was all development work?

TB: It was just breaking onto the market, but with any drug development process, what you're looking for is to extend its profile, the market franchise, whatever you like to call it. In my book, paroxetine is still a very good antidepressant. There's been a lot of criticism because, I think, there was something like 17 studies, and only two or three actually were accepted by the FDA [Food and Drug Administration] for registration. During this time, there were major concerns for antidepressants increasing suicidal thoughts, which is now the concern with all CNS agents and at the forefront of regulatory approval for any CNS drug, whether an antidepressant, anticonvulsant, or any other CNS drug. We know now that the developing brain, particularly of depressed adolescents, is vulnerable to suicidal thoughts. It's this issue that sadly turned many pharmaceutical companies away from developing novel antidepressants for mental disorder. A disorder that is still so insidious and prevalent today. Ask any GP or primary care physician. To me, that is one of the sad aspects of drug development. Sometimes a compound is tainted when we don't fully understand how it works. How the drugs are prescribed, given and taken; there are always compliance issues. But what we are trying to understand more and more about our bodies and about the personalized medicine, we're all different. So we are now looking at precision medicine and the genetics of it, and how one patient can take, say, one antidepressant, and another patient can't, because of differences, say, in their liver enzymes or particular 5-HT receptor subtypes or transporters that are not as sensitive to that particular drug. With many of the older drug therapies, it's like a blanket effect, a biochemical straightjacket that older drugs have on many receptor subtypes, particularly in mental disorders. This has sadly been so for many years now. It's only now with advances, say, in cancer chemotherapy. We're starting to see how precision medicine is coming in more and more to medicine. So, yes, there are issues with all antidepressants and

drugs in general. There are issues with all antipsychotics, there are issues with all anticonvulsants, but what you're trying to do is give/titrate the drug to the patient's needs, so that a particular drug will be more effective, and hopefully relieve the symptoms or eventually cure the disease.

When I left the UK in 1999 to go to the States, my wife and I were looking around an apartment in Hoboken New Jersey. We wanted three bedrooms so our daughters could come over and stay. The agent who was showing us around wanted us to fill out the contract, and I had to put my occupation down. You're always very wary of what you put down and what you've worked on, particularly these days. I put down 'neuroscientist' or something like that and she said, 'Do you work on drugs?' I said, 'Yes, I have done.' And she said, 'I can't thank you people enough.' She said, 'My husband is a failed actor on Broadway and he's been on a compound called Paxil. Do you know anything about this compound?' So I said, 'Oh yes, a little, a little.' She said, 'It's given me my husband back.' She then said, 'I want you to come down and have a look at a two-bedroom apartment. You'll walk in the door and you'll fall in love with it.' So my wife and I went and we walked in the apartment, and there was this view of the Manhattan skyline with the Empire State right in front of us and the Hudson River; it had everything.' So we took it and that's one out of a number of stories where people have told me that they have had therapeutic benefit from Paxil. So all drugs have issues, but there are benefits. Each and every one of us react differently to drugs, and we should question doctors who prescribe them. Sadly, some people will just take tablets and not understand the problems they may cause. We're more fortunate today that we can Google everything and find out more information about drugs we are prescribed, which is great. It helps our understanding as what is good for us, what is not so good for us.

TT: Was it quite a leap moving to the States? Or did it seem an obvious move in 1999? Had you come to some sort of endpoint with SB?

TB: The Beecham/SB days were great days – 1989 to 1999. Then, the merger with Glaxo was on the cards in 1999. As with the merger with Smith, Kline & French, if you wanted to become a major player, you really had to have great marketing people. That's what Smith, Kline & French had brought to the table. They gave us that big foothold in the States. Five of the Beecham drugs became billion dollar plus drugs after the merger. When I left SB in 1999, I left one of the drugs that was a $4.9 billion product, Seroxat®/Paxil®. Today the life expectancy of a drug peak sales (four years) is less, because of generic competition and 'me-too' like compounds, such that you hit the top

of the profit curve earlier. So no matter how much money you're throwing at the marketing, your market share is eroded quickly; this eventually happened to the SB antidepressant. Your returns are eroded because of competitors. My role started to disappear, we lost the momentum. Also, the 1990s was the time that the SB genomics revolution started, so everything was molecular and we were looking for a molecular mechanism all the time. The 90s were very productive for me with regard to Paxil®/Seroxat®, potassium-like compounds, 5-HT_{2C}, 5-HT_{2B}, although $GABA_A$ lost its way. I'd always wanted to go to the US and into the biotech world. There's a famous quote by Sir John Gaddum that a pharmacologist is a "Jack of all trades", and I'd been involved in all kinds of bioscience skills and techniques: drug discovery, clinical development, lab/department management, regulatory affairs, formulation; so many aspects of drug discovery and development. And all those things came together and I thought, 'Okay, Tom, things may not be going so well for you at SB with management changes etc.' and I'd been offered a few jobs in the States, prior to this, with one or two other companies. So I had this calling 'Let's go to the States and join the biotech world.'

Thankfully, my wife backed me and my daughters were in relationships then, and it was just as quick to fly across the Atlantic as to go around the M25. So I accepted a job with Synaptic Pharmaceuticals in 1999. The company were one of the leading companies in de-orphanising GPCR [G-protein-coupled receptors] receptors, they were very molecular based and I wanted to get more into that myself. I was given the job of Head of R&D [Research and Development]. That was perfect, as I thought then.

TT: You must have been very familiar with American companies; you'd worked for British companies with American partners or headquarters: did you find a great culture shock moving to America?

TB: No not really. I think it all depends on you as a person, and I just felt the States were right for me and my family. I was approaching 50 and this was a new chapter in my life. I wanted to be in the biotech world because the bureaucracy of the big organizations with matrix management was becoming overwhelming and unproductive for me, trying to get decisions made across different departmental silos. It was very political. I'm not saying it isn't political in biotech, but you could get things done faster, smarter and reach critical scientific/business decision points quicker. I would go into lab and say, 'Look, why don't you try this? Or can we do that? Or that's a great experiment, well done, that's really set us off on the right track.' You can have all these corridor/

lab conversations and get things moving a lot quicker, rather than trying to spend all your time or your secretary's time booking or arranging meetings in a meeting room which you have to book months in advance.

TT: It's not unique to industry.

TB: I know. But people like to spend their time in meetings. 'Oh, my calendar's full of meetings. Yes, I'm sorry, I'm such a busy person.'

TT: As Head of R&D at Synaptic, did you have any particular remit? Were you expected to deliver in a particular area, on a particular project? Because you took quite a portfolio of experience with you.

TB: Synaptic were doing all the 5-HT receptor subtype screening for Eli Lilly, and they had an α-adrenoceptor programme with Merck, and some other very interesting programmes, some in the depression/anxiety area. I liked the idea of (a) going in and learning the biotech way, and (b) living in the US.

TT: So you reinvented yourself or rather, by moving to Synaptic, you were accepting fresh challenges? You seem to thrive on challenges.

TB: What happened was I wasn't five minutes into the company when the collaboration with Merck fell apart, and the collaboration with Warner-Lambert fell apart, and the Eli Lilly project was coming to an end. So within months of me being there as Head of Pharmacology Research, I was going back to basics. I looked at their portfolio of "failed" drugs, and asked the senior management of Synaptic, 'Can I take a look at some of these compounds in some tests which I think might show something?' I got their support and one of the compounds was SNAP 37889, a galanin 3 receptor (R_3) antagonist, which I tested in an electrophysiological study I previously used at SB. I showed the company and said, 'Look, this is a very similar profile to what I was seeing in the past with SSRIs, but it's working through the galanin R_3 receptor.' I then took the compound into more studies to build a profile and see if it was a potential development candidate. I then got support from the board to move the compound forward as the company was seeking further finance, and a proposed development candidate would add to its value.

So then I became VP & Head of Drug Development and Officer of the company at Synaptic. It was a bit like at Beecham: I had my chemists, my DMPK people and I'm training chemists up into producing API [active pharmaceutical ingredient] and clinical trial material, and work as formulation people. I built a drug development group up within 18 months of getting that compound and

was IND [Investigational New Drug] ready for Phase 1 testing in 2001. Just as we were going to start clinical trial in Phase 2 with Duke University, the Danish pharmaceutical company, Lundbeck, bought us. Lundbeck wanted Synaptic's expertise in molecular biology and the novel compounds we had. Unfortunately, these compounds were up against Lundbeck's internal compounds and lost their way for various internal reasons.

TT: You were with Lundbeck for just a year or less than a year?

TB: While I was with them, they gave me this beautiful office in New York City overlooking Madison Avenue on the 34th floor. My job, Director of Medical Affairs, was to build relationships for Lundbeck in the US with the likes of Columbia, NYU [New York University], etc., which I did. I tried to get the company to be part of a neuroscience hub on the east side of Manhattan. But Lundbeck had other ideas.

TT: What happened then?

TB: I asked Lundbeck, 'Could I spin out of the company with the galanin R_3 receptor compound? Could I have a license to develop it?' And Lundbeck agreed, I'm one of the few people, if not the only person, allowed to take a compound out of the company. The terms they offered me were sadly prohibitive at the time. I went around the various investment banks and VC [venture capital] people in New York, but could not acquire the finance. So I ended up not taking up Lundbeck's offer.

At that time, Dr John Tallman approached me. He headed a company called 'Helicon Therapeutics' on Long Island, and wanted an R&D development person because he had some interesting compounds. He asked me if I would join Helicon and basically set up a development group with them. I joined Helicon, and was there for about three years again I was VP, Head of R&D. I set up a whole series of tests to support their ongoing work, and I was also interested in some other projects, and I'd also told John, 'I know a compound you'd be interested in' and that was the galanin R_3 compound. So John completed the due diligence on it with Lundbeck, and in-licensed the galanin R_3 antagonist for Helicon (HT-2157).

TT: So it was rescued?

TB: Yes, I was using another company's resources to move this compound forward, and were developing it as well for clinical studies. And everything seemed to be going hunky-dory. John and I were excited about the potential

of the compound to treat depression. However, there was a problem with the formulation and we eventually visited a company in South Carolina who could fix it for us, and flew home. The following day we had two teleconferences with AstraZeneca and Glaxo. I was waiting for John to arrive and he never turned up for either call. To cut a long story short, we got the police eventually to go to his house to sadly find John dead.

TT: Oh my God.

TB: That was quite a shock for me, the company, and, of course, his wife. That was a very sad day and very intense period of time in my life. Not long after, the company were forced to move out of Long Island and find other premises and the Board wanted to move to California. I was going backwards and forwards to San Diego and eventually found a beautiful facility. I did all of the groundwork for moving the staff and everybody out there, took my wife and my family out there to show them. But my wife and I didn't go, which caused a few ripples and surprised a few people. It just was not for me for various reasons. I left the company in a good way and with my integrity intact, which is so important to me. It's what I've built my long career on in the pharmaceutical/biotech world. I just felt it was time to pursue something I'd always wanted to do – set up my own virtual drug development company.

I formed my own company and I was doing very well initially, but along came the whole financial crash of 2007/2008. Around that time, I had some financial support, I had the chance of compounds from Merck, I had things moving forward and then, all of a sudden, 2008 hit me. The NYC [New York City] Investment Bank I was working with closed down, like many financial institutes in NYC and around the world, and we decided to come back in 2011. Since then I've been doing lots other fun things, some consultancy, writing book chapters and a textbook on pharmacology for chemists with Terry Kenakin and Ray Hill. I'm lecturing and examining at UK Universities, and I'm sitting here talking to you about my life! What else is there?

TT: One thing we've not talked about is the influence of professional societies. The BPS is the obvious one. When did you become a member?

TB: It was in the early 1970s, well before I'd left ICI. The BPS, was a highly regarded society at ICI. So as a young pharmacologist, I enjoyed going to the meetings and I was in awe of these wonderful Professors who used to sit on the front bench and ask you all these very difficult questions, and sometimes a very nice question that you could answer! And it was a great learning,

training experience for me. To be able to stand up and give a presentation in 10 minutes and have roughly five minutes of questioning, from very eminent pharmacologists in the academic and the pharmaceutical world was quite a challenge. So it was tremendous training, and I used to enjoy those oral and poster presentations. There was one oral presentation in Dublin, which was my first presentation, and I was the last one on the Friday afternoon to present with hardly anyone in the lecture theatre. The Professor (Philip Bradley) who was chairing the session had fallen asleep, not because of my presentation, but because of, I think, the excellent dinner and wine the evening before. And, I had one question from Professor Gordon Arbuthnott from Edinburgh, which was one I could answer.

TT: Was that on the 6-hydroxydopamine rotational model?

TB: Yes, that was on the 6-hydroxydopamine rotational model, a model you also worked on Tilli. I enjoyed, and still do, the BPS poster sessions in particular, because you could be presenting a poster on say 5-HT research, and next to you could be a poster outside your field, say, on the activity drugs that acted on earthworms! And then you'd have an idea to take back to the lab. It would spark another idea off and you'd say, 'I wonder if I could apply that to my research?' The interaction and networking that goes on is so much part of, as you well know, the BPS, and still is very strong within the Society. You can see that passion of the young investigators and the enthusiasm with regard to presenting their work. Now, those young investigators look at me as being one of those old guys asking the questions on the front row or at their poster.

TT: You became the Meetings Secretary? That can be quite onerous?

TB: Yes, very, as you come across all kinds of different people, egos and whatever. I was fortunate in many ways, a number of people took me under their wing, like Professors Bill Bowman, John Vane, Geoff Woodruff and Tony Birmingham, all people I admired very much. I worked very closely with Norman Bowery over the years before and during my tenure as Honorary Meetings Secretary (four years), Honorary General Secretary (two years) and President, Norman really helped me with regard to the workings of the BPS. I became Honorary Meetings Secretary, 1994/95, when we had four meetings a year, three of them in universities, then the big winter meeting before Christmas, which was generally held at a conference centre or a big hotel in the UK. When I go to a conference the first thing I do is look at all the audio visual facilities etc., to see how good they are and if I could do better. It was such a privilege and an honour

to be part of the BPS and still is (I'm Chair of the Industry Sub-Committee for the next two years). I held a joint meeting with the American Society in San Diego and worked with ASPET [American Society for Pharmacology and Experimental Therapeutics] very closely and we had a very successful meeting. One little caveat: the Americans couldn't get their head around this 'Honorary General Secretary' title, and there was some amusement at this name.

When I became Honorary General Secretary, with Nigel Baber heading the clinical section, we decided to do a SWOT analysis; the Strengths, Weaknesses, Opportunities, Threats to the Society moving forward, for revenue issues for the journals, like open access publishing, and other matters that were possible concerns for the Society, such as the membership and the number of pharmacology departments closing in the university system. We held a strategic workshop and looked at all aspects of the Society's activities, and one of the proposals was to change the name of society officials to be in line with our sister organizations. So we now have a President and Vice President of meetings etc. I'm the only person who, for one year, was Honorary General Secretary and the following year, President, of the Society. It was one of the most fun times of my life, one of the most hardworking times in the sense of balancing the day job and the honorary position, which did at times bring me into some conflict with my employer.

TT: This is when you were still at Beecham?

TB: No, it was SB management at that time, who questioned the time I was spending on BPS activities. However, all the time for BPS meetings I'd taken off as holidays, so for the summer/spring meeting, that was all taken out of my own personal time. That was never an issue with me, as I was meeting so many wonderful people/scientists from all over this country, Europe, America. I set up the joint BPS meeting with the Australian Society before I left SB. That was a joint meeting between the Australian Society and the British Society. Unfortunately I'd moved to the States when it was held, I'd set it up with Jim Angus, it was held in Melbourne and I didn't get to go to that meeting. I had a great time and it was a great privilege working with superb BPS staff. Now we have a very young, dynamic team and the CEO, Jonathan Brüün, he is doing great things with the Society. We have one big meeting a year which is called "Pharmacology 15", "16", "17" etc. The Society's in good financial shape, with a very good team in the office and is moving forward with the times.

TT: What kind of upset did it cause with you leaving, effectively a year early?

TB: Some people were annoyed with me but if you have a new job, you have to move with that job. Most people were very supportive and Norman Bowery was still very much involved with the Society, and he took over for that year, for my final year.

TT: Did you then join the American Society?

TB: I did for a while, but their meetings always fell at a very awkward time that often fell in with Board meetings at work, and with various other things, which I could never abandon! I think I went to about three or four of the meetings, and they got me to review posters.

TT: Did you encourage people in your lab to join the societies?

TB: Oh, absolutely. Particularly the young people.

TT: Moving back to your own career, could I just ask you to elaborate about the pressure of being innovative compared with doing generic work. Have you ever felt under pressure to get something slightly different?

TB: There was a period within the industry where everybody was a lemming. They were all falling off the same cliff. Paroxetine is an example of that, we weren't the first SSRI by any means, but the company made billions from it. So it's like every product we deal with in life, there are lookalikes, similar products, bioequivalents, whatever, and it's your market share that is the goal. You're seeing companies today now exchanging franchises in vaccines, basically to build their strengths around vaccines, and giving away some part of their empire which perhaps in another company would build that company franchise to differentiate themselves from the pack.

TT: Have you found much difference going into different companies with their different corporate policies, or have you chosen very carefully companies that would fit you?

TB: The fit comes beforehand in the sense that I look at the people, I look to see if those people inspire me. Will those people take me to another level? And how much respect I have for them and their science. Once you lose the respect for the people you're working with, then is the time to move on. When the people in the coffee room are grumbling about this, that and the other matters, you don't want to be in a coffee room with grumbling people.

TT: What about personal ethics and integrity.

TB: I don't like anything associated with abuse, fraud or lack of integrity. We see so much of it in our lives where people are being taken advantage of. When I read or hear or see or have possibly been subjected to poor decision-making, I quickly walk away and don't want to have anything to do with. Particularly when you're dealing with human life and medicines.

TT: Have you ever been aware of any tensions between academia and industry?

TB: Not really. Well throughout my career I've seen a lot of academics come into industry. Some have made it, some haven't. I've seen industry people move into academia, some have made it, some haven't. I think it's all about the people in charge and how they interact. We're not getting the creativity perhaps, or we can't afford to let the creativity move forward as we once did in the past.

TT: I think you're giving us a master class in innovation as well as oral history, Tom. I'm sorry we have to finish there. Thank you very much.

Figure 5: Professor Roderick Flower

Professor Roderick Flower PhD DSc FMedSci FRS FRSB HonFBPhS HonLLD HonDSc (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 BPS (2000–2003).

5 Flower, Roderick*

Tilli Tansey: To begin with Rod, could you say something about where you come from, your family background and your early education?

Roderick Flower: My father was in the Royal Air Force and so he was absent for a lot of my childhood. He was still on active service and posted around the world, and we sometimes used to go with him, for example, when I was about seven we were three years in Ceylon as it was in those days, and after that Penang. Then father was posted somewhere else, and it was thought appropriate that I should be put into a boarding school, as were lots of children from service families. We're talking about the late 1940s and 1950s. We never really seemed to have a family home that was a central, unmoveable fixture. When I got back to this country, I found I was years behind in educational standards, which was always a bit of a handicap. I always loved science and mathematics. One of the things that really turned me onto science was living in Ceylon and looking up at the starry sky at night and seeing the Milky Way and all the fantastic constellations in a crystal clear firmament. I became very interested in astronomy, and that interest has persisted throughout my life, although not in a very serious way.

I was not a good student at these boarding schools. I now recognise that, in order to perform well, I have to be interested in something. So if somebody bored me, I switched off straight away and just lost interest. When I look back on my career, the people who were most important were not necessarily the cleverest teachers, but they were the most inspiring. Some people were really inspiring. For example, I spent a short time at an academy where there was a mathematics teacher there whom I found very inspiring, so much so that I spent a lot of my free time doing recreational mathematics. At my junior school, there was a Russian teacher of maths who also was very inspiring. He had lots of interests, for example in earth sciences, and I used to go with him in the morning to take readings from the school weather station and log them onto charts, and that's another interest which has persisted throughout my life, and I'm actually

* Edited passages from the interview conducted by Professor Tilli Tansey, 14 April 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

a Member of the Royal Meteorological Society. I didn't really emerge from my school career with a very creditable performance, to be honest. And although I was interested in science, I really had no clear vision of where to go. Incidentally, it's a bit strange because I was never taught any biology, which is extraordinary considering the fact, for example, that in the 1950s, Watson and Crick did all their fundamental work on the structure of DNA! So I knew nothing about biology at all, which maybe in retrospect wasn't a bad thing, because when I did become interested in it, I was able to come at it with fresh eyes.

My favourite subjects were mathematics, physics and chemistry, but I didn't do academically well. After a few odd jobs – including working in a bank which my father thought would be a good career, I became interested in a very novel field, and that was computing. In those days, computers weren't things you buy from Apple and stick on your desk. They took up one or two rooms with special air conditioning arrangements and so on, and which used to operate using reel-to-reel tapes. And these required computer operators, people who knew how to handle them if they went wrong and repair faults. A lot of my friends had that job, it was very well paid, and it sounded very interesting. So I applied for a job, which was advertised in the *Daily Telegraph* in the Department of Pharmacology at the RCS in Lincolns Inn Fields, under Gus Born and John Vane, to look after a rather basic computer, which they used for logging animal behaviour because there was somebody there in the lab at that time who was interested in the effects of drugs on animal behaviour.

I had no idea what pharmacology was, I had no interest in anything biological, but I had this idea I might be quite good as a computer operator. However, when I went for the interview the first thing that John Vane said was, 'I'm sorry, that post has gone. We've just given it to somebody else. However, we're looking for a general technician to help around in the lab. Would you be interested in that?' I suppose it's one of those things I look back on as a defining moment. I said, 'Yes, sure, I'll do it' and Gus Born also interviewed me, and so they offered me the job. Within a month or two, I suddenly realised this was what I really wanted to do. I studied in the evenings for a Higher National Certificate, which was in those days a way of alternate entry into some universities including Sheffield, your own *alma mater*. I then left the College, and my job as a technician, and went to Sheffield University to read physiology, using my HNC as an entry qualification.

TT: What did you learn as a technician, what did you do? Studying for your HNC – this was not part of your technician's training?

RF: No it was not, but they would pay for you to go in the evenings or half a day a week to college so you could further your education, which was a very, very enlightened attitude really. I learnt a lot about the practical skills involved in animal work, in bioassay, which is one of the main things that John Vane used, and general lab skills, weighing, measuring, all those sorts of things, making up solutions, making up drugs. I also picked up a lot of knowledge from the people in the lab who were always willing to share their insights with me, even though I was nothing in terms of the overall organization of the laboratory. That Department was pretty interesting for a number of reasons, it was run jointly by John Vane and Gus Born. The Department was like a very long corridor and they had one end each. Gus was more interested in platelets and thrombosis, and he had his own people working on that, and he made huge contributions. John's end was mainly concerned with disappearance of hormones in the circulation and using bioassay to measure their half-life, and so on.

I worked mainly with John. I learnt a whole range of practical skills from taking blood from humans, to preparing tissues from rats and even doing some large mammal surgery. This was very helpful when I went to Sheffield as a physiologist because I was probably the only one in the class who could walk straight into a lab and know roughly what they were doing.

TT: Who else was around in the lab then?

RF: There was about a maximum of 30 people together at one time, roughly split into two halves with 15 people working with Gus and the other 15 working with John. There were some absolute stars there. One who had a huge influence on me was Sérgio Ferreira, a Brazilian scientist who visited the lab for extended periods of time. He was responsible for a lot of the early work showing that peptides from snake venom can potentiate the action of bradykinin, which led John to make that seminal suggestion that since the enzyme that destroys bradykinin is the same one that activates angiotensin I to angiotensin II, an inhibitor of that would be potentially good anti-hypertensive drug. One of my jobs as a technician in those days was with that whole angiotensin project very much in a technical capacity. It was very exciting to live through that and see it, eventually, become captopril some years down the line. There were a number of others, we also had a lot of academic visitors there, which is very good for research departments, and I met people from all over the world.

I'll just say one other thing about that Pharmacology Department at the RCS, which was very seminal in lots of people's career actually. The conditions were incredibly cramped, but that didn't seem to make any difference to the productivity. One good thing, which you can't do these days, was that in the middle of the two ends of the Department there was a huge coffee machine and a trolley with cups and saucers. Every day we met at half past ten for coffee, again at lunch time, and for tea at about half past three to four o'clock. I know it sounds awfully trivial, but everybody clustered around, from the Professors right the way down to the cleaners. It's surprising the number of ideas that were generated at that time just by bouncing things around in conversation with a cup of coffee in your hand and discussing somebody else's results. You can't do it these days, because you can't have coffee machines in labs!

TT: What encouraged you to go back to academic study?

RF: I decided I wanted to make a career in pharmacology, but obviously I needed a degree in those days. I was studying for my HNC and the tutor was very supportive and said, 'You ought to go to university and I'll help you with your application form.' It's another example of somebody just helping in a very disinterested way, but making a big difference. I didn't tell John that I'd done it until I got the offer from Sheffield, partly because he was such a powerful man, even in those days. He said to me afterwards, 'If you'd wanted to go to university, I would have rung up somebody,' but I didn't want that, because I would have always felt a bit of a fraud.

TT: You went to read physiology, not for a pharmacology degree?

RF: There weren't that many around really. I was a bit constrained, because not all universities accepted HNCs. I really enjoyed my time at Sheffield. I made some very good friends, and professional associates.

TT: You then did a PhD; you went back to work with John Vane.

RF: I really wanted to get back to pharmacology. Doing a degree in physiology gave me a fantastic basis for understanding drug action. The practical skills I'd acquired in Sheffield were very, very good. It had always been my intention to go back to John's lab, and in fact I worked back in that Department in pretty much every vacation from University. So we'd actually done quite a lot of work together. I was lucky in a way because everything seemed to come together. I got back to the lab just as John's original paper on aspirin had been published in *Nature*, together with two others from John's colleagues, Sérgio Ferreira and

Salvador Moncada, who was also a PhD-student. There's an interesting point about that Department at the same time as John published his paper in *Nature*, two people working with Gus Born had a very similar idea, which John didn't know about and they didn't know what John was doing. So much for the coffee machine discussions – they didn't work on that occasion! In the end all the papers came out in the same edition of *Nature*, and what they showed was that aspirin blocks platelet aggregation if you give it to humans. But they reached the wrong conclusion about its mechanism of action. John's paper was significant, because it was a very simple paper. He only looked at three drugs: aspirin, indomethicin, and salicylate. But the important thing he did was, he used an homogenate of tissue, which could catalyse the conversion of arachidonic acid to prostaglandins directly, and showed that you could block that by adding the drugs directly to the solution, so there was no way the results could be equivocal. These two papers had just come out as I joined the lab. We knew already that aspirin blocked the appearance of a biologically active substance coming out of perfused tissues. John and I had done something on that the previous summer, and John's great 'eureka' moment was he realised that this material was derived from the cyclooxygenase enzyme that makes prostaglandins, which nobody else had thought. So immediately, because aspirin prevents it, he said, 'The obvious thing is that aspirin is blocking at cyclooxygenase,' and that was the intuitive leap that he made, that nobody else did.

TT: What was your PhD on?

RF: It was on that, and the first paper we published was looking at all the non-steroidal anti-inflammatory drugs we could get, and I tested them all on the cyclooxygenase preparations that we made, and we found out that the order of potency matched their therapeutic order of potency, and that the levels at concentrations you need to inhibit the enzyme, were the sorts of concentrations you could find in blood after taking an oral dose. Drugs like morphine, which is analgesic but not anti-inflammatory, and drugs like gold and chloroquine, which were anti-inflammatory but not analgesic, had no effect on the cyclooxygenase at all. So it was very, very specific effect.

One of the pieces missing in this developing story was the following question: if you take aspirin, does your tissue prostaglandin level go down in response to a normal therapeutic regime? I'm not talking about one-off doses, but the sorts of doses you'd take therapeutically. Joe Collier had, before I got there, designed this small trial using medical students at St George's, and the problem was how to measure prostaglandins. There was one tissue where prostaglandins are very

abundant, and that's in seminal plasma. So Joe Collier arranged this rather tacky clinical trial with medical students from St George's, male medical students of course, and the net result was I had dozens of samples of human seminal plasma, which I kept in the fridge by the coffee machine, until I was able to extract the prostaglandins and measure them by bioassay. The upshot was after about two or three doses you could see the levels of prostaglandins diminishing. We published that in *The Lancet*, and I think that was the first time aspirin had even been shown to inhibit prostaglandins in human subjects after a therapeutic regime.

TT: You mentioned using 'all the non-steroidal anti-inflammatory drugs we could get', did you go to ordinary pharmacists or use drug industry connections?

RF: A mixture really, we had samples of all the major non-steroidal drugs, which we used in these enzyme assays.

After a couple of years, the Department began to change. Gus was offered the Chair of Pharmacology at Cambridge and went in, I think, 1972. John was offered the job of R&D Director at the Wellcome Foundation. In those days this was a completely independent non-profit making pharmaceutical company based in Beckenham, with a very interesting history, as you well know, with Henry Dale having been perhaps the most influential scientific member of that early enterprise. And Henry Wellcome having arranged in his will: that all the profits should go to a Trust. So it had a very interesting ethos, people never felt that they were working to make money for shareholders. When John took up this post, he was inspired by some of Dale's thinking about what pharmacology should be. He said to a few of us, 'I'd like to keep this Department going down there. Would you like to join me?' So there were about four of us, Sérgio Ferreira, Salvador Moncada, although he left shortly afterwards to go back to Honduras for a while, Gerry Higgs and Geoffrey Blackwell. We recreated the laboratory. One of the things that distinguished working at the RCS was this very free interchange of ideas, everything was considered carefully, even some ideas originating from the cleaners. We managed to transplant this ethos to Beckenham. We didn't have the coffee machine in the middle of the Department, but we did have a coffee room upstairs. The coffee there was better, actually.

TT: As you say it wasn't "industrial" industry, like moving into one of the other drug companies. It always used to be called the "University of Beckenham".

RF: It did and that was very much the atmosphere. I was a bit apprehensive to begin with, but found it incredibly pleasant and interesting to work there. I learnt an awful lot, interacting particularly with the organic chemists. I was able to ask people, 'If you want to design a drug to do this, how would you do it?' They had some very good natural products chemists there, and they turned out to be important later on for me, because I was quite interested in extracting natural products and naturally occurring substances from biological fluids.

We had lots of visitors and having that Department, the Department of Prostaglandin Research, changed the nature of science at Beckenham. It had always been a little conservative, and the general tenor was you didn't publish too much, you kept things under your hat. When we got there we were publishing left, right and centre. John was very keen to recruit top notch people, and he really gave us our head. He didn't come into the lab and do experiments, as he did in the RCS, but he maintained a very strong interest. He used to edit manuscripts, make suggestions which were always very valuable. He had lots of other responsibilities, so we didn't expect him to be a lab participant.

The first fruit was the discovery of prostacyclin, and of course the marketing department said, 'That's not really a drug. You'll never make any money on that.' Nevertheless, analogues of prostacyclin are used for the treatment of several conditions now, including some life-threatening diseases such as pulmonary hypertension. In the area of prostaglandin research things were really very exciting. The endoperoxide intermediates, which exist between arachidonic acid and prostaglandins, had been isolated, and we were able to use these as experimental reagents. There was Richard Gryglewski, who was a visiting scientist from Poland, Stuart Bunting who was a very talented pharmacology student from Chelsea College, and Salvador Moncada. They noticed that if you applied these endoperoxides to vascular tissue, then somehow the biological activity disappeared, and that it may be transformed into something that they could not detect. Then they found out it had profound effects on platelets. I realised that the breakdown product was probably a compound that we now call "6-keto-$PGF_1\alpha$" [6-keto-prostaglandin F1 alpha]. Three simultaneous papers came out describing these discoveries, the one that I had worked on was published in *Prostaglandins.*

TT: That journal was quite new then. The whole field was just starting.

RF: It was at the time, that's right, it was very exciting. Once the potency of prostacyclin was realised and its biological properties catalogued, it became even more interesting.

TT: You mentioned chemists. Did you have any involvement with other scientists in the labs?

RF: Yes, we were embedded in what originally was the Department of Pharmacology at Wellcome and so we became good friends with the pharmacologists there, and we did a lot of good work together over the years. Not just on prostacyclin, but we were also interested in looking at other types of anti-inflammatories, and at least a couple of them looked very promising at the time although they subsequently died for other reasons, as drug candidates often do. That's just the nature of the field. It was an interesting place to work because of Wellcome's strong interest in tropical medicine, there were a lot of people who specialized in malaria and HIV [human immunodeficiency virus]. It was during this time that the very first antivirals were produced.

TT: By this time, you're a staff scientist building up your own team as part of the Prostaglandin Research?

RF: Because of my interest in aspirin, I began to think about other anti-inflammatories and how they worked. In those days, prostaglandins were considered to be the most important inflammatory mediators, because we hadn't yet discovered cytokines, chemokines and so on. So I began to look at other ways in which steroids could affect prostaglandin synthesis, and steroids were a very interesting group of drugs. It's funny how different disciplines have their own intellectual territories. For example, neutrophils and macrophages had always been regarded as 'pharmacologists' cells', but no card-carrying pharmacologist would be seen dead near a lymphocyte! On the other hand, immunologists worked mainly with lymphocytes in those days. So the whole area was carved up into different zones. The steroids were a good example of this: because they were hormones, or hormone derivatives, it was never quite clear who 'owned' them – certainly not pharmacologists. Everybody knew they were the best anti-inflammatory drugs without question, and there were a number of ideas about how they worked. The most influential at that time was an idea that Gerry Weissmann had originated, was that steroids could stabilize the membranes of lysosomes inside cells. On the other hand, there was a whole community of endocrinologists who were looking at steroid sex hormone action, and they'd

observed there were receptors for these sex hormones in the uterus and they'd found out using radioactive oestradiol, that it became transported into the nucleus. Those two parts of the field never really met.

We looked to see whether we could find a receptor for glucocorticoids (steroids) in guinea pig lung tissue. We did find one, and we showed that antagonists of that receptor could block the ability of steroids to inhibit prostaglandin synthesis. Then the question was, how's it doing it? I had the idea that we would see if steroids were causing the synthesis or the release of something in these cells, which was actually blocking the production of prostaglandins. I set up a rather complicated experiment using two lungs perfused in series, and we found out that's exactly what was happening, much to our surprise, and it was very, very dramatic. This steroid-conditioned medium contained this factor, and we found that this had very powerful pharmacological properties. In some circumstances it mimicked steroids, and it possessed very powerful anti-inflammatory properties in rats. We were convinced that we'd found something important. We called it 'macrocortin' in those days. We then made several attempts to purify this material, which we'd identified as a protein by now, and this proved to be very difficult. We published a paper showing this very prominent biological activity and we explained why steroids do some of the things that they do. We never made the claim that it was explaining all steroid anti-inflammatory effects but, nevertheless, looking at this particular subset of effects, this acute anti-inflammatory action, this macrocortin turned out to be the effector, which was exciting.

TT: This is still at Beckenham?

RF: Yes. I'd hit a bit of a full stop, because there was no one at Beckenham who could purify and characterize this protein. In the end I decided I'd leave, and I saw a job at the University of Bath, Professor of Pharmacology, and I got the job and I left in 1985 and in 1986 Wellcome was taken over by Glaxo and John himself left in either 1986 or 1987.

TT: You moved to Bath and it was a fairly new University?

RF: It was a 1960s' University. It had been formed by the amalgamation of the Bath School of Pharmacy, and Bristol College of Science and Technology following the Robbins report. Pharmacy was important in the creation of the University and the School of Pharmacy and Pharmacology was very important. The demand for pharmacy undergraduate places was so high, they always got people with fantastic A level results, and they turned out really good graduates,

like they still do. I used to teach all the molecular biology to the pharmacists, and I remember one putting their hand up and saying, 'Do we really need to know this?' If only they could have seen all those biologicals in the clinic now!

TT: A constant refrain from students [laughs]. What about your own research? Did you take people from Wellcome?

RF: I didn't take anyone from Wellcome, but I recruited people who I'd known in London, who had similar interests. There was one big advantage to being in Bath: when I was at Wellcome I had been approached by Biogen who said, 'We're very interested in this protein of yours.' Well my hands were tied, but as soon as I left Wellcome they contacted me again saying, 'Would you be interested?' and I said 'Yes.' That was probably the best decision I ever made, because their people were right at the very cutting edge of molecular biology and protein chemistry, and it didn't take them very long to isolate and sequence my protein. And so very early on in my time at Bath, they published a paper describing the cloning of a gene for what we then called "lipocortin" and, subsequently, "annexin A1", and they demonstrated it had pretty much the same properties as the biological material. They sent samples of the pure recombinant protein to me and it turned out to be a very potent anti-inflammatory compound in rats, and had lots of exciting properties.

There were other problems though, and my administrative workload was increasing so much that I woke up one morning and thought, 'If I don't do something, I'm never going to ever get back in the lab again.'

TT: How was your research funded at that time?

RF: John gave me a little bit of money when I left the Wellcome Foundation, I got grants from the ARC, the Arthritis Rheumatism Campaign, and Biogen gave me some money because they were keen to explore this protein.

I'd kept in touch with John, who by this time had left the Wellcome Foundation and then he was offered some space, through the intercession of a man called Derek Willoughby, who said, 'Why don't you come to Barts? There's a huge amount of space going begging there, you could just move in'. John moved there; he had one office, his PA [Personal Assistant] from Wellcome with him and a couple of PhD-students. On one occasion I visited him and he said, 'I think it will be a good idea if we try to expand this operation, gathering together old friends who know how to work with each other. Would you be interested?' I thought about it and said, 'Yes.' It was a difficult thing to do

because I had to give up everything: I had no research money, no apparent career prospects; everyone thought I was nuts. Derek Willoughby was helpful, because through his connection with Eli Lilly he'd found out that they wanted to fund an academic Chair in inflammation research and I went down to see them and they said, 'Okay, we'll give you some money for five years,' which was great. When that ran out, I obtained a Wellcome Programme Grant.

TT: You were a Professor; just doing your research, or did you have obligations to the Medical School?

RF: No, none at all.

TT: So really, this was almost back to the old Wellcome days?

RF: Exactly so, absolutely. A number of people joined, and we took a big step forward in 1990 to 1991 by creating this completely independent, free-standing, self-supporting institute, the William Harvey Research Institute and having it registered as a medical charity with the AMRC, the Association of Medical Research Charities. By this time the Institute had grown from about six people to about 50 we negotiated an agreement with Ono Pharmaceutical in Japan, a company with a big interest in prostaglandins as therapeutics and they gave us some money for five years, saying 'if we see anything that we really like, we'll pick it up and run with it. But otherwise you can do what you like with it,' which I thought was very generous.

Things went very well until the mid-1990s really, when the world financial situation began to deteriorate, although Ono extended their grant by a few years they said, 'We can't renew it any further'. In the meantime, I got a Wellcome Trust Programme Grant and after that, I went for a Principal Research Fellowship, which, luckily, I got and held onto for another 13 years.

We had to make a decision about where to take the Institute. John was partly retired and one of the things we considered was merging with the Medical College and becoming their "Division of Pharmacology" in effect. From 1998 to 2002 I was Director of the Institute, and we decided we would go down that route, the deal we did was that we would exchange our assets in exchange for certain key people in the organization being taken onto the permanent staff. We're probably one of the biggest pharmacological organizations in the world now, there's over 350 people are on the Charterhouse Square site.

TT: During all these other perturbations of the Institute, Rod, what about your own research? Were you getting back to the lab?

RF: I was getting back to the lab, and it was going very well. We had plenty of pure, "annexin-1" as we now called it. All our predictions about its biological activity were pretty much fulfilled; it was a very powerful anti-inflammatory: it stopped white cells from migrating. It became clear that what it was really doing – and it's a bit of a fine point, but it wasn't really having an anti-inflammatory effect - it was having a pro-resolving effect. It's become obvious over the last five years or so, that what actually happens is the body produces a panel of anti-inflammatory or pro-resolving substances, which are phased in when the inflammation begins to wane. These substances appear to restructure the tissue, to enable the engulfment and removal of white cells, and so a very important part of the healing process. It turns out that annexin is one of these compounds, so it has anti-inflammatory properties, but, actually, they really are pro-resolving. There are several other compounds that have been identified, for example, lipoxin A_4, and resolvin D2, which are other lipid compounds derived from arachidonic acid.

TT: If we get to the more recent past, you were Head of the William Harvey until 2002?

RF: I was doing a lot in the lab, but I also had lots of other things which I did born largely out of my dissatisfaction with the way that science, the culture of science, at universities was heading. I became very seriously interested in learned societies because they were a place where you could go and talk about research, without bargaining about space and promotions and that sort of thing. So I became very committed to the BPS and I was on their main Committee for a while, then I became Meetings Secretary.

TT: Could you say a little more about the BPS in particular, when did you become a Member?

RF: It was in 1975 or something I think. I was actually my earliest experiences were with the Phys Soc [The Physiological Society], because of my connection with Sheffield, which I enjoyed a lot.

TT: So you did your first communication?

RF: I did. It was The Physiological Society where I got a couple of important lessons about science. One of them was you can argue all day long about data in someone's poster, but still sit down together and have dinner in the evening in a civilized way. The other experience I had which left a deep impression on me was that I'd written a paper on choline transport in the intestine and I'd sent it

off to *J Physiol* [*The Journal of Physiology*] and, this is very early on, the 1970s. The Departmental PA came in one day and said, 'Rod, there's a phone call from Professor Feldberg.' He was somebody I knew because he was also working on prostaglandins and fever. He said he wanted me to go and see him at Mill Hill [National Institute for Medical Research]. I thought, 'Oh God.' But I put my best suit on, took the train to London, got to Feldberg's lab. 'Come in,' he said, 'Sit down beside me.' And he said, 'Now then, I've got this paper of yours here. Now you start off saying this, I think what you really mean here is that.' And he corrected it. 'Is that right?' And he went through the paper line by line and he said, 'Are you happy with those changes?' I said, 'Yes.' He said, 'Okay, I'm accepting it for *J Physiol*.' He was a real gentleman. When I went back to work with John we all joined the BPS.

TT: And did you regularly go to BPS meetings?

RF: Yes, I used to go all the time. We used to go to pretty much every meeting there was. Again the ethos was different in those days; we were encouraged to do that. It was part of our training and it used to be a matter of pride to get an abstract in at every single meeting if we possibly could. And it's surprising how often we managed it. There were four meetings a year and in fact in those days of course, four meetings of the BPS, plus IUPHAR [International Union of Pharmacology] every three or four years or whatever it was, that was pretty much all the meetings you went to. You just can't do that these days. And even the Phys Soc's gone down from, you used to have six or seven meetings a year, didn't you?

TT: Yes, you're describing my background as well. It was just a wonderful education; you went to so many things. Now you go to these huge meetings with so many parallel sessions.

RF: I hate them!

TT: Can we continue your account of the BPS?

RF: I can't remember when I first went on the Committee because I was on the Committee a few times actually, it might have been when I was at Wellcome. When I got to Bath and got a bit dissatisfied with the way things were going from the point of scientific culture, I realised learned societies were the only places anyone could go really and get that support that you need. The BPS was very different in those days – older Members used to look out for younger Members' careers, for example, I remember Alan Cuthbert ringing me up and

saying, 'Rod, there's a good job coming up in so and so. I think you ought to apply for it.' It just doesn't happen these days, you've lost that relationship between the senior Members of the Society and the younger people coming up the system. It's partly because the number of meetings has been reduced. It was more of a community.

TT: When you were at Bath you decided to get more involved?

RF: I took a conscious decision and I went onto the main Committee certainly there, and was involved in organising a meeting there at Bath, which was very successful. When I got to the Harvey Institute, after a year or two of settling down, I said I'd be interested again, and I was eventually voted in as Chair of the main Committee, and subsequently as Meeting Secretary. In those days you became Meeting Secretary for three years and then, automatically, became what we used to call "General Secretary", which we now call "President". So it was a big commitment. You had six years of work for the BPS, which I enjoyed. It was a lot of work, but I really enjoyed it and I met a lot of great scientists and other people. I got to see almost everyone in the country who worked as a pharmacologist, got to see their labs, what they worked on, it was quite an eye opener actually. So when I retired from that, I still kept some low level interactions with them and I'm now Honorary Archivist.

TT: Talking about learned societies, you have been rather heavily involved in some of the more unusual activities of the Royal Society (RS)?

RF: I suppose like most undergraduates, I was a voracious reader and during my first year I came across a series of books by Steven Rose called *The Chemistry of Life*, which was fantastic, just the right level for a first year undergraduate. And I remember going back to the bookshop looking for other books by him, and I found a book on chemical and biological warfare and I bought it. It influenced me a lot, it's a bit odd in a way because it's like saying: 'Would you prefer to be blown to pieces by high explosive or poisoned with Sarin or something?' Ideally you wouldn't need any weapons at all, but as it happens there are Conventions in place to ban chemical and biological weapons, and they are ground-breaking Conventions in the sense that they ban entire classes of weapons. I became interested in that, but I didn't do very much about it until I was elected to the RS in 2004, and by that time I'd spent a lot of time with the BPS, and so when I got to the RS, they immediately made me Chair of what used to be called, the Scientific Aspects of International Security Committee. This was a Committee that met about two or three times a year, which surveyed the international

security scene, reviewed developments in, for example, nuclear physics that might impact the construction of new weapons, new advances which may facilitate biological weapons, and so on. It was very interesting actually.

TT: And it was purely the RS?

RF: It was run by the RS but had a number of illustrious non-RS folk on it as well. I learnt a lot and I got also to go around and visit nuclear facilities, and learned how they detected nuclear tests using seismographs. I was Chair for three or four years, and then I handed it over to somebody else. But no sooner as I'd done that than the RS asked me to chair one of their panels for their "Brainwaves" project. This was a series of four projects designed to explore the impact of neuroscience on society generally, and various specific aspects. The fourth one was on the use of neuroscience in warfare and conflict and security.

That was an interesting panel to be on and chair. There was this whole process of gathering evidence from various experts and welding them into a report, which took six to nine months. The press were very interested in it because it raised many intriguing possibilities such as controlling drones using brainwaves, smart drugs to promote pilot performance, and things like that. So it was full of all the things that make good scientific headlines as well as being a very interesting study.

From that, I became more involved with, first of all, the Chemical Weapons Convention (CWC). One of the problems at the moment is, it's difficult to say what's a chemical, and what's a biological, it's called the 'convergence problem'. There's sometimes a bit of a grey area between the Biological and Chemical Weapons Conventions on what's covered and what isn't. I was involved with providing advice to the CWC about how to manage this type of phenomenon, so there were no loopholes that could be exploited. Simultaneously, and I'm still doing it, I did quite a lot of work for the Biological Weapons Convention, chairing meetings which discussed advances in technology which might have an impact on the production of biological weapons.

I've done three conferences on that topic, usually in conjunction with the American National Academy of Sciences, and these have been very good. I've learnt a lot and I'm doing one in two weeks' time in Geneva, because one of the problems with the Biological Weapons Convention is that it needs new ways of feeding scientific advice to the Convention. It has review conferences every three years or something, but three years in biology is a very long time.

TT: So that's when they pick something up?

RF: The CWC has different arrangements and the Biological Weapons Convention doesn't have anything comparable. So the purpose of this upcoming meeting really is to come up with recommendations for the best way of providing scientific advice, and in a form that diplomats need. What's the best format? What's the best frequency? It's interesting, and you meet a lot of people who are not mainstream scientists but also social scientists and so on, who have an interest for other reasons, but have been placed by their government into this frame so they can take back ideas. When I started doing it I was deeply sceptical about the whole process. You can talk forever about these things: does it actually have an effect on the people who frame the Convention? But I've come to the idea that it probably does.

TT: One of the other interests you've shown throughout your career, and that's history. Could you say something about where that came from? Did it seem something natural when you were reading scientific papers or was it an older interest? Or did you suddenly realise, actually, I'm interested in history?

RF: I was interested in history of science, I have to say that, getting back to what I said at the beginning, when I was at school my history teachers were so awful, it put me off for life. When I became interested in science, I became very interested in history of science and the history of ideas, and so I read a lot of books on the subject. Actually it's a big disappointment to me these days that you stand in front of a class of 100 medical students, as I used to do regularly, to find that no one's heard of Alexander Fleming, let alone John Vane, or perish the thought, Watson and Crick. The best response is 'Oh, it rings a bell.' That's comparatively recent history as well. So, it's a great shame because they're missing the matrix which supports their entire discipline.

TT: You've talked about relationships at the lab level, then the national level with the BPS, and just now international relationships and networks. One relationship that you've not mentioned is with clinicians. Practitioners taking your drugs into the clinics. Have you had much direct involvement with clinicians?

RF: Yes, quite a lot actually, and when I was at Wellcome for example, there were a lot of clinicians there. I got to chat to them a lot, and got to see what their points of view were regarding drugs. They would do the "first-in-man" studies actually in-house. People used to volunteer, and they had a few beds in the Unit on the Beckenham site. I volunteered for a trial myself. I had a bit of interest

because they were collecting blood after giving me hydrocortisone, and so I could measure my own blood lipocortin levels. When I went to Bath I had even more to do with them, and one of my achievements there was to incorporate clinicians into the University structure by starting off the School of Postgraduate Medicine. I thought this was a good initiative, because there were lots of very good clinicians in town who would dearly love to interact with academics, but didn't have a framework for doing it. And likewise the pharmacologists at Bath and other people who would dearly like to have a close link with clinicians, but they couldn't do it either. When I went to the Harvey Institute, they had a Department of Clinical Pharmacology in Barts Hospital, which was run by Paul Turner, who, after a succession of heart attacks, retired on medical grounds. The Medical School wanted to close the Department down, and I went to see the Dean and said, 'You shouldn't do this, clinical pharmacologists are the last real generalists in medicine.' They were very amenable to my intercession and the Dean said, 'Alright you head it up!' So I took over this Department on a part-time basis and later I advised College to move the Clinical Pharmacologists over next to the William Harvey Institute, and they did, so the Clinical Pharmacologists and the Basic Pharmacologists could actually talk to one another. I think that's been pretty successful really.

TT: Lovely accounts of interactions with clinicians. Were you ever formally involved with drug trials of some of these compounds you were working on?

RF: Only as an advisor.

TT: You've talked quite a bit about animals and *in vitro* or *in vivo* experiments, but one thing we also talked about is the platelet. Of course there's this paper about platelets as an experimental animal. Were you one of the people who pushed platelets in terms of teaching?

RF: This is going back many years now, we certainly used to use it as a teaching aid, and my point was that it was an easily obtainable single cell preparation from humans, and that differentiated it from just about every other test system you could think of in those days. They are easy to assay, they responded to agonists, antagonists, you could study metabolic events, and so on. You could learn a lot by studying platelet aggregation, and I thought it was an ace teaching aid. At one time, I rather facetiously considered writing a book called *A Thousand Experiments with Platelets* for undergraduate students. Of course now it's a bit

different, because you can use U937 cells or some other immortal cell line, and it's a single cell population from humans but, in those days, platelets were pretty much the only one that was available.

TT: You have quite a few single author papers, which is quite unusual. Is this something that you have particularly wanted to do at particular times, write review articles, editorials: is that something you initiated?

RF: I don't know quite how it came about really, but I think the first one I wrote on my own was *Pharmacological Reviews* when I was a PhD-student, which I wrote on my own. John made some comments and I said, 'I'll put your name on it.' And he said, 'No, don't. You did this, so you take the credit.' I have written reviews with other people, it's often a nice experience, but it can be frustrating. It's easier to write on my own, although it's a lot more work.

TT: Do you see it as any kind of obligation or as something you're passing onto another generation, your views and experience?

RF: I suppose so, if I write it on my own I can be quite idiosyncratic about what I put in and what I leave out. If I write with somebody else, people reading it are never quite sure who said what, and very often it turns out to be a bit of a botch in terms of opinions. I have written a reasonable amount on my own, and of course one of my jobs now, which has been going on for years, is co-authoring Rang and Dale's textbook [*Rang & Dale's Pharmacology*], which comes around every four years. It's a major effort. Next year is another writing year.

TT: How did you get involved with that?

RF: Well, John and I and Salvador Moncada and Sérgio Ferreira had written chapters for Goodman & Gillman's textbook [*Goodman & Gilman's The Pharmacological Basis of Therapeutics*] before, and we'd done three or four years of that. We'd also written another couple of textbook chunks and I'd got into the frame of mind. Then one day, Humphrey Rang telephoned me and said, 'Can I take you out to lunch?' Over lunch he said 'We're looking for another author for *Rang & Dale's Pharmacology* and I think your writing's okay, I've read some of the stuff you've written. Would you be interested in joining?' I said 'Yes.'

TT: When did you first get involved?

RF: This is my fourth edition now. It's an enormously influential textbook, and it's very important to have these types of textbooks, knowing how textbooks influenced me when I was an undergraduate. I think they're very important as teaching aids and I already mentioned Steven Rose's books on the chemistry of life and how influential they were. And you think of the other physiological books we had, [of] Guyton, Samson Wright etc. They were enormously influential. So *Rang & Dale's Pharmacology*, it's a nice project to do, it's very demanding, but Humphrey and Maureen Dale set a tone for a book, which is a bit unique. It has jokes in it for one thing!

TT: It's much chattier, isn't it, than others?

RF: It's much chattier, deliberately so, to engage students. And also, although it's notionally a pharmacology book, it also deals with basic physiology and biochemistry, and lots of students say, 'I go to it because it's got everything in it. If I want to know about the heart there'll be a bit about heart biochemistry, bit about heart structure and so on.' It's a lot of work, but on the other hand it's very rewarding. I might add, parenthetically, that one of the absurdities of the Research Assessment Exercise is that people who write books never get credit for them. It takes a year of writing to do that, but if I can't put it on my return, people will think, 'Flower hasn't done anything this year.' And so it's just not right, it's just not fair. It's not fair on authors.

TT: I entirely agree with you Rod. And on that note of accord, may I thank you so much for contributing to this project?

Figure 6: Professor Richard Green

Professor Richard Green PhD DSc (b. 1944) completed his PhD (1969) with Gerald Curzon and following two years at the 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 (BAP). He is a President Emeritus of the BPS and a former President of the Serotonin Club.

6 Green, Richard*

Tilli Tansey: Richard, could we start with a little bit about your background, where you come from, your education and how you became interested in pharmacology?

Richard Green: My father was an entomologist, with the Department of Scientific and Industrial Research in Slough, interested in pest control. I don't think I ever thought of doing anything other than a biological subject and at A level I was aiming, I guess, to think about biochemistry, which in those days 1962/63, was more biological chemistry than it is now. It tended to be more what we think of as pharmacology now, because it was often whole animal biochemical mechanisms. I blew my A level physics and so I worked for a year at the Aspro-Nicholas labs before going to university. Aspro was the premier branded aspirin and they were manufacturing everything from pharmaceuticals to household products. I worked in analysis of raw materials. Then I went to Chelsea College to do chemistry and physiology. I absolutely loved it.

TT: Who taught you?

RG: In physiology there was a wonderful guy called John Dimsdale, who went off to Hatfield Poly and became Head of Physiology. Biochemistry was taught by David Plummer, a good teacher. I don't know why I thought of carrying on doing a PhD, and saw this advert for work at the Institute of Neurology with Gerald Curzon. Gerald wanted me to work on how giving steroids, corticosteroids, would raise the levels of an enzyme called tryptophan pyrrolase in the liver – there had recently been an indication that people with depression had raised corticosteroids. Gerald's idea was, 'Tryptophan comes into the body it's made into 5-HT in the periphery and in the brain. If you increase the activity of this enzyme then more tryptophan would go down the pyrrolase pathway to be metabolised to niacin, so there'd be less available for 5-HT to be made in the brain.' That's what I started on, and it was hugely successful. We injected rats with steroids, and brain 5-HT decreased, so my second paper was in *Nature*,

* Edited passages from the interview conducted by Professor Tilli Tansey, 17 December 2015, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

a full paper, not a "Letter" [laughter]. Gerald generously put me as the first author on that. My PhD degree was Biochemistry, because at that stage in the University of London you couldn't actually have a PhD in Pharmacology unless your first degree was in Pharmacy.

TT: You were at the Institute of Neurology: where was that affiliated?

RG: They were part of the British Postgraduate Medical Federation. I was so lucky, because there wasn't a grant for that investigation. Gerald had a three-year MRC grant, and I was employed as a graduate technical assistant and the second and third year money came from the Mental Health Research Fund.

TT: That you got really hooked on doing research?

RG: Absolutely – giving drugs to an animal and changing brain biochemistry, most of my research obviously was on that. Then Roger Maickel in the States came out with a new method of measuring 5-HT, where you reacted 5-HT with o-phthalaldehyde to produce a hugely fluorescent derivative. Gerald noticed this paper and said, 'We ought to try this.' And the method worked. The method was so sensitive that we realised that we could measure in small regions of the brain. As a result, we published the method for measuring small regions of the brain for 5-HT and 5-HIAA [5-hydroxyindoleacetic acid, the main metabolite of 5-HT]. It was only a three-page method in the *BJP*, but until HPLC [high pressure liquid chromatography,] came along about 10 years afterwards, it was one of the most important methods. We got something like a thousand citations of that method.

TT: This was all in rat brain? How did you do the dissections? How did you get your discrete areas?

RG: Just by learning how to dissect. There was a method by a couple of the neuroscience greats, Les Iversen and Jacques Glowinski, on how to divide the brain into six regions. We're not talking discrete nuclei, but until that time people had tended to take the whole brain. Les said to me one day, 'My God, we take a whole brain, we mash it up, we measure something and think we can understand how the brain works.'

It was work with Gerald that influenced my future career. I thought I'd like to go to the States, because a lot of really good stuff was going on there in neuroscience in the late 1960s. I tried to get into Ted Sourkes' lab at McGill, who was doing some really interesting things, again on pyrrolase but the Canadian MRC would only give grants if you were a landed immigrant, and

I didn't want to do that. I wrote to a friend at the University of Nebraska in Omaha, who had a neuroscience friend called Mike Ebadi, who said, 'You can come and work with me.' Then I then had another letter saying, 'I've got a year's sabbatical to work with Eminio (Mimo) Costa at NIMH, you should come here, it's fantastic. I'll give your name to him.' I would never have dared apply to Costa – he was sort of near God. By the time I got to Costa's lab, Ebadi had gone back to Nebraska. Just before this, while I was wrapping up my PhD, I wanted to measure tryptophan hydroxylase, which had recently been identified and measured by David Grahame-Smith at St Mary's Hospital. I trotted off to St Mary's and we had a long chat and he said, 'I'm hoping to expand here. We must keep in touch because I hope I might have something for you.'

I went to the States. I'd been in NIMH for about a year and *Nature* reported that David Grahame-Smith had been appointed the first Director of the MRC Clinical Pharmacology Unit in Oxford and Professor of Clinical Pharmacology. I wrote and said, 'Well done, David. Will there be a job for me?' So I ended up in Oxford [laughs]. Things happened without plans. I've generally let my career go the way it follows; it seems to have done okay doing it that way.

TT: When you went to work with David, did you have any particular project? Because David had a much more clinical approach?

RG: David always was very keen on what these days we'd call translational. His big interest was biomarkers of drug action, and it didn't matter whether it was preclinical or clinical. If you get preclinical markers and they go onto clinical, then do it. The lab was always 50-50, that's for sure.

David had recently been looking at measuring the function of 5-HT by giving tryptophan, a 5-HT precursor, and a MAO inhibitor that builds up the concentration of 5-HT in the brain, and the animals show very distinct hyperactivity syndrome. It's generally called the 'serotonin syndrome' and you can see it in humans as well. He said, 'I think it's a way into showing how drugs can alter 5-HT function in the brain.' So I started working on that. I did lots of other things as well but that was always the background, and we looked at all sorts of drugs like tricyclics, like lithium and then onto ECT [electroconvulsive therapy] as well. I got involved in lots of other things because of other really good people I've got involved with, but that's what I started working on.

TT: And this was all neurological?

RG: David was an inspirational person. Sometimes, I heard on the wards, some of the young clinicians say 'God, this guy's a Professor but that is a silly idea,' because he would throw out a lot of ideas, and perhaps, of 10 ideas, five or six might be silly. And it's easy for anyone to think, 'Hmm.' But two or three would be viable, and one or two might be really great. I used to have wonderful times sitting with him in his office where he would start off with, 'Well, let's imagine, and I don't know exactly what I mean by this but…' I suppose it's called 'brain storming' now. I loved working with him for that, because he'd have some fantastic ideas. He was also terrific for me in that after a while he said, 'For goodness sake, you don't need to have my name on this,' even though we'd often discuss things. He let me establish my own place in science and that's just generous.

Even more generous is that he had some terrific young clinicians, usually psychiatrists, who wanted to come in and do some preclinical work, whilst continuing clinical work, and he essentially handed them over to me and my group. So I got David Nutt who was just like an over-excited Labrador. He wanted to do everything. Nothing phased David Nutt, still doesn't. There were a lot of people I interacted with, and I never found a big barrier between preclinical and clinical in psychiatry. I didn't find that same openness, interaction and bonhomie with neurologists. Psychiatrists are much less: 'Well, you may say that, but I know I'm right.' I found neurologists, with the exception of one or two people like David Marsden, who was a delight, not to be anywhere near as pleasant to deal with as psychiatrists.

TT: Interesting comment. When you arrived in Oxford to work with David Grahame-Smith, you went as a scientist, a member of MRC scientific staff, and you set up your own lab?

RG: That really wasn't the way it worked. David had a full clinical programme. His other peak interest was digoxin and very early on Jeff Aronson came into the lab to work on that. David was always an on-take physician, because he said you couldn't do proper clinical pharmacology without being a hands on physician. What I mean by having my own group: I had was a couple of technicians, and often these psychiatrists, generally registrars to senior registrars, in training. All the day to day running was with me and we would meet with David every so often and review things. Because of the structure of the MRC, there wasn't separate money as such. Money was still fairly available in those days, we just worked.

TT: So we're talking about when?

RG: 1973 to about 1985. David had a sabbatical and made me Assistant Director, which didn't mean anything in important terms other than it taught you a little bit more about trying to manage. Gerald Curzon taught me how to do research, Erminio Costa in his true Italian way taught me one had to be passionate about science. David taught me that science has to be managed, people can't go off in every direction; you've got to have management.

TT: So how big was the unit when you joined it?

RG: The unit was around 27 to 28 people altogether, but you had people coming and going. It wasn't that big, but it was always hugely exciting.

TT: What would you think that a main achievement of that period would be?

RG: Two main things: one was we started looking in the mid-1970s at ECT. We'd been looking at various antidepressant drugs and how they might work, and I managed to get hold of an old clinical ECT machine, very crude. We gave daily electroconvulsive shots to rats and found it totally changed their 5-HT responses in the direction you expected antidepressant drugs to do. We kept working on that and did all sorts of things on the mechanism – ECT was going out of favour by then, and the work proved it didn't 'just shake the brain up'. The thing that was important about it was that it showed – which excited psychiatrists – that it seemed to have a defined pharmacological-like mode of action. There were things it changed, there were things it didn't change, and those changes were consistent with some antidepressant drugs. We were also working on the 5-HT_{1A} agonist, 8-hydroxy-DPAT [8-OH-DPAT] which produced behavioural changes. We thought we would look at electroconvulsive shock on 8-OH-DPAT effects, by then we'd shown that even if you only gave five shocks over ten it still had the same effect, and we'd shown that it wasn't the electricity that was important. We went on with the 5-HT_{1A} behavioural response and showed that if we gave ECT over ten days, the response, which was exactly the same that we saw with antidepressant drugs, lasted for about a month. It was truly amazing, and we got that published in *Nature*.

TT: These were in patients?

RG: No, these were all in rats. But it then gave the clinicians a chance to say, 'This does have a clearly defined mechanism of action.' Whether it actually has any relationship with how the drug actually works or the treatment works, I don't know, but it was consistent at any rate. That was an exciting thing to find.

TT: You said there were two big achievements?

RG: Well, the ECT work, which I thought was really important, and in general all the work on 5-HT, especially trying to measure 5-HT function leading onto then the 5-HT_{1A} receptor and using that as a marker, are the two things that I'm most pleased with.

TT: Why did you decide to leave the MRC?

RG: Chance. David looked after his staff very well and in about 1984 an advert appeared for the Professor of Pharmacology at University of Bath. David pointed this out to me and he said, 'You're just getting to 40 and this unit has only got a defined life until 1992,' which was when he was 60, 'You should think about flying the nest and that would be an interesting job.' I went down to Bath, and was shortlisted and interviewed, and Rod Flower got it! Which we have laughed about subsequently. I came back and then I got a letter totally out of the blue from Hans Selander, the Research Director of Astra Södertälje. Astra then had three centres: Södertälje, which is just south of Stockholm; what was called 'Astra Hässle', which was at Gothenburg, and Astra Draco, which was down at Lund. They did CNS in Södertälje, GI/hypertension at Gothenburg, and respiratory at Lund. Hans Selander was Head of Research, Head of CNS, a delightful man. Pretty well all the people I met at Astra were pleasant people, and they were really good scientists as well.

It was before you had bean counters in very senior positions, you had scientists. Anyway, this letter came, 'We're thinking of setting up a new unit in England to examine possible approaches to dementia/Alzheimer's, and if you might be interested, come and have a talk.' When I think of all the interviews and psychometric testing these days, we just went out for a meal together. We had a long chat and I said, 'It does sound quite interesting. Who are you thinking of heading this unit? He said, 'That's why I'm talking to you.' And I went, 'Oh! I don't know anything very much about Alzheimer's' and classic response, he said, 'Here's your chance to learn.'

They settled on the old Royal Free School of Medicine labs in Wakefield Street, just north of, the Institute of Neurology. Astra were going to rent floors in this old building and part of the Institute of Neurology, where I'd done my PhD, were going to move in also. Gerald Curzon was on the second floor, and we were on the third and fourth. David Bowen, the big dementia expert, was in the building as well, and the idea was very much something that the Swedes had

done for years, which was interact closely between universities and industry. There were some really good neuroscientists in that company at that stage, but they'd felt that they were rather enclosed in Sweden and wanted to get outside.

I remember going back home and thinking, 'Can I do it? I'm not sure but no one is ever going to offer me the chance to set up something again, choosing my own staff from scratch.' Normally you go into a department with probably someone who tried for the same job, a couple more who might resent you or are set in their ways. The chance was to set up something from new, just as David had done in Oxford, and so I thought,' I'm going to go for this.'

TT: Was there any sense that you were letting the side down by going to industry?

RG: No, it was just at the time 1985, Les Iversen has just gone off to Merck, Humphrey Rang was setting up the Sandoz unit, John Hughes was setting up the Parke-Davis unit. It was about the time whole attitudes changed. The MRC was starting to say that if you want to interact with industry you can, and there was much more openness. I was just on the wave when an attitude of 'them and us' was dying.

TT: This was a tremendous opportunity but an awful challenge as well – to set up labs and hire staff in a field that you hadn't worked in before.

RG: I hadn't worked in dementia nor did I really understand how industry worked. This was just before Astra's world changed totally with what became omeprazole, Losec, which totally altered their funding base. And CNS had suffered two very severe delays and setbacks. They had with zimelidine, the first SSRI, and this went onto the market and the sales went through the roof in 18 months, and in about 1984 it was producing a rare but problematic peripheral adverse effect, and the drug was withdrawn. Then they had remoxipride, which was a D_2 [dopamine D_2 receptor] selective drug, very successful for about 18 months, and then again they got some rare but severe adverse effects. CNS had gone through two very ground-breaking drugs and they then saw follow up drugs from other companies then reaching new heights. The sales of fluoxetine, the next SSRI, went through the roof. So money was tight for our first couple of years setting up the unit, then it eased up a bit as the new drugs came along.

TT: What was your remit?

RG: We started with the idea of running two or three projects. The first thing I did was get in as Head of Pharmacology, Alan Cross, and a very good chemist called Robin Boar, who had been with Janssen in Belgium. We set up with the

idea of doing work on a cholinesterase drug, fairly straight forward, but it was an obvious way to go. I'd been working on $GABA_B$ [gamma aminobutyric acid B] receptor when I was in Oxford, and I thought that looked an interesting way to produce a $GABA_B$ antagonist. Astra had an old drug called 'clomethiazole', which was a sedative and hypnotic. It's also used for alcohol withdrawal, and it works a bit like a benzodiazepine, it works at the GABA receptor.

One of the problems with dementia patients is when they're active and aggressive, so settling them down and getting them to sleep is important. Benzodiazepines, at that stage, were felt to produce memory impairment. And I said, 'There's no reports of that on clomethiazole, let's try and produce a new clomethiazole-like drug with a defined mechanism which will provide symptomatic treatment for dementia.' We did produce one drug on the cholinergic side, a very good cholinesterase inhibitor. Unfortunately, Astra had licensed one a little earlier, and in the end our drug was dropped at the preclinical stage, but it looked very good. I think we could have had something there, but companies only have so much money to push things forward.

The $GABA_B$ we dropped after a while, because it wasn't going anywhere. Clomethiazole, we were looking into the mechanism of action and we found that it altered calcium flux into cells, and we set up a stroke model and clomethiazole was protective in it. We thought, 'Let's see if we can produce new clomethiazole derivatives that also are neuro-protective.' So we dropped dementia basically and got on to being a stroke unit more than anything else.

TT: What kind of animal models did you use?

RG: At that stage we were predominantly using the rat transient ischemia model. I would never use a transient model now; you've got to use permanent ischaemia models. In fact, I would probably question all the animal models. I was a huge defender of animal models of stroke but when I think back on it now, people have got it wrong. It was Eng Lo from Harvard who said a few years ago, and I think it sums it up, 'What we have forgotten is that stroke is primarily a vascular effect with a neurological outcome.' I don't think we really understood that the vasculature and glia talked to the neurons and back again. We've learnt and learnt but at that time looking at a neuroprotective drug was where it was at and I don't have to defend it too strongly in that it just seemed very logical. You give something straight after the stroke, or as soon as you can within six hours, whatever, that will protect the neurons from dying.

TT: When you were doing this work, Richard, did you get involved in aspects like regulatory affairs and clinical trials or was that passed to somebody else?

RG: Not at that stage, no. We developed up clomethiazole and that was moving forward and went into clinical trial in about 1994/95, and then in 1995 we suddenly heard that Astra had bought Fisons at Loughborough, which meant that they had bought Fisons CNS Research Unit in Rochester, in upper New York state, who were also interested in stroke, because they had glutamate antagonists because they were interested in epilepsy. Whilst you can do CNS research at two sites, three is too much, and we immediately knew we were at risk. We were about 27-28 people strong, and covering everything from behaviour through to neurochemistry through to medicinal chemistry. Astra announced fairly quickly they were closing us and I moved up to Loughborough which provided an office, library, e-mail and everything, and then started flying once a month to Sweden to oversee the preclinical control of the project, because clomethiazole was then in clinical trial.

TT: You continued overseeing the same project?

RG: I did at that stage. I also got involved in a new area. Amphetamines produce damage in the brain and we wondered what chlomethiazole did to methamphetamine-induced damage. We tested it and it protected. But methamphetamine is a difficult thing to produce brain damage, and so we moved to thinking about MDMA [3,4-methylenedioxy-methamphetamine; ecstasy]; it was just at the time when MDMA was shown to produce damage to 5-HT neurons and clomethiazole protected against that. And I was then lucky enough to meet María Isabel (Maribel) Colado, who turned out to be the most fantastic scientist. She started working on MDMA as well, and we carried on that collaboration between Astra, who let me continue to work on MDMA. The collaboration with Maribel carried on for years, even when I went up to Loughborough, even though I didn't have a lab there.

TT: You were going into this more managerial role in Loughborough, so where was the lab, how were you doing this collaborative work?

RG: I was again lucky, I think you're going to find my whole career was luck. Alan Cuthbert was a governor at De Montfort University (DMU). When I was Meetings Secretary and General Secretary of the BPS he was Chairman of the Board. He'd been the Editor-in-Chief when I was on the Editorial Board. Alan was always above me with whatever I did with the BPS, and he wrote to me and said 'bet you're missing the lab. I know they need people down at DMU to

boost their research a bit. Why don't you go and talk to the Vice Chancellor?' So I did and he offered me a PhD-student, and half of another one who worked on a different area. I then had a very successful PhD-student at DMU. I mentioned this to Astra and they gave me time to become an Adjunct Professor at DMU and continue with that work.

My main job at Astra was 'overseeing' any new preclinical work that needed to be done, and getting it done externally because we didn't have anything done internally by then, right through to things like when the FDA wanted evidence. So I was involved in going and seeing people in different universities saying, 'Will you do work on our drug?'

TT: Almost commissioning? It's quite a shift from you being in the lab?

RG: Yes, it was but it was very exciting because I saw a whole new world that I didn't know anything of, and I was part of – one might say it was then the trendy word 'global' – I was part of the global project team. That meant I was sitting in with everyone from regulatory to marketing, to patents, to pharmaceutics, everything. There were about 10 or 12 of us sitting around the table updating every month where we were to try to bring everything through. And it was a very exciting time because we got our particular neuro-protective drug, called NXY-059 into clinical trial, it was incredibly safe, it was said to work by being a free radical trapping agent. It went on to Phase 3 which was about 1,700 patients, and was positive. But we needed another even bigger trial. I always joke with my students subsequently that we should have been worried by the fact that the result of that trial resulted in the *Daily Express* calling it 'a new wonder drug' [laughs]. If anything is going to be the kiss of death, it's going to be the *Daily Express* telling you you've got a wonder drug. And it went into the second Phase 3 trial, and it failed totally. No indication of effect. And the company stopped it. I was then setting up projects to look at head trauma and things like that, where it worked, and the company, a day after the results said, 'That's it, the end.'

It's almost like a death in the family. If you've worked on something for the best part of ten years, you wake up in the middle of the night thinking, 'Why do I feel so depressed? Oh yes, I remember.' It was awful. What motivated people I knew, the scientists and clinicians in the company, was we felt we could produce benefit to patients and we really felt we got something. That was really very hard.

I had moved on from DMU to Nottingham University, where I was working with Charles Marsden and Kevin Fone particularly. We were still doing some work on MDMA, which I was still doing, because the DMU got much less enthusiastic about any lab work. They'd got limited funds and it's cheaper to teach nurses and social students than it is to do animal studies. Charles had said, 'Come here,' so I went there to Nottingham. I then – this is the end of the stroke story really – got involved with Philip Bath, who is Professor of Stroke Medicine there.

He'd been on the Data Monitoring Committee for Astra, the independent committee that oversees the projects, because he's not only a very good stroke physician, but he's an expert on statistics and all that sort of stuff. And he said, 'I'd like to take all the preclinical data and do a meta-analysis to see if it really works.' This happened just as I was about to retire from AstraZeneca and to the company's total credit they let us do the meta-analysis. It could be of course have meant that we were going to show that the preclinical data didn't look very good at all, in which case they were going to have people coming down on them saying, 'Why did you go and put this drug into all these patients? Your preclinical data isn't very good.' But they said, 'Yes, go ahead.' So he and I and his PhD-student, fed all the data from every single animal into the analysis. There were a few trials with mice, some marmosets, and mostly rats. And all of this was fed in. I did say to Philip, not understanding necessarily meta-analysis, 'Why are we putting the mice in? They gave the drug intraperitoneally and I know it's not absorbed that way.' He said, 'You can't make decisions like that, it will come out in the wash.' And the drug worked in the animal studies. No doubt about that.

There are different ways of going forwards nowadays, giving statins, giving thrombolytics, mechanical clot extraction, but apart from a couple of Japanese companies, and I don't know where they are now, no one's working on neuroprotection in stroke anymore.

TT: When you retired from Astra, you had the Honorary Chair at Nottingham?

RG: I'm still at Nottingham. I do a little bit of teaching there, but not very much. I had a PhD-student who worked with Kevin Fone and Maddy King and we've moved on from ecstasy, we looked at the drug mephedrone to see whether it was the same sort of drug. And it's not, it's different. It's related in its mood altering effects, but it doesn't have the same profile For 20 years,

MDMA was the recreational drug of choice. Mephedrone came along partly because it became much more difficult to get ecstasy for a while, so people moved onto other things. But there is so much coming onto the market – every week something new, quite horrendous actually, because kids are taking things where we have actually no idea about the pharmacology at all. With ecstasy we could say, 'Let's learn more about this because it's continuing to be used.' Now if we went to any grant-giving body and said, 'We want to do some more work on mephedrone,' they'd say, 'Why bother? There's 30 new cathinone-like drugs come along and on the street in the last six months. Why study just one in-depth?' And I couldn't argue with that.

TT: Who does fund your research?

RG: The study done at Nottingham was actually funded by the university. It was a grant for a PhD-student Kevin found, which was very nice of them. I think she's paid them back, we've had three or four very quick papers, we've written a big review on mephedrone and one on MDMA as well. I used to be fairly convinced, again the animal work, that ecstasy in high doses produces brain damage in humans. I am now totally unconvinced by that, mainly because when you actually look at the pharmacokinetics of MDMA in rats versus humans, it is totally different. In rats it's metabolised extremely rapidly, it produces very high temperature in rats, which they get over, and it does in humans as well. But it's fairly short-acting, and then of course it's metabolised through to these other derivatives that probably produce the free radicals and the damage. Its half-life is about 40 minutes in rats. In humans it's about eight hours. So you get the temperature effect, and that's what can kill people, because it goes up and it stays up for a long time; it's metabolised very slowly, but it is metabolised. I think the free radical scavenging, trapping activity, that we have naturally in the brain can mop these up normally.

I think ecstasy can produce damage but that's because few people take just MDMA. They take several other recreational drugs and we found, and others have found, and it's true of mephedrone and it's true of ecstasy, that caffeine, which many people are taking, particularly if they're partying with Red Bull and things like that, caffeine alters the MDMA responses. I think if you could take pure ecstasy and nothing else as a human, you would be relatively safe. But, immediately, you start mixing with other things, then there may be problems.

TT: One of the things I noticed, Richard, looking through your CV is how enormously productive you've been. Some years you're publishing 10, 11 papers and a book chapter. It's just staggering.

RG: Generally, we've had nice projects to work on. If things look bad there are plenty of other things, go and look at something else then. There's a certain luck element in these things, certainly on one or two things, like the $GABA_B$ drug. We worked on that for a while but there came a point of saying, 'Why are we doing this? There have to be other things to do. Don't just keep hitting your head.' I've also worked with some really good people, like Phil Cowen, Dave Nutt, Guy Goodwin, David Grahame-Smith. Maribel Colado and then her student Esther O'Shea in the MDMA area was really amazing. Maribel has what I think of as the scientific equivalent of green fingers. She didn't work enormously long hours, she wasn't one of these people who was there until ten o'clock at night, but almost anything she did seemed to work.

TT: One thing you've mentioned and started talking about was scientific societies.

RG: Well, my two are Pharm Soc, BPS, more than anything else, and then BAP. I helped organize the 50th anniversary meeting in 1983 of the BPS in Oxford. It was a committee of four of us, Bill Paton, John Walker from Pharmacology and David Grahame-Smith and myself, from Clinical Pharmacology. Well, you can work out: the two professors oversaw, John Walker was extremely senior and organized the dinners, and I did everything else. That's not a complaint, it's just a statement of what happened. Tony Birmingham was the Meeting Secretary at the time, so I interacted with him a lot. Democracy came reasonably late to all the major societies. Committees, Councils, tended to suggest names and it was pretty well the expectation that no one else would ever stand against them. Tony I worked well with, the meeting was hugely successful. Tony obviously said, 'Richard Green did a good job there. I think he could be the next Meeting Secretary.' So my name came forward, I asked David Grahame-Smith 'Can I do this? It's going to take time.' And he said 'Well, it would be great, wouldn't it? We'll find space for the secretary somewhere, you know.' We were pretty crowded. And then when Astra came along, I said, 'I've been offered this job at the BPS and accepted it and I would quite like to do it.' And they said, 'It'll look very good for our company, that you're doing it. The Astra name will go on all the note paper and everything as your address. Well, do it.' When I think about

it, because the Meetings Secretary in those days, did most things with the help of the local host organising their team. All the abstracts came to you, you got them in the right format. Whether I should have really done it, I don't know.

Luckily the first year or so, when I was really finding my feet, was when the lab was getting going and perhaps there was a little less science than I might have had. And I then went on to be General Secretary. As Meetings Secretary, I enjoyed it the most because you met everybody. Everyone comes up to you 'about my abstract,' so you got to know a huge number of members. But it was enormous fun, and again, the way these things link up. I did three years as Meetings Secretary, three years as General Secretary. I've mocked Tom Blackburn subsequently, because I think it was Tom who converted the name because a lot of international societies didn't understand the term 'General Secretary', and converted it to 'President'. It was an enormous amount of work, but you got to know so many people, and people I might not have met, like John Vane. John was marvellous because he was just setting up the William Harvey Institute at the time, and we were so busy, we used to run four meetings a year, and everyone used to present because it used to take so long to get stuff into print in those days. If you wanted to establish primacy, it was by presenting at BPS, which published your abstract. We were getting up to 400 abstracts for meetings so I said we would only allow one abstract per author. John Vane phoned me, I'd never even talked to him at that stage: 'Ah, it's John here. I've just sent some abstracts in. I hope you'll be kind to me because we're just setting up the Institute. We do need to make a bit of a splash.' 'Yes, Sir John, I'll do my best' thinking to myself, 'Well, I'm bound to do something here; he's our most senior member and Nobel Laureate.' Anyway we put them all in and then a few days later, 'Ah, John here again. A few more if you could squeeze them in!' I thought, 'I am being manipulated here.' But it was not, you know, 'I am John Vane and I want these in.'

It was a fantastic time and a couple of years ago they were looking for a Trustee and I put my name forward, there was supposed to be going to be an election, I'd heard, and then the other person withdrew. I've no idea who it was, but you know when I say that I've had a lucky career; moved into being a Councillor, a Trustee, without even an election. I've got another year of that.

TT: When were you elected to the Pharm Soc?

RG: When was I elected? 1973. It was just after I'd come back from the States, and certainly in those days, once you'd done your post-doc and you'd got a few papers it was a career move. You'd got your degree, you joined the Pharm Soc. As I remember, you had to have done something like two abstracts to the Society, one of which you should have presented. And three papers. Nowadays they take anyone with some pharmacological interest. We've got undergraduate members, graduate members, post-docs, so you can move through. When I was General Secretary, we wanted to make Harry Holt a Member. For years Harry had been, in charge of our journal while he was on the staff of MacMillan Press. We just thought it would be nice to let him join. And there were one or two people saying, 'I've worked my way through the Society, why are we letting this non-scientist join?' We pushed it through without any trouble. But I do remember a couple on the Committee being a little less generous about it.

TT: Can you remember your first communication to the Pharm Soc?

RG: I suppose I can, to Pharm Soc. The very first communication I gave actually was down at the Institute of Psychiatry to the Biochemical Society, because Gerald was a Member of the Biochem Soc. I presented our work and someone asked me about cerebrospinal fluid changes in depression and I said, 'We haven't looked at that. But Ashcroft and Eccleston at the Edinburgh Brain Metabolism Unit have looked at serotonin.' And he said, 'Thank you very much.' I came off and Gerald said, 'That was good. And do you know who asked that question?' I said, 'No idea.' He said, 'That was George Ashcroft,' [laughter]. So I went, 'Oh!' He said, 'Everyone is delighted when you quote their own work back at them.' So that was my first experience.

TT: What about other societies?

RG: Well, the BAP. As you know I've just written a history of it. The original aims did talk about both clinical and pre-clinical, but over 60% of the founders and people involved were clinical. They've worked very hard ever since to make sure it's not dominated by one side or the other, and just by the best efforts, whatever, it's remained roughly 60 to 40 clinical ever since. But it's very translational and it's done well to avoid becoming cliquey, and I do think the first President, Max Hamilton, worked hard to make it inclusive. They'd chosen someone very high up – in the early 1960s and onto the 1970s everyone knew the Hamilton rating scale for depression. Max wasn't part of the original founding group, but they needed a big name, and he had no particular axe to grind.

Then there was a fuss to make it more open and I joined immediately after that. I was on Council in the early 1980s. I was an Editor when the journal started, and that had incredibly rocky start. When Dave Nutt came back from the States, he took over the editorship and I left the journal soon after because by then I was involved, more in stroke. But I remained a member and once the MDMA work started getting going, I was much more actively in psychopharmacology and I got more involved, and then, I have to say, I got a complete shock. I got a letter in 2010 from Susan Chandler, the Executive Officer of the BAP, and it said, 'Dear Richard, hope you're well. Attached is a letter for your attention.' And I thought, 'Oh God. I must have forgotten to pay my membership fees.' I opened it up and it said, 'We're delighted to offer you the Lifetime Achievement Award.' It really strikes home in so many ways. I was staying in a hotel in Dundee, just about to go to see my then seven-day-old granddaughter. Everything happened in the last week of April or whenever [laughs]. It was quite amazing, actually.

But again, that takes one back to David Grahame-Smith. It wasn't that big a unit he ran. Out of that, David and I got second prize in the Anna-Monika Prize for depression. He got another, the Paul-Martini Prize with Jeff Aronson; an international award for their digoxin work. Jeff and I have both been Presidents of the BPS. David Nutt and Guy Goodwin have been Presidents of BAP. Phil Cowen and I have both got the Lifetime Achievement Award of the BAP. For a not very big unit, it had an incredible influence on British pharmacology and psychopharmacology. It's one of the great sadnesses to me that when one or two good things have happened, I've thought I would like to have told David that. He was such a big influence and he just rejoiced when things happened well for people, and a lovely man actually.

TT: What about international societies. Have you been very involved?

RG: I gave a talk at the 1972 IUPHAR. That was an outstanding thing in its way because I gave a talk with Costa's name on as well. Gerald Curzon asked me a question and to Costa, you were his family – you really were – so Costa immediately jumped up, and started shouting at Curzon, defending me. Immediately after Costa came up to me and said, 'I had no idea that was Curzon. I would never have done it.' And I thought, 'You shouldn't have done it to anyone, but we'll let that one pass.' But Gerald laughed, he said, because Costa came up to apologise and said, 'Ah, you are the father of Green.' Years later some of my more inhibited Swedish colleagues would wonder, at some

international meeting when some Italian would come up, hug me and kiss me on both cheeks, 'Who is that kissing Richard over there?' You were family, and it was fantastic.

So that certainly is notable. I became an IUPHAR rep for the BPS when it was in Amsterdam. All the representatives went to a dinner, and it was when England was playing someone in the World Cup, which was on at the same time. And the waiter kept coming up, whispering to Alasdair Breckenridge who was next to me, who was the other BPS representative, what the score was. The dinner went on interminably, I suddenly realised that several people, including Alasdair, had disappeared. There was a café downstairs and everyone was watching England lose the penalty shootout. And I was also EPHAR [Federation of European Pharmacological Societies] representative for the BPS. And I spoke at the Barbican Centre, where the World Pharmacology Congress was in 1984. That was quite fun, you know, such a huge audience then.

TT: Yes, I remember talking at the BNA there, the British Neuroscience Association.

RG: I've never really been involved with the BNA. I've stayed just really with the two main pharmacology societies. There was a small group in the 1960s when I was doing my PhD, which was I think the forerunner of BNA. We used to meet occasionally at a pub called the 'White Horse', which was in an alley off Tottenham Court Road. And you used to get people like Steven Rose attending.

TT: Steven has just written a history of the BRA, the "Brain Research Association" as it was originally called, which starts with that pub.

RG: It was quite an active group that there was a lecture each time and a few beers. And I think the whole thing grew up from that. I'm not sure this wasn't even before the BRA. I think the BRA might have grown out from it.

TT: It's been great listening to you, Richard. Thank you very much.

Figure 7: Professor Patrick Humphrey

Professor Patrick Humphrey OBE DSc PhD HonFBPhS (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 there, 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 RS'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 South San Francisco 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.

7 Humphrey, Patrick*

Tilli Tansey: Thanks very much for coming, Pat. Would you like to say something about your background, which part of the country you come from and your schooling?

Patrick Humphrey: I was actually born in South Africa. My mother's an Afrikaner and my dad was in the Royal Air Force (RAF), and that's where he was during the war. I left South Africa when I was 10-months-old, so I'll never forgive my mother for not teaching me Afrikaans. Until I was 10, I think, I supported the South African cricket team. Now being 70-years-old, I've long supported the English cricket team. I was very proud of being my Afrikaner background. None of our family and friends supported apartheid and many left to go to Australia many decades ago. Many that emigrated were doctors and so, I think from quite an early age, I quite liked the idea of being a doctor. I went to grammar schools and my first one was the Beckett School in Nottingham, I went to 13 schools because my father was in the RAF, we moved every year or so [laughs].

TT: It wasn't as if you were expelled for bad behaviour?

PH: Well, maybe a bit of that. At 11 I went to the Becket School which, in those days, was a terrific school. We were taught by Augustinian Brothers and I really was very excited by Latin, I loved maths, and I became a bit of a chess guru, so I was probably a pretty good scholar. I always remember, in the second year, I started on ancient Greek as I was good at Latin, I was really excited about that and then two weeks later Dad said, 'We're moving.'

TT: That must have been so disruptive for you.

PH: Well, a lot of people say that, and it was to some extent. You kept changing schools and you ended up doing the same bit of the curriculum you'd done before, and not the new bit. So I had to learn a lot on my own, I guess, but as I joke to people, my geography was pretty good [laughter].

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* Edited passages from the interview conducted by Professor Tilli Tansey, 8 February 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

TT: It must have been quite difficult on the social front as well, always leaving, making and leaving friends?

PH: In some ways it was, and that was interesting too. Many schools sat you at the front as the new person and you could feel all these eyes boring into your back, and it took quite a while to get familiar with people. Lancashire was a place I loved and I went to school at one stage in Lytham St Anne's, and all the kids rushed to the front to say, 'Who are you? Where have you come from?' So I have a soft spot for Lancastrians. Then my second senior school was at Chippenham, so we lived in Wiltshire for a while and I really liked that school. I won the Wiltshire Chess Championship, under 15s, and my favourite subjects were maths and Latin and zoology.

TT: Certainly maths and Latin and the chess, there's a very logical structure to them? Were you aware of that a t the time or do you think that in retrospect?

PH: Yes, to an extent, although I must admit most of my friends went and did the arts, and I was quite interested in languages and other things as well. But I am very logical I think.

TT: Then you would have done O levels and A levels.

PH: At Chippenham Grammar I was in the top of the top class and about half a dozen of us did O levels a year early, and we didn't go into the Fifth form, we went straight into the Sixth form, which I didn't mind. My subjects then were pure and applied maths, two subjects, and physics and biology. I liked the maths for the reason we just heard, it was very logical. Physics just seemed a natural follow-on from applied mathematics. And biology, I was always interested in biology. The first book I ever read myself was Enid Blyton's book of garden birds, which was about a little boy and his sister who live in the city and all they ever see is pigeons, and then they go to stay with their auntie and uncle in the countryside and they suddenly hear all these noises they've never heard before. And so it goes through bird species but it's always part of a little novel. I lost my copy and just recently found the book in a Cambridge book shop. It was printed in 1947 and I've got a copy of it again.

TT: You mentioned relatives who were doctors. Were you still thinking of medicine?

PH: Not quite at that stage, you will laugh at this, but I decided I was going to be a biophysicist and sort of invented it. I almost made it up, and then I found out there was no such thing as a biophysicist, and I wouldn't get a job. I thought I'd better think of something else. Today it's an obvious thing but in those days I don't think it was. We're talking about the late 1950s.

TT: It would be about the time the word was coming into common usage.

PH: Yes, precisely. But it wasn't on most people's radar. I'm sure my science teacher didn't know anything about it. And then that influence of family: one of my uncles worked on the polio virus in South Africa and so I thought about medicine. Then I had to change schools again, and I went to another grammar school, then my father went out to Singapore and he said, 'Do you want to come to Singapore or do you want to go to boarding school?' Oh, what a choice. Singapore would have been great because we'd have been sailing every day but I would have done no work, because by then I was starting to grow up and get older, I was about 16. And there's all sorts of other activities like, well, I won't go into that.

TT: We all remember what it's like to be 16.

PH: I decided I'd better go the boarding school route so I went to a school called St Peter's in Bournemouth, Southport. That was run by the De La Salle Brothers, it was a bit of prison type of boarding school.

In going there, in transit, as it were, I decided I was going to do medicine and not biophysics. I decided I was going to do a single maths, they didn't do biology, so I did zoology, which I preferred anyway. And I decided to do chemistry in one year. Anyway, I spent most of my time climbing down a drainpipe as far as I remember at that school so suddenly I went a bit off the rails [laughs]. I didn't get particularly good A-levels, was having trouble in fact. I went to 16 Medical School interviews and didn't even get offered a place. That was before I got my A levels and my A levels weren't brilliant. My parents were abroad and so I didn't get much support. So this idea about doing medicine was a bit of a problem. I ended up doing pharmacy, and I was very fortunate that I was good at maths. I got to the School of Pharmacy, University of London, I had heard that was the best School of Pharmacy and the Dean interviewed me, he was quite a character and, Hartley his name was, Professor Hartley, and he interviewed me. I am sure it was only because I could answer his questions on calculus that he gave me a place.

I've actually missed out a bit here. Because I was too late to apply to start with, or I was trying to get into Medical School, I ended up going to do an apprenticeship with Boots. In those days you could do the pharmacy apprenticeship before university, now you have to do it after. I was probably the last person in England ever to do the pre-university year.

That was Boots in Dover. I did pretty well there and so when I turned up to the School of Pharmacy I thought I knew it all and in fact, I remember we had a big practical exam and I remember the pharmaceutics guy came across and he gave me 95 instead of 100 and he said, 'I'm taking five off because you've got a dirty lab coat.' Anyway, the interview with Frank Hartley was quite tough and he was obviously throwing out a lot of people, and he asked me a lot of pharmacy questions, which I knew for the reasons you've now discovered, and then he asked me to do some calculus, some maths. Apparently he was getting everybody to do the maths, because he believed you had to have maths as well as the chemistry, the physics and the biology. And I was able to do all the calculus for him straight off, so I got in and I was so lucky because it was a brilliant School of Pharmacy, I learnt so much. I did medicinal chemistry to a very high level but more particularly, they had a fantastic Pharmacology Department and I was just hooked on pharmacology, absolutely hooked.

TT: Why pharmacy, which almost implies vocational training to become a pharmaceutical pharmacist, as opposed to say a degree in pharmacology or physiology?

PH: There wasn't a degree in pharmacology in those days. That shows you how long ago it was. There may have been one in the whole of Britain, at Chelsea. And I didn't really know what pharmacology was as such.

TT: Who were your pharmacology teachers at the School of Pharmacy?

PH: In those days the Professor of Pharmacology at "The Square", as it was known, had to be medically qualified and the Professor at the time was Gladwin Buttle.

TT: Ex-Wellcome Foundation.

PH: Yes. He was an amazing guy. He'd been in the Second World War in the desert in Africa, and came up with this idea of using milk bottles to take blood around for people injured on the battlefield – that was his contribution. He was a real character, and he would always walk around with a big cigar in his mouth and he was really funny. Because it was always the butt end and it was

always splayed out. It looked as though he'd walked into the wall with it and got crushed. I don't think he was a great pharmacologist, but he was the medic they wanted. He was a great character and greatly motivational but the key pharmacologists were Bowman, Rand and West, who wrote their textbook at the time. So we were being told what was in their textbook and if you missed the lecture you just bought the textbook at the end of the year [laughs].

TT: You got hooked on pharmacology, was there anything in particular?

PH: There were two things; one is the mathematical side of it. I still very proudly proclaim that pharmacology is the only biological discipline that involves mathematics and numbers, and you treat numbers seriously and they mean something. So obviously drug receptor theory and all that sort of thing appealed to my mathematical inclinations. But not only that, but it was the medicinal chemistry and designer drugs, we were learning about Ehrlich and people like that who spotted the opportunities. Ehrlich was fascinated by the fact that drugs such as dyes could get into bacterial cells and not into human cells, so you could actually see the colour. He talked about the 'magic bullet', so that you could design chemicals that actually target a particular cell. Subsequently, you could extrapolate that to a receptor, and he did actually talk about receptors, so that if you put together the medicinal chemistry that I'd done and that we were doing in pharmacy, the mathematics and then the discovery side, you get my career! I was always interested in people who had achieved things, and that went beyond even medical things. Think about Shackleton in the Antarctic and Hillary climbing Mount Everest. I always liked the idea of doing something that nobody else had done before. So it just seemed it was all there really.

TT: That seems an amazing confluence of these three things coming together in pharmacy. So that inspired you to think of becoming a professional scientist and doing a PhD?

PH: Well, it did and it didn't. I was really excited about it, but I was so determined to become a doctor in my early days that I went to see the Dean about getting a place at the Royal Free Medical School next door. I played rugby for them, so I might as well go and be a student there, because the Royal Free at that time had very few men, so I think in the first 15 there were nine pharmacists. Bit by bit, it took on more and more men and it became 50-50. The Dean looked into it and said he could get me a place because my pharmacology was particularly good. But I decided that I'd done a year as a pharmacist apprentice, I'd done two years almost; I might as well finish it. I do like to finish things, and it seemed

silly to walk away from it. So I decided I'd do medicine at the end, but then I thought, 'To go back to Medical School I've got to learn every bone in the body and this, that and the other. I think I'd rather do a PhD and use my brain.' I did eventually get a place at the Royal Free, I've still got the letter, but I did not take it up.

Anyway, I had a place at St Mary's Medical School to do a PhD and that really appealed because the Professor there was Richard Creese, quite a well-known physiologist, and it was a Physiology Department, not a Pharmacology Department. Creese purposely went to The Square, he said, 'I want somebody who can actually use analytical techniques and mathematics,' because he was into dose-response curves and understanding them, so it was right for me, right for him, I guess.

TT: So Richard recruited you? Trying to find somebody with your particular skills and interests? How very fortunate. Did he supervise your PhD?

PH: Yes. It was on the neuromuscular junction, which is quite interesting from a medical point of view, diseases of the neuromuscular junction, problems of locomotion and everything else are very important. But my PhD was also the physiology of it, in terms of neuromuscular transmission, on decamethonium.

TT: So it's very much the Paton and Zaimis era?

PH: Precisely, yes, Eleanor Zaimis. The electrophysiology, neurophysiology appealed. It was related to a medical condition, which also appealed. We were looking at decamethonium and how it was taken up into skeletal muscle. We were trying to work out how it got taken up and why it got taken up, and so I was excited to go there. Anyway, Richard said to me, on the first day, 'You're going to do my teaching, Pat. Tomorrow we've got the first lot of students coming in, you're going to teach the ophthalmoscope.' I hadn't got a clue how to use the ophthalmoscope, but he showed me how to use it and the next day there's me with my lab coat on, showing them how to use an ophthalmoscope. That was fun because we did lots of studies on students in those days so, you would never have been able to do that today, it would be impossible.

TT: These were studies as part of their course?

PH: Part of the second MB course, yes. I used to take blood out of students, I'd taken blood out of plenty of rats and rabbits, but I'd never taken from a student before, but they didn't know and I was pretty good at it [laughs]. And one of the experiments I actually loved was I used to put a Ryles tube down the

nose of the student into their stomach and then they had a syringe on the end so they could take out stomach secretion, acid and everything, and measure it. Every time I put that down their nose, they were quite frightened because it's not particularly pleasant, but they said 'Have you had this done yourself?' And I said confidently, 'Yes.' I think it was one of the few times that I told a lie, but I thought it was appropriate to tell a lie [laughs]. This is the amazing thing, I used to inject them with histamine to stimulate acid secretion, and obviously it was very effective but they had to take an antihistamine in order to stop the systemic side effects that you get. They would not allow that today.

TT: How you would get ethical committee approval nowadays?

PH: Precisely. So that's in 1968 to 1969. Oh, by the way, I was in sole charge. There was nobody around, and I think I was one of the few or almost the only non-medically qualified person on the staff at that time. I stayed for year after my PhD, when they made me a Lecturer then. Prior to that I was paid as a demonstrator. I think that's what I was called during my PhD years.

TT: And then you decided to leave?

PH: Well, I'd taught students and I'd done a PhD which I really enjoyed, it was more pharmacology than physiology, but I'd interacted with all the physiologists and knew that if I stayed on as a Lecturer I'd be teaching physiology to medical students. I'd have some research and maybe I'd have a line or two in a textbook one day, but it didn't seem to me a very attractive end target. I was interested in medicine, interested in pharmacology to a great degree, could see what it could do, and I wanted to discover a drug. That's what I wanted to do. I wanted to discover a drug. It was overriding, and I thought that's how I could fulfil my interest in medicine, that if you could make drugs that make people better and change their lives, that would be it. Many years later I got to know Jim Black very well and he said in a book he wrote, but he also said it to me several times, that although he was medically qualified, he was a pharmacologist as we all know, and he said, 'I've done more for patients by being in a laboratory than I could ever have done in a clinic.' I had foreseen getting that sort of satisfaction, so I wanted to find a drug.

Now this is the next step. I've been so lucky it's unbelievable, because David Jack, Sir David Jack, was head of Allen & Hanburys in Ware in Hertfordshire, and he was looking for somebody to start a migraine project. He was looking for what he used to call 'bright young things' because they hardly had anybody who had a PhD at Allen & Hanburys. Even the Head of Department, Roy Brittain,

didn't have a PhD when he started. So David Jack was looking around and the School of Pharmacy was the obvious place. He went there and people sort of knew me at St Mary's, and I think that's how he offered me the job.

TT: Why were Allen & Hanburys looking for a migraine drug?

PH: A very good point. David Jack had this maxim that we, the people who work for Allen & Hanburys, had to find better drugs for diseases that were poorly treated. But then he had another addition to this, he said, 'It's also got to be a common disease, there's got to be lots of people who have it, because we're a pharmaceutical company, needing to make money. It's no good if one person in the world has got the disease.' So he said, 'How do we know it's common, laddie?' And the answer you had to give him was, 'I know somebody who's got it' [laughter]. He knew several people who had migraine and his daughter I believe had migraine, and he realised that it was a disease that was very poorly treated and it was very common.

TT: You've got your PhD, you've done some teaching and now you go to Allen & Hanburys, Ware. Was there any tension from your academic colleagues that you were going into industry from academe?

PH: Not really. In physiology they were all medically qualified anyway, and I was well accepted and I had no problems like that. I think they always thought that people like me would go into industry because it was the perceived thing. Today I think somebody like me would have been in an academic department of pharmacology or bioscience or whatever.

TT: You have spoken about this before, but it would be good to have it on this record as well, about you arriving at Allen & Hanburys.

PH: I'd already met Roy Brittain who was the Head of Department, I'd met David Jack several times; all this was through the interview process. I actually went, even when I was at the School of Pharmacy, to Allen & Hanburys to look around, and David Jack had told me, 'You're too bright, laddie, come back when you've got a PhD' [laughs]. I took him at his word in a sense, and he approached me as well so that was a meeting of minds. I was really looking forward to going to Allen & Hanburys, and when I got there and met everybody, it was really nice. Then they said, 'This is your lab,' and I walked in and there was a lab and there was nothing in there. Then I found out there was really nobody going to work with me except one person that they'd assigned and that was Eira Apperley. She was a young graduate and she's sitting there on the bench and

says to me, 'What are we going to do?' [Laughs]. It was interesting, nobody told me what to do because the Head of Department was away, and David Jack was somewhere else, so it was pretty clear that it was down to me to find something to do. Retrospectively, it was fantastic because nobody would have that opportunity anymore, now you'd be told what you're going to do and it was probably the wrong thing, and you couldn't do much about it anyway [laughs]. I think industry has got itself into a pretty abominable state now. Anyway, at the time that was the best place to be without a doubt and to have that freedom was fantastic.

The first thing I said to Eira was, 'We're going to find out about this disease. We're going to talk to clinicians.' It was obviously a question of doing a lot of reading but also contacting various clinicians and going to see them. I'd already decided from what I'd read, especially the teachings of Harold Wolff, that migraines seemed to be a vascular disease of the cranial blood vessels. So we ordered a whole lot of stuff to look at isolated blood vessels and we started on the rabbit ear artery, because ostensibly that's a cranial vessel, extracranial, it was easy to get out and to put a catheter into it. You could look at a whole vessel, you could look at contraction and you could measure blood flow through it and so on and so on. So we ordered that equipment while we went to various places. We particularly went to the City Migraine Clinic, which was a place where migraineurs in the City could ring up and they'd even get a taxi to bring them into the clinic, and they'd try and treat them. The person in charge was Marcia Wilkinson, who is quite a famous person, and she was charming because she didn't know me from Adam. I was just someone who turned up from Allen & Hanburys, which was hardly a well-known pharmaceutical company. She took me around and showed me what they did and gave me a lot of information on how she treated people. She was a bit anti-drugs, which was ironic given what I was going to do. They liked to get people in a dark room and let them rest and in the end it can go away although some people can be in bed for 24 hours or more, so it's not overly helpful.

TT: Was there sweet tea involved as well? Didn't she always give people tea?

PH: Yes, I think tea was involved. There's obviously always been this link with caffeine. I don't remember that being obligatory, but it may well have been.

TT: Marcia Wilkinson was against drugs? Was that common?

PH: I don't mean that in a pejorative way, that was typical of the conservatism of the medical profession at that time. The one thing I learnt at the School of Pharmacy from our medically qualified Pharmacology Lecturers was that drugs are dangerous, most people in hospital were there because of wrongly prescribed or overdosed drugs. Iatrogenic problems were manifest in a big way.

TT: As far as migraine was concerned, what about ergotamine?

PH: One thing that I got out of Marcia Wilkinson was that ergotamine worked. She didn't like giving it but it worked. If people had a severe condition she'd use it. This was one of the key parts of the hypothesis that I put together, which was that ergotamine works. The question then is, why does ergotamine work? I think it's pretty obvious that it was probably a vasoconstrictor, and that coincided with Wolff's teachings that vessels in a migraine attack were dilated, distended, inflamed, and therefore it would be beneficial if you shut them down. This was 1972 to 1973? Wolff, in 1938, had shown that ergotamine constricted extracranial vessels in humans and correlated the constriction with injected ergotamine that was also causing the ablation of the headache. I used to float this around when I used to talk about migraine in the very early days, trying to convince people about my ideas and they did tend to pooh pooh them a bit. The reason, I think, is that Wolff selected subset of migraineurs where you got extracranial vasodilation, they were red, but most migraineurs go pale, totally white, the extracranial vessels are not obviously dilated. But nevertheless, he'd done it and the key thing is the dynamics: ergotamine's constricting and at the same time it's doing something else; i.e. removing the headache or making the headache get better.

TT: You've talked to clinicians, you're developing some ideas, and you've got the ear vessel preparation. How does this develop, Pat?

PH: Marcia Wilkinson's views helped, Wolff's hypothesis or mechanistic sort of ideas were still in my mind, but the question is whether they were real, and I started to firmly believe them when James Lance, a very famous neurologist in Sydney, told me that ergotamine really did work. I really respected him as a clinician. He said ergotamine worked, he thought it was a vasoconstrictor. That's where we were in terms of the vasoconstriction concept, so I decided we would work heavily on the migraine vasoconstriction hypothesis as a treatment. The logic is that blood vessels somewhere are dilated and the distension causes pain. We can talk later why that might be so in migraineurs and not in normal subjects, because it's well known that people who, say, drink alcohol, who are

migraineurs, get a headache, a migrainous headache. Normal people don't get a headache unless they have ridiculous amounts. This idea of dilation by alcohol, constriction by ergotamine, seemed to fit quite nicely, although people were going off the Wolff ideas and not many people really accepted the idea that I was trying to push, to come up with a mechanism that I could pursue to find a new drug.

The other thing about this constriction is 5-HT. 5-HT injected in migraineurs would abort an attack as well. So you have to say, 'What's 5-HT doing?' We all know that 5-HT is a brain neurotransmitter and a lot of people don't appreciate that 95% of the 5-HT is in the gut. It is also a vasoconstrictor, but that turned out to be a real can of worms because when we started investigating it, we found that Irvine Page, who discovered 5-HT had also proved it would dilate. So it's got dilator actions, and constrictor actions. I later got the Vane Prize for Neuropharmacology, so I did get into 'neuro' in a big way, but at that time I was hard-core cardiovascular with regard to the cranial blood vessels as opposed to anywhere else.

TT: You mentioned Wolff's ideas not being so popular when you were developing your own ideas. How were you own ideas accepted by Allen & Hanburys? How were you regarded?

PH: They were fine because internally I developed my hypothesis fairly quickly, and they could see there was some rationality in it, and David Jack was prepared to go along with it because it seemed plausible. Interestingly, they were quite wedded to vasoconstriction in the company, so they were open to the idea of vasoconstriction, but the question is which blood vessels, how do you explain it. The salvation for me being able to put the idea forward of a vasoconstrictor was Pramod Saxena who had been working in Rotterdam on shunts. He was developing it beautifully in animal models in relation to migraine, and he'd shown that you can dilate the vessels and then if you constrict them you find that most of the constriction is not the arterial supply but it's what are called 'carotid arteriovenous anastomoses'. Basically what you're saying is that a lot of the blood is just diverted away from the normal brain circulation.

There was a German Professor Heyck who put forward the hypothesis that in migraine there are carotid arterial shunts that open up, and you can show in the jugular venous blood that oxygenated arterial blood that should be going to the brain is being diverted on the jugular side. Nobody really was able to confirm that hypothesis but I argued that maybe 5-HT which will abort an attack, will

constrict these shunts. Ergotamine constricts these shunts, why couldn't we try and constrict these shunts selectively? At the same time we were working on peripheral blood vessels and we discovered a new 5-HT receptor now called a "5-HT_{1B}" receptor' on blood vessels in the dog saphenous vein and also that it was predominantly in these carotid arterial shunt vessels, predominantly in certain cranial vessels, and nowhere else.

We went to Pramod Saxena's lab in Rotterdam to take one of our prototypical agonists and we were just euphoric when we saw that all it did was constrict the shunt blood vessels, cranial shunt vessels, and no other vessels in the head, no other vessels in the rest of the body. Just amazing. The whole thing is very complex and what I was able to do is drive through the complexity and get simplicity. Some people believe 5-HT caused migraine, some people thought it didn't. But one of the problems that I had was that if 5-HT causes migraine, why don't the 5-HT blockers really work? We had this vascular hypothesis put together, we discovered a new receptor, and we actually got it right.

TT: Can we talk a little more about the 5-HT receptors, and that whole morass that you got involved in sorting out.

PH: David Jack once put it another way, he said, 'Pat. That was the most amazing pharmacological detective story that you solved.' The reason it all came together, we'd got to find a migraine drug but we'd got to solve the pharmacology. Within two years we'd switched completely to 5-HT, and there we were, approaching it through the vasculature. We only knew of two receptors: Gaddum and Piccarelli's receptors, the "M receptor" and the "D receptor". The M receptor wasn't the one on the muscle, it was the one on the nerves, but it was called 'M' because it was blocked by morphine, and the "D" receptor was blocked by dibenzyline, and that was the muscle receptor, which we now know is 5-HT_2.

Because of my background in zoology I thought, 'We've got to get some proper classification here,' and "receptor classification" became a strong theme in all my work and all my career. I didn't like the idea of "M" and "D" because they were named after two very poor drugs, they were lousy drugs to name the receptors after. So I thought, 'Well, why don't we have "S receptors" after serotonin, the Americans call 5-HT "serotonin", we can have "S_1" and "S_2", that would be a good start' and that was frowned up by some of my colleagues. Ultimately, when we did get the nomenclature sorted out it remained as 5-HT, which was quite nice. But we were just looking at receptor types there are and when we discovered this dog saphenous vein receptor, we called it the "S_3 receptor". We

had S_1 and S_2, why not have S_3 [laughs]? I started to talk to a lot of people to see if we, the scientific fraternity, could intellectually get together and come up with a sensible classification. So we did.

TT: I have to stop you there. 'So we did.' Come on, Pat, it was much more than that.

PH: Well, it was a long road in a sense, and I don't think people would necessarily call me diplomatic, but I had to be pretty diplomatic in those early days. I invited a lot of people to a meeting in Birmingham. People got to like each other and I broached some of my ideas a bit tentatively, and that was the beginning of an amazing fraternity of people who did share a lot of things. That ultimately led to this meeting on Heron Island, which was amazing because of such good interaction. People were really excited about the idea of sorting all these things out, it was the beginning of a whole era where people realised there were multiple receptors for a single neurotransmitter.

When we started in 1972 there were two 5-HT receptors and suddenly we realised there were more 5-HT receptors than we'd realised because at Heron Island, that was in 1987.

TT: So you were working together, talking together, you set up or became the international nomenclature commission?

PH: In '86, I think, Paul Vanhoutte decided that 5-HT was the up and coming neurotransmitter and started the Serotonin Club. Quite a few people joined that and we had this meeting in Heron Island, a sub-conference of the IUPHAR meeting in Australia. It was a small conference hall on a small island, there were about, 50, 60, people there and everybody was talking. This meeting was phenomenal and I was made Chairman of the Nomenclature sub-Committee, and we eventually wrote this big tome, it was an official IUPHAR thing really when it came out in Pharmacological Reviews. What's amazing is that now you look back on it and there are 13, 14 5-HT receptors, and even today people say to me, 'How could you have discovered, a selective drug for migraine out of 14 receptors?' Or they probably ask it the other way. They say, 'If you had to do it today would you discover it?' And my answer is 'no' because you have to start with physiology, you have to start with medicine, and you have to understand mechanisms and you have to understand the whole body and you have to understand how blood vessels work and nerves work

TT: By this stage, Allen & Hanburys had moved to become Glaxo.

PH: Now we had a prototype, AH 25086 and it worked, and quite dramatically. We knew we had a drug, but that drug was not quite suitable in terms of duration of action and there were some other issues. It took us another four years to find sumatriptan.

But it didn't really matter because we had the prototype, we knew what we were doing and we had to set up the clinical trials in the appropriate way. That was largely down to Jes Olesen, and he did a very similar job to what I'd done in the nomenclature side of things.

TT: How do you feel as a drug discover, your baby being passed on and going into other people's hands?

PH: There was a selfish desire to make sure the drug was properly tested and that when we got the answer, we knew if it worked or it didn't work. I felt good about it, in a way I'm a bit of an ideas person, pass it on and make sure somebody else does it, you don't have to do it [laughs].

I ended up being Head of a Division of Pharmacology and was effectively sort of second in command at Ware. I always felt a bit uncomfortable in marketing but rationalised it to myself, 'If we're going to find drugs we need money. If we need money, we've got to find drugs.'

But I felt the company became more political under Richard Sykes, the end game came when I didn't like a lot of things he was implementing. He said he would set up a research centre, he said I could have some money and go off and do my own thing basically [laughs].

TT: This was the institute in Cambridge?

PH: Precisely. I was talking to Alan Cuthbert at Cambridge, realised that he had a whole floor he wanted to sell to a pharmaceutical company. It worked out fantastically. Richard said, 'You can take 15 to 20 people from Glaxo and we'll give you 10 years.' Great! But I only took five people because I didn't need tons of people from Glaxo. The annoying thing was that we had some brilliant ideas and Glaxo would just not take them on, because the people running it were molecular biologists and they just couldn't see the point of some of them.

TT: What was your remit from Glaxo? Did you have any?

PH: No remit really. I had to report to the R&D Director in the UK and that changed seven times in nine years. That shows you something? And they couldn't care less what I was doing, so that was fine by me. I did feel responsible

to them. They were providing the money and I felt I needed to provide drugs for them. Because I'd set up this GI Pharmacology Department, I was the only one who really knew GI pharmacology, so I remained the head of GI drug development even though I was at Cambridge. In the migraine area, I was still helping them out. When I was Head of a Division in Ware, I started up a GI Pharmacology Department with a view to finding new drugs for GI diseases, for which there's still great need. I was interested in irritable bowel syndrome (IBS), which I've claimed to be "migraine of the gut". IBS is a malfunction of normal gut function but it's also associated with pain and sensory perceptions, very analogous to migraine. We heard stories in the US of people actually buying a second house on the way to work in case they got caught short when they were driving to work. And our drug, alosetron, a 5-HT antagonist, turned out to be amazingly effective in diarrhoea-predominant people. It was marketed by Glaxo, it was hailed as big blockbuster and I think that was where it went wrong. By the time we got to the alosetron years, when I was at Cambridge, so it would be 1992 onwards, the company had been taken over by Americans and they wanted to sell it to everybody and anybody, whereas it should have been for the people who had this profound condition of IBS associated with diarrhoea. It turned out that bowel ischaemia occurred in several patients and the drug was withdrawn. It's now back on the market for certain patients, under certain conditions, given by an expert clinician.

We did some pretty pioneering work in terms of ATP receptors which a lot of other people have been looking into with not much success for a variety of reasons, because I think, technically, getting the right drugs is difficult and maybe people aren't pursuing it in the right way. Somatostatin we worked on. That's been a difficult nut to crack because it's a big peptide, and trying to find ligands for the receptors has not been easy.

TT: Then after 10 years, time was up.

PH: I was effectively made redundant when they become 'GlaxoSmithKline' (GSK), and I decided I really wanted to find one more drug, and I searched the world for a company I thought could do it. I was approached by a company called "Advanced Medicine" (later "Theravance") and I don't quite know how they got hold of my name but we had a look at each other and I thought, 'Well, this is the only company in the whole world I can find that I think could discover a drug in the next five or 10 years.' I was interviewed by Roy Vagelos,

an ex-CEO of Merck (Merck, Sharp & Dohme), and a very famous man in his own right for all the things he's done as a clinician and a drug discoverer, I suppose, rather than as a pharmacologist.

TT: Did you discover another drug?

PH: We discovered quite a number of drugs actually. It's really amazing. Temporarily I became Head of Microbiology. They had an antibiotic and they weren't quite sure what to do with it and we carried on and in the end we got it to the clinic, and it turned out that it was not only anti-MRSA [methicillin-resistant *Staphylococcus aureus*], as we thought, but it was actually effective in individuals who had MRSA that were resistant to vancomycin, which was the compound of choice at the time, and to some extent, still is.

Right at the beginning, I said we needed to develop a 5-HT_4 agonist for IBS, and we have a fantastic drug, and we published on it, but unfortunately that class of compound has got a bit tarnished, because the compound that Novartis developed, tegaserod, was found to cause heart effects. Theravance: it's now a phenomenal company, it's still got phenomenal people in it and it's going places.

TT: You came back to the UK and you leave being directly involved in research?

PH: I'd said I was going to go from pharmacology to ornithology and I see my bird surveys for the BTO [British Trust for Ornithology], as my new labs. It's analytical and it's numerical and so I'm pretty happy with doing that. I keep being asked by people about this, that or the other, and you realise you do know quite a lot about pharmacology. And I still just tell people what they should be doing and leave them to do it [laughs].

TT: One thing I wanted to ask you was – you've been an academic, you've been in a drug company, and you've dealt very closely with clinicians – you talked about going to see Marcia Wilkinson at the beginning of your career: would a lot of pharmacologists have gone and talked to the clinicians in that way?

PH: It wasn't like going to a meeting. I made the approach. But today the world is a bit different, I think you've got lots of clinical meetings, medical meetings that scientists do go along to, and I think they actually cultivate the medics these days with a view, not necessarily very altruistic, but just to get people on board with their approach and their drug, and maybe do their trial for them. I think the reason I've been successful in drug discovery is because I was interested in medicine, I was interested in physiology. Pharmacology should always involve physiology and when I was taught pharmacology it did. But now,

it's all molecular, molecular, molecular. So medicine, physiology, pharmacology in the old fashioned sense, are absolutely critical, and if you want to discover a drug, chemistry, medicinal chemistry is critical too. But I haven't mentioned pharmacy. I'm on the board at the moment of Verona Pharma and I've been involved in getting the medicine into the right formulation, because if you can't give it, it's no good as a medicine, particularly with inhaled medicines, it's a real art in itself. So I think I'm very fortunate to have that background, medicine, physiology, pharmacology, medicinal chemistry and pharmacy, and I think they're all critical. And I didn't learn them because I just wanted to learn them, I sort of picked them all up because I was interested in medicine in the first place, so the umbrella is medicine.

TT: Thank you so much Pat for sharing so many memories.

Figure 8: Professor Charles Marsden

Professor Charles Marsden PhD DSc HonFBPhS (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 period he was President of the BAP (2000–2002) and of the Serotonin Club (2008). In 2002, he was awarded the J R Vane Medal by the BPS 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 BAP. In 2014 he was made an Honorary Fellow of the BPS (HonFBPhS).

8 Marsden, Charles*

Tilli Tansey: Charles, could we start off with your background? Where you came from, education, family life and how you became interested in science?

Charles Marsden: I was born in 1943 in Cambridge and we lived there until 1950, when we moved to Saffron Walden, which is not far from Cambridge. My father was in the army throughout the War, he was a journalist and he was on the D-Day landing. When he came back, he worked in the new European part of the BBC World Service and had book programmes and an early version of *What the Papers Said* type programme.

My mother was involved in psychiatric social work and worked at Fulbourn Mental Hospital in Cambridge. She used to bring patients home and they used to tell us the most extraordinary stories, which, of course, I had no understanding of at the time. That was one of my earliest interests in mental health, though I was really most interested in zoology and, of course, then they hadn't really made the connection between mental health and science, and it was still a rather grey area in my teens. I went to Gordonstoun when I was 13, and I was there for four years. I'd done English and biology A levels, and then I went to the Cambridge Tech and did the three basic sciences in a year, as was customary then. The Cambridge Tech was a fantastic place, it's now, I think Anglia University, because most of the people who taught there were either related or linked to the University in some way, and they were fantastic teachers. I had a brilliant chemistry teacher and a biologist as well. And that really set me up. Then I ended up going to London, I went to Chelsea College where a lot of fellow pharmacologists met up. I did zoology, some were doing pharmacy, some were doing other things, but we all met up as pharmacologists in later life.

TT: Why Chelsea and why zoology?

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* Edited passages from the interview conducted by Professor Tilli Tansey, 19 April 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

CM: I'd been at a boarding school and I wanted to get out of that environment. I didn't want to live in a college and London just seemed a great place to be. It's one of those places where you have to be at some time in your life. And Chelsea, well I had heard of the Professor at the time, Professor Purchon. He was a mollusc expert. I just wanted to go to London. Why zoology? I liked animals basically and I was interested in them and how they worked, and certainly my father – though he had done history – he was also interested in animals and always made sure I had appropriate books to read. So I had quite an interesting collection of science-related, zoology books before I ever went to university.

TT: During your degree you decided to develop your career in science?

CM: One of the things I did during my undergraduate time, was to organise an expedition to the Azores with five other students. We made quite a large entomological collection; I was supported by the Natural History Museum as one of their summer scholars, to actually do all the classification work there, and then to publish the data. That taught me a lot about the need to be very careful about detail, and how important it was to get information correct and to record it correctly.

TT: Coming to the end of your degree, what were you thinking of doing?

CM: I got a place at Durham to do ecology, because I was very keen also in travel. Whenever I got the opportunity, I would go off. That came from my background because my father and mother travelled a great deal. And the whole family travels, and this has gone on through our next generation as well, our children. So ecology seemed very relevant at the time, but also an opportunity to do things around the world.

TT: This would be quite an early period really for ecology?

CM: Yes, it was beginning to make its impact. I graduated in 1966, but I had also become interested in the brain and had begun to read various books and I had become aware of this particular technique for mapping neuronal pathways. It was as you know well, you use it yourself, not immunohistochemistry, but fluorescence histochemistry, which made such an impact then. I saw pictures of these tracts in the brain all lit up and almost on a whim I decided, 'I'm not going to do ecology I'm going to do pharmacology.' I went to Southampton on their new biochemical pharmacology course. One of the Heads of the Pharmacology and Physiology Department, was Professor Gerald Kerkut, and I ended up staying on to do a PhD with him on snail brains.

TT: That MSc was quite an innovation at the time, wasn't it?

CM: Yes, I think it was the first year they had it, and Geoff Woodruff set it up. He was young, not much older than me, it was his first job and he'd recently got his PhD. It seemed a way into pharmacology and to get some understanding of drugs, how they worked and what they did. I think the fluorescent mapping of the brain pathways for dopamine, 5-HT and noradrenaline opened up a lot of ideas about how drugs might work. I got on quite well with Gerald Kerkut, he was an interesting character, and I did a project using fluorescence histochemistry and, obviously, I made it work. It worked. You know all about that! [Laughs]. The art was to get the formaldehyde in the right condition. I decided I wanted to do a PhD and Gerald encouraged me. I went for an interview at Pfizer's and was offered a job, and I said I wanted to do a PhD, so they ended up providing some of the money and so it all evolved like that.

TT: Was there any expectation you would go and work for Pfizer afterwards?

CM: I went for an interview, and I said I was interested in doing a PhD and they said 'That's good, that's what you should do.' They had, you may remember, a drug called 'para-chlorophenylalanine', which inhibited 5-HT synthesis. So some of the work that I did on the snail brains involved use of the drug, and that's how the funding and help came.

TT: When you finished your PhD, you moved to Norway. How did that come about?

CM: It's one of these things that happens in life. I had a great Norwegian friend, a guy called Trond Hafting. I'm still very close friends with him and know him very well and all his children, one who is a very well-known neuroscientist Morten Hafting. Then just by chance a medic and pharmacologist called Hans Cato Guldberg, who was working at the MRC Brain Metabolism Unit in Edinburgh, this was 1966, he was going back to Bergen the Pharmacology Institute, and he wanted to set up fluorescence histochemistry, but he didn't want to hire a Swede.

TT: [Laughs]. That was almost compulsory in those days.

CM: I shouldn't say that, but that was one of the reasons, and he approached me as he knew the work I had been doing. And so I said 'Yes.'

TT: To be offered a job in Norway must have been quite astonishing?

CM: I'd got married and we were keen to travel, although you normally went to America. But I was very keen on cross country skiing, so it seemed a good idea. Possibly not the best career move, but it led to three very happy years.

TT: Did you go on a fixed-term contract? Or did you and your wife think, 'Right, let's go for three or four years.'

CM: We went with open minds. The first year was quite difficult, it always is. The Norwegians where I worked all spoke English and later my wife got a job with what was the equivalent of the Free University in Bergen and taught English. We both worked, but we also travelled around the country a lot and she became really fluent in Norwegian. We had a great time. It was there that I moved from the snail to rodents, as a group we used the rat and I became much more orientated towards the mental disease area.

TT: That comes back to when you were a child and meeting people with mental health problems. At what point did you make the connection between what you were doing in the lab and brain chemistry and mental health?

CM: In my later years in Norway. Towards the end we had a visit from Arvid Carlsson, because I'd set up the rotating rat model, the Ungerstedt model, it had just come out in Sweden and we were able to make it work. I'd begun to look at how that 6-hydroxydopamine model interacted with the serotonergic system. We did this by doing lesions in the raphe, as we thought there might be a link between dopamine and 5-HT. When Arvid Carlsson came, he was very supportive of what we were doing and he'd already made a major presence for himself as a dopamine expert. Years later he came to the BAP when I was the President-Elect, to give the annual lecture. I took him out for a meal and he said when he looked back, his career would have been impossible now. He published all his brilliant dopamine research in very low impact journals. A handful of people read them and he said he could never get a job now with the profile he had at that time. How things have changed, and whether it is for the better in terms of science is an open question.

TT: Please finish off your Bergen story.

CM: We got involved, that is myself, Hans Guldberg and Ole Jacob Broch, with catechol-O-methyltransferase [COMT] and trying to identify its role. MAO had taken a major functional role in the amine story due to the development

of MAO inhibitors as antidepressants, but there was always COMT as well, and we did quite a lot on the functional role of COMT: first in the peripheral system using salivary gland preparations, and later in the brain.

TT: In which species?

CM: In the rat. Ligating the salivary glands and I did the fluorescence histochemistry, but then we moved into the brain. Hans Guldberg and I wrote a review for *Pharmacological Reviews* on COMT. Then after three happy years when we needed to think about future plans. For several family and personal reasons we did come back. I came back to Queen Square.

TT: You came back to work with Gerald Curzon?

CM: I think I wrote to him, he'd got a programme grant, and I'm pretty sure I wrote to him to ask about positions. I don't think it was advertised as such, and I came over and he offered me a job. My particular role was to look at the importance of tryptamine, as opposed to 5-HT, and the interactions between the two. It took a lot of work to get the assay going for tryptamine, and I don't think we really ever absolutely got the best one, because the techniques were not available, there was no HPLC or mass spectrometry at that time. But the levels of tryptamine did shoot up if you gave a MAO inhibitor; they rocketed up. So the potential for producing tryptamine in the brain was certainly there. But my driving ambition was to look further at the relationship between dopamine or 5-HT and its influence on behaviour. How could one begin to look at that?

Gerald, who was a biochemist, was slightly reluctant to get involved in behaviour, but he did. I was interested in getting behaviour going, really a pharmacological model that we could use to assess the effects of drugs. Gerald got a renewal for the grant and some point later, about a year before I left, we decided to go back to the MRC and ask for video equipment to record the behaviour. We had a visitation by the MRC, and a real behavioural person from Cambridge came, and was extremely rude about us using behaviour as part of pharmacology; he just couldn't understand why pharmacologists would want to measure anything to do with behaviour at all and he was incredibly rude. But we had some money in the bank and we just bought all the video equipment and it was a great success.

TT: What kind of behaviour were you recording?

CM: To begin with, it was very simple or that is what we thought. This included sexual behaviour and that's where we came a bit unstuck with the MRC visit, because the behavioural expert said things like 'There are 59 different steps in a sexual encounter between two rats.' He was absolutely right, but in terms of trying to determine whether drugs affected sexual behaviour, we didn't need to go into that detail, and we didn't have the experience to do it. But anyway, so we did that and also measured exploratory behavior.

TT: I hadn't realised that you'd obviously infected Gerald with this approach; that was how he got into this behavioural stuff.

CM: He hadn't done any behaviour. In about 2008 I invited Gerald to the dinner at the 5-HT conference in Oxford for the "International Serotonin Club" which both myself and Richard Green were organized. Gerald said what a big contribution we had made to his research life, because after that he did a lot of such work. He also said he felt rather bad that he'd been so difficult about letting us do it and hadn't acknowledged what a contribution that it had been.

TT: By this time in your career you've built up quite a repertoire of techniques and approaches, because you started off with invertebrates and of course brain chemistry and receptors in invertebrates are somewhat different. You then moved into rat, and fluorescence histochemistry, morphological techniques. You then are starting to think about function, with basic pharmacological/ biochemical approaches, and behavioural experiments. You've built up a considerable technical portfolio.

CM: Yes, and I still hadn't got to where I wanted to be. Really what I wanted to be able to do was to measure release and tie release and behavior together. I was lucky with my PhD in that I had a lucky break and found a very large dopamine cell, because in invertebrates all the dopamine cells were very small. There was a student who was doing a PhD in the same lab, who wanted to measure haemoglobin in snails and snail brains. She used *Planorbis corneus* and got in 500 snails, and I helped her dissect them in exchange for a few snails that I'd look at with the fluorescence histochemical technique. And there was this enormous dopamine cell.

TT: These are the kinds of things one cannot write in a grant application. It also says something about different species and getting the right animal.

CM: Yes, it does.

TT: Going back to the Institute of Neurology and Gerald, and this portfolio you've built up. You've been there for four years, five years?

CM: I went there in 1972 and left in December 1977. I was looking for a permanent job and I was offered a Lectureship at Dundee, which I turned down because I didn't see in terms of pharmacology that there was much future there for what I wanted to do. I also went to industry as well and I developed a very good link with what was then ICI. But having met them all and, particularly, Tom Blackburn, who was very junior then, we developed excellent research links that lasted many years. Then I got an interview at Nottingham and I was offered the job. It turned out to be very successful, because I went there with the strong support from the Department to set up a neuropharmacology lab. They were very supportive.

TT: Before we talk more about Nottingham…

CM: There is a very important spell in between, because we went to America. In 1977, an electrochemist called Ralph Adams in the States, published a fairly short letter in *Nature* about the possibility of using electrochemistry to measure amines. He had been developing the HPLC technique, to measure dopamine, noradrenaline, 5-HT etc., which of course totally revolutionized the ability to measure very small levels of amines relatively simply. And I was fascinated by this idea that he was suggesting, that one might be able to put a very small probe into the brain and measure amine release electrochemically. Ralph had already done a lot of work with the new HPLC technique doing microdissections of the human post-mortem brain and being able to measure 5-HT and dopamine in very small regions. He was interested, as I was, in being able to try and measure the transmitters *in situ* and, of course, I knew which drugs to use to see if we could measure changes in release. I was going to a meeting in Wisconsin, called the 'Tryptophan Club' and, to cut a long story short, I went to Kansas to see Ralph, and while I was there we did an experiment with chloramphetamine, a drug that releases 5-HT, to see if we could get an increase in the signal from what we thought might be 5-HT. And the signal went up. It was so exciting. I've still got the original trace. Then I had to go home, and I went back with this trace and was able to persuade the MRC to fund the remainder of my time before I began in Nottingham on January 1st, 1978. So I spent eight weeks in Lawrence, Kansas doing experiments and we got a lot of data out on what we thought was the dopamine signal and what we thought was the 5-HT signal, using drugs that increased release, like amphetamine and fenfluramine.

Then I began my new job, but I came back from that eight weeks with two things: the knowledge and skills to do the HPLC; I think probably the first in the UK to have this new electrochemical detector, and in conjunction with both a company in America and a company in the UK, the detector very, very quickly was on the market. Not with any financial gain for me of course, but they were very pleased to have an expert in the UK who knew how to use it.

TT: So were you able to set that up in Nottingham?

CM: By the end of the first year we got all the HPLC going. Some initial funding came from the Department. Most of the equipment was loaned to me, or given to me, because we were the people who could do it, and people used to come from far and wide to see how to do amine HPLC in particular. So there was quite a lot of interest. So that was the HPLC side, which at that time we simply used to measure amine brain tissue levels, and then there was voltammetry. Ralph Adams had given me a "black box" with which to do "chronoamperometry" as the technique is called, and we were able to get that going. What I did do very quickly was to get two BBSRC [Biotechnology and Biological Sciences Research Council] CASE [Collaborative Awards in Science and Engineering] awards, one with Reckitt & Colman and one with ICI. That brought in two PhD-students right from the beginning. So with the PhD-students came a bit of money and also some from the Department. But it was fairly shortly after I was appointed, I think 1981 that I got a Wellcome Trust Senior Lectureship, so I gave up the security I'd fought to get [laughter], which again I think in the long-term was the right move to make.

TT: One of the things that is fascinating about your career is the importance of techniques and how you have adopted techniques or developed them. It's always an interesting question: whether you're technique-led or ideas-led?

CM: I think I was ideas-led, because I knew what I wanted to use the techniques for. What I wanted was the ability to measure release during behaviour and that was still the driving influence. So the voltammetry went alongside the co-development of the microdialysis technique.

TT: And during this time, where are your concerns with mental health?

CM: At that stage it was very much concerned with depression, we weren't trying to model the disorder at all; that came later with the isolation-reared rats and the link up with Trevor Robbins. We were interested in trying to get better anti-depressant drugs, because the biggest issue was of course the slow

onset of action, and so we were beginning to think about how one might find a faster-working anti-depressant. We were using very simple behavioural testing of anti-depressant drugs, to identify the receptors involved in their action, and we were particularly interested in 5-HT receptors. At that time, throughout the 1970s and even into the early 1980s, the Americans were noradrenaline-led and we were 5-HT-led. Our interest was the 5-HT field, and I remember talking to Ray Fuller about this, because he was always frustrated because he couldn't get his compound fluoxetine off the shelf and into the patient in those days, but then of course, later, it was an enormous blockbuster.

TT: You say you weren't particularly interested in modelling at that point? But you must have been using some models?

CM: I wasn't vain enough to think I could model depression, and still don't think I can. But I was moving towards certain ideas, such as what are the key features in the brain that are important for depression, schizophrenia and so on. What is it that goes wrong with the brain? But it took us from the paper on microdialysis with dopamine in the anaesthetized rat in 1983, until 1991 when we published the first paper that used microdialysis in a freely-moving rat during behaviour, and we used the elevated X-maze. The elevated X-maze is a very simply model of anxiety. It is raised off the ground and it's a cross maze. One length of the arm are open, complete no sides, and the other has a closed arm, and the normal rat will spend the majority of time in the closed arms because that's where it feels safe, and decides it doesn't want to go into the open arm, but it might skittle across the middle bit to get into the other closed arm. We and Sandra File in London, who really developed the elevated maze as a test of anxiety, had shown that if you give a benzodiazepine, an anxiolytic drug, the rat will spend more time in the open arms. We thought this would be a good simple model to test our microdialysis system, and very quickly showed that when they went into the open arms, 5-HT was released. So exposure to an aversive situation, it's not real anxiety, but an aversive situation, produced an increase in 5-HT release.

TT: When you say 5-HT release, where from?

CM: We had our microdialysis probes at that time in the hippocampus, in the ventral and the dorsal hippocampus, and they both worked. We were able to show that there was a link between the 5-HT release and the behavioural situation. It's been done for lots of other situations since then, looking at 5-HT, dopamine, noradrenaline etc., and a lot of people have worked on aversive

situations, because several transmitters are released during aversion in various brain regions. So we jumped into the 1990s. At that stage we linked up with Trevor Robbins in Cambridge with the isolation-reared rat. I'd become interested in early brain development because that might be the time of key changes resulting in altered mental state and mental health, and you could model some of the environmental influences that might alter brain development. And the isolation-reared rat was just an extraordinarily simple way of doing it. It's not terribly sophisticated, but very enlightening.

TT: Would you like to explain what that is?

CM: The isolation-reared rat has been housed in social isolation from the time it is weaned. Rats are either kept in groups of five, socially-housed, or live on their own in a cage. Rats are social animals and interact – particularly young rats – they play together and touch each other. We found a very marked difference between rats that had been reared from when they were weaned on their own, compared to the group-reared ones in all sorts of measures. We began with behaviour. They were more rigid in their learning, they found it more difficult to adapt, they more actively sought drugs of dependence, they were more anxious, they responded more to an aversive situation than a normal rat. So, cognitively, and behaviourally, they were altered. And then we began to look at the link between the behavioural changes and the neurochemistry, and the most interesting were the changes in transmitter release measured with microdialysis. In rats reared in isolation, their 5-HT did not respond to aversion, it didn't go up as in the group-reared rats. The increase in 5-HT release is to alert them to the danger they're in, and that just didn't happen. There were similar sorts of changes in other behavioural and neurochemical fields, but we very much concentrated on the 5-HT side. There were changes in the sensitivity of the 5-HT receptors. And then we've gone on to show that the factors that are important in determining neuronal plasticity and so on, are also defective in the isolation-reared rat. They have fewer synaptic contacts, less branching of the neurons, and so forth. So developmentally, they're very different. Drug companies jumped on this and have very much used it as a model of schizophrenia. It's much more than that, it's a model of what can happen if you're subjected to isolation during development, rather than being a specific model of a disease. But it does show that a fairly small environmental change like being reared in social isolation for a period of time when you're young, if you're a rat, can have a very marked effect on brain development.

TT: What was the impact of this work? First of all, to other scientists.

CM: Clearly the microdialysis work had a very large impact not just within the academic scientific community but within drug companies. Every drug company by 1990-odd had set up microdialysis often with our help and collaboration. That was very nice for us, because it kept research money flowing in. It also had a big impact on the drug industry at that time as they were very much into neuroscience; sadly, they have dropped out now.

TT: Did it have an impact in actually developing a good drug for anything?

CM: Well, that's an interesting thing because at the moment we are still working on 5-HT_6 receptors, though not me now as I've retired, but Kevin Fone and other colleagues. I can't say that our work has led directly, at the present time, to a drug that's become a blockbuster, but I think it has certainly improved the understanding of the mechanisms and the way some drugs work, and by doing that, this has improved understanding of their possible clinical value as well of side-effects and potential side effects.

TT: During this time, have you always worked principally on rats or did you move into other animals or even into clinical work?

CM: Principally on rats, and mice in recent years because of the use of transgenic animals. Our most recent work, since 2008, on glutamate transporters was using mice, which we've genetically-engineered. I have done quite a lot on IBS and the role of serotonergic mechanisms in IBS in patients with Robin Spiller at Nottingham, that's human studies, of course, though we have also done some mouse-based IBS work with a grant from the BBSRC, but the vast majority has been in humans. I was involved in the early clinical trials with the SSRIs in the UK with paroxetine, and that was human studies; there we measured the changes in serotonergic platelet function. But in terms of the neuroscience experimental work, it's been animal-based. I was lucky and very much protected, because I was funded by the Wellcome Trust throughout that time so I was able to maintain a behavioural whole animal approach, which became very run down in the UK. But then, in the 1990s, when the transgenic animals came, everybody wanted functional work. I was very grateful that the Wellcome Trust have actually allowed us to keep going or else we would have had to change direction and drop our approach. I think I was funded directly by them for 11 years, certainly my salary was until basically the Wellcome scheme came to an end.

TT: Money also came from drug companies. This was mainly for students?

CM: Not just students, but also for projects and postdocs. I had a lot of BBSRC studentships and PhD-students over the years, I think 70+.

TT: Can we just go back to the collaborations you had with drug companies because you're quite unusual in having had a completely academic career. A lot of people dip in and out of academia and industry. Were there never any approaches from people saying, 'Come on, Charles, come over'?

CM: Yes, there were. But I was very lucky as Nottingham had excellent facilities for what I wanted to do. I had a superb animal facility, and over the years have built up specific behavioural labs for rats and mice, all computer-controlled and monitored. I loved the research, I liked the people I worked with, and I had great colleagues. We got on really well and the money continued to come in. I did a lot of collaborative grant applications so we had money from the Wellcome Trust, the MRC, the BBSRC. Also some fellowships from industry as well which were not related compounds, they were pure research, particularly with GSK.

TT: Quite a few of your students…

CM: Went to GSK, yes. I had one extraordinary meeting with GSK at Harlow about a schizophrenia project, and how we might develop a better drug that could treat the cognitive symptoms. There were 10 people in the room and I think eight or nine of them had been through my lab [laughter].

TT: Were you the tenth?

CM: I was the tenth. It was a bit incestuous really.

TT: That's an astonishing achievement. You must have a quite specific desire to supervise PhDs or to have PhD-students in your lab.

CM: I would take up to three a year. I do think it's a very important part of an academic's life training the next generation. I was very lucky as we got good PhD-students both from the UK and abroad. We developed a good reputation and, also, we had at various stages, different places where they came from. The BBSRC scheme, as it was then, the CASE award scheme was very good because it gave them the chance to have a project that they could use both an academic approach, combined with the ability of industry to provide aspects that we couldn't, because they were just too expensive. I also had quite a big international link as I represented the University in South East Asia, particularly

Thailand from where we had some excellent PhD-students. From about 2000, we've had a joint medical degree with one of the universities in Bangkok that I developed with a very cheerful and positive Thai colleague.

TT: Can I just go back to your amazing list of PhD-students? I think you've had somebody in practically every drug company. And several have gone into medical journalism?

CM: Yes, that's interesting. Most of those who did that had specific reasons. John Stolz was one of the very first PhD-students, and he now has his own company; he was very good at writing. Ian Wright, was a very able student, but became terribly allergic to animals of any form in labs. A surprisingly large number do become allergic. There were others who just wanted to do other things,

TT: Do you feel disappointed if your students leave the lab, if they go into alternative careers?

CM: Not really. Some you feel it's the best route [laughs]. You probably know the feeling. But some you think it is the best thing for them. The international students, the ones from abroad, are all in academia and many have done extremely well. But they all know about science and they are usually in areas related to science. I think to have a PhD and know how difficult it is to get reliable research information makes them useful in a lot of related jobs. You hope as a supervisor that they have all developed their critical abilities and in particular their abilities to assess information, which I think with the internet these days, has become more and more important.

TT: Another lengthy item in your CV is what you might call "service". The Faculty and University Committees, the Societies, and the Editorial Boards, some of them of very long-standing. You joined *Neuropharmacology* in 1982?

CM: University Committees are not terribly taxing. The advantage of being on them is that you do get to know what's going on in the University and who is who. Plus, I find people very interesting. I find students very interesting, whether they're postgrads or undergrads. I really did enjoy the teaching side of my job and I never gave that up. Some people suggested I could have dropped all my teaching when I had my Wellcome Trust Senior Lectureship, but I wanted to develop neuroscience teaching both to the medical students and then, ultimately, we developed the first full neuroscience degree in the UK. I was always very pleased that we did that and it's worked very, very well. Now it's extraordinary as the drug companies have given up neuroscience, but young

people haven't given up neuroscience. We began with an intake of 12 and they all went on a placement. Some science subjects have lost impact, genetics has crashed. I don't really know why it's gone down, apparently it's gone down a lot – there's less interest in genetics. In neuroscience, we are now seeing more and more good students.

TT: What about your editorial duties?

CM: I was involved with *Neuropharmacology* for a long time and edited special editions on ADHD [attention deficit hyperactivity disorder] and 5-HT. I found reviewing articles quite interesting; it was very much a learning process as people would write things in different ways and also I don't think I am a person who particularly bears grudges or is antipathetic towards certain aspects. I think I was fairly even minded in the way I dealt with the reviewing process. I've obviously been at the other end where you've had people who have really gone for you and quite unnecessarily I often thought; I felt it was job that I should do. I now, together with Mark Geyer, Bart Ellenbroek and Thomas Barnes am editing a series of books called *Current Topics in Behavioural Neuroscience*, which we've got up to volume 33. They have been enormously successful, not in terms of sales of the whole hard copy books, but the individual chapter and whole book downloads are incredible. Combined, they run on average to 35,000 per volume and the one on addiction went up to 50,000 or something. And, yet, that exposure, in terms of the research assessment exercise is considered to be meaningless.

TT: People are increasingly having this problem; we have it also. The other thing in terms of academic service is learned societies. So I want to ask you about two organizations in particular. The first is the BPS. When did you join the BPS?

CM: I think I gave my first communication in 1969 so around then.

TT: What was your first communication on?

CM: It was on COMT, it was when I was in Norway, and because Hans Cato Guldberg had been in the MRC in Edinburgh and was a Member, he came to maintain the contact. I had a very nice Chairman, and there was a person that I really admired in the front row, Hermann Blaschko who was a lovely, lovely man, and he asked very nice questions. He was very incisive but asked good, fair questions. And I had been viva'd by him for my MSc degree at Southampton. And like everybody says in those days, there was a whole front row of very famous people. I never had a bad experience with the BPS. I haven't given

a communication there for years, but the same applies for my students. We always used to encourage them to present at the BPS. We would rehearse them through an nth degree, but they all found it a positive experience. I never had a student savaged, like one witnessed in the past at the Phys Soc.

TT: Oh, blood was drawn there, yes. I remember my own first communication to Phys Soc and yes, you look at the front row and they're all Nobel Laureates. Terrifying. You seem to have much more of an involvement with the BAP?

CM: The BAP began later and the BAP didn't exist when I joined the BPS. Richard Green's just completed a history of the BAP. I was loosely involved in the BAP in its early days. I then lost a certain amount of interest, it was very much taken over by clinicians from its early days. It wasn't initially, but then the clinicians stepped in rather heavily and they had meetings in the Channel Islands and things like that, which I didn't approve of. Anyway, I then got involved, it was David Nutt who said that 'You know, it's time you came into the fold, it really has improved,' which it had by then. I joined the year I got elected onto Council. I think that I joined in 1990, and was elected that year onto the Council.

TT: What is it that appeals about the BAP?

CM: Partly it was the mixture of clinicians and basic scientists, and the aim was strongly that there had to be communication between those groups. And so all the meetings were organized with that in mind; that we, as scientists, needed to talk to clinicians. I've always supported that view and the clinicians who were involved in the BAP are very much academic clinicians, so they are more like a basic scientist; it's an easy communication to have. I think that was the main aspect that appealed to me, together with the excellent atmosphere of the Association. They have a very good meeting once a year and there was increasingly a need to put across the importance of psychopharmacology and the use of drugs in psychiatry. There is a school of thought, I'm sure you know, that all drugs are bad. But I don't hold to that view at all. Not just because I'm involved in drugs, but because I have seen throughout my life the benefit of good treatment by good psychiatrists.

TT: Is it a similar meeting to say the Phys Soc or the Pharm Soc where people submit papers?

CM: What they tend to have is organized symposia in the morning followed by plenary sessions, themed poster sessions and themed oral sessions and on one day there is a symposium organized by postdocs and also a session when the BAP prize winners present their research. They have one big meeting a year, and that lasts three days.

TT: And as Meetings Secretary and Programme Secretary, Membership Secretary, President, what was your role in developing the themes?

CM: Very much in terms of what the themes were, we don't have a fixed list of themes, the themes are created each year depending on what proposals come in from the membership. Putting the programme together was one role, and particularly reviewing all the abstracts for the poster and oral sessions. We make sure that none of the posters are just drug company propaganda sheets; there's always quite a big blitz to avoid that, because that has been a problem in the past. The abstracts must contain real research.

TT: Were there any particular themes you really pushed yourself? Has there been synergy between the BAP and your own research career, and the ideas and the things that you have thought important?

CM: I've been very keen to bring in things like brain development and environmental factors. It's a difficult process, because there is a move now away from just talking about schizophrenia, and rather than talking about schizophrenia discussion is about the cognitive aspects of schizophrenia, the social aspects, and you actually do completely move away from talking about depression, anxiety or schizophrenia and break those up into the behavioural characteristics with which they are associated, and you find a lot of cross talk between the specific disorders. The BAP has gone some way along that line. There are certainly some clinicians who feel happier to stick with depression, but depression is a cognitive disorder as much as schizophrenia is, and there may be a lot of cross talk there. So how you break it up, I think, is an important question, and certainly we have begun to do that.

TT: Are there any that you are particularly proud of organizing or you think, 'That was really innovative or really worked,' or you're surprised that something really interesting came out of a meeting?

CM: They tend to be very successful, informative meetings. There is now an increasing feeling that we need to put across the problems that pharmacology in general and psychopharmacology in particular, are facing in terms of the lack

of interest by drug companies and relevant psychopharmacology research. In the last few years there has been a much greater effort to try and not have the drug companies there just because they want to sell their drugs, but to bring them into the core in terms of having open plenary sessions that deal with these issues, and to get them to say why they're not involved in such research. I think that that's been successful.

TT: Was that a quite deliberate, conscious move to do that?

CM: That was really in the last few years and there has been a conscious move to do that. One of the great strengths of BAP has been their guidelines, and their guidelines are very widely used.

TT: Ethical guidelines?

CM: No, treatment guidelines. Ethical guidelines we have discussed in our book series, *Current Topics in Behavioural Neuroscience*, we have produced a volume on the ethics of behavioural testing in humans and animals.

TT: That brings me onto the next question. You've worked on rats most of your career, so I want to ask you about animal rights. Have you ever had any problems from your work?

CM: Not violence in any way, we had protests and so on. I was, together with Trevor Robbins and one of my collaborators, we were named by the, was it the *Daily Mail* or was it *The Mirror*, as the most useless people in the world for our research on the isolation-reared rat model. I didn't respond and took it at face value so to speak, but I asked the University whether there should be some response from the University and they were very, very reluctant to do anything. They'd been very supportive of animal work, but not in terms of responding. I understand people's views, my eldest brother was extremely opposed to my research, but it hasn't affected our relationship. There is an issue, and it has become more apparent, but we have tried to address it. I wrote a paper with one of my postgrads, a review for a special issue on MDMA, about the translational value of animal versus human work. There is an issue about the translational importance with some of the animal work to human work, and that's why I'm very conscious of saying with the isolation-reared rat, much as the drug companies like to call it a 'model of schizophrenia', it is not a model of schizophrenia. We are looking at the development of the brain and how it is influenced by environmental factors. And that may be of real importance

in terms of our understanding what might happen in the human brain. We know that maternal deprivation is very harmful. You only have to look at the Romanian orphans' study from the Institute of Psychiatry to see that.

TT: Sir Michael Rutter's work.

CM: Yes, there are lots of parallels with our isolation-reared rat. The same bits of brain are affected and we're trying to get understanding of what might happen. With the isolation-reared rat if you touch them, if you handle them every day, you don't get the effects. It's all to do with contact.

TT: One final question: could you say something about the 'Monitoring Molecules in Neuroscience' group?

CM: One of the key things when you have a new technique or a new approach, you can either keep it to yourself, or you can expand it and let everybody get hold of it. With the development of the electrochemical HPLC technique for measuring the amines, we were very keen to make sure that it was widely available. We began a meeting in Nottingham, I think the first year was 1982, and then we held other meetings, but after the third or the fourth one, we decided to expand the scope and we came up with the idea of 'Monitoring Molecules in Neuroscience', which would be all-embracing for everything – not just HPLC – but all the emerging techniques. That attracted a lot of attention and we had a very successful event in which one of the people who came was Urban Ungerstedt and his plane was late, so to get to Nottingham in time to give his talk he hired a Porsche at the airport, which was quite an amusing way to get there. That's his character. Anyway, since then those meetings have been held every two years and they still continue to this day, and they tend to alternate between Europe and America. It's been an excellent way of bringing people together, both the experts in the techniques, but also the way in which they're being applied, both in basic science and in clinical science. So both in animal and in human research. In the latter years at Nottingham, about 2000, we, together with Peter Morris, who is the Head of the Sir Peter Mansfield [Imaging] Centre at Nottingham, obtained a large grant to set up a small animal fMRI [functional magnetic resonance imaging] and MRI [magnetic resonance imaging] Unit from the MRC. We were able to do that because Zeneca, who were based in Knutsford in Cheshire, were going to get rid of their magnet of a suitable size, so we got the magnet from them the rest of the money from the MRC. That is one of the first applications of fMRI to look at the effect of drugs in different brain regions to try and identify where the drugs might specifically

be acting and whether procedures such as the isolation-reared rat only produced morphological changes in the brain, which we were able to measure with the MRI, but also produced functional changes in response to various drugs in the brain. This is an approach that has really all come out from 'Monitoring Molecules in Neuroscience' approach.

TT: The membership of that group, has there been a consistent core group of people who come to all of them?

CM: The initial core group, which was very much in the UK was myself and Michael Joseph, Ian Macdonald in Nottingham, Ziggy Crook in Portsmouth, and Marianne Fillenz in Oxford. They've all really moved on now and luckily younger people have come to take over the role and maintain the interest and enthusiasm for bringing together the people who are interested in trying to understand how function can be monitored in the brain.

TT: At this point we have to stop. Thank you so much for taking part in this exercise Charles.

Figure 9: Mr Wesley Miner

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 (GSK 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 the nausea and vomiting induced by anti-cancer chemotherapy and radiation. This seminal experimental work translated very well to the clinic when granisetron (Kytril) was shown to be highly efficacious in patients. Importantly, this discovery became one of a very select few where research into 5-HT mechanisms culminated in a marketable drug that markedly improved the quality of life for patients. Following this ground-breaking research at Beecham, he relocated to another major international pharmaceutical company and became a key member of the biology team that discovered darifenacin (M_3 selective antimuscarinic), which is now indicated and marketed for over active bladder and urinary incontinence.

9 Miner, Wesley*

Tilli Tansey: The first thing I really want to ask you, Wes, is about your childhood, schooling, and influences, and how did you become a scientist?

Wesley Miner: I kinda suspected this might come up. I was brought up around the Chicago area and lived there for a number of years. How did I get interested in science? I put it all back to one of my aunts who for a birthday present bought me a book club subscription, which got me a book every month, and it had a series called *All About* books. The first book I ever read, I got from the book club, was *All About Dinosaurs*. I was about eight-years-old and it struck me that, oh my gosh, you can get all this information, in a book like this. The next one I read was *All About the Solar System*, and then *All About the Atom*. I went through school, enjoyed science and also enjoyed mathematics, had one teacher in particular as I'm sure we all kinda do, and she got us into mathematics quite early. We were only about nine and she started us off in algebra, and I saw equations and how to solve x and I just found it absolutely fascinating. But I was quite a lazy child and never really kinda excelled, certainly in my younger years. My sister was superb at everything, [laughs] and about three years older and she went through school and did exceptionally well. I was really kinda a dozy kid and I just lived in a little land of my own, although if a subject caught my interest then I would do very well at it. Then when I was 11-years-old I had a pretty sharp change in direction in life. I was in an airplane crash and my mother, father and cousin Ritchie were killed, and only my sister and I survived. We ended up living with my uncle and he was very interested in education, and made sure that we got pretty much top-notch educations. But I was still a bit of a slacker, and by the time I finished high school I got about half Bs and half Cs. Nothing outstanding by any means.

I was thinking about, well, what am I going to do? But one of the things that influenced me was I had a trust fund set up by my parents. I finished high school and thought about going to university, I was interested in science, but

* Edited passages from the interview conducted by Professor Tilli Tansey, 15 July 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

didn't really know where I wanted to get to with it. This trust fund became all mine when I was 21, by today's standards it would probably come out about $800,000(US), so it was a good size trust fund. This was a bad combination, somebody who is really lazy, and knowing the money is going to be there. I went to a couple of junior colleges, not gaining qualifications, and then at 21 all of a sudden money is there and accessible for me. I had this $800,000 and from the time I was 21 till I was 24, I spent 95% of my inheritance on fast cars, fast women, and booze and wild parties.

TT: Did you enjoy it?

WM: Enormously. And it did kinda got my interest going more along neurology, because what can I say, we did dabble, and I got interested in the effects that psychoactive drugs could have. Then I was 24, I'd spent all my money and it suddenly dawned on me I was going to have to go to work to actually support myself and feed myself, and that was pretty appalling I had $10,000 left and I thought, 'I'll go to Europe and I can kinda string the $10,000 out for a couple of years before I have to go to work.' I bought a one-way ticket to Munich, Germany, a really good sleeping bag and a backpack, and got on the plane.

TT: You're 24, you arrive in Munich. Did you speak German?

WM: Not at all, not at all.

TT: You went to Munich rather than London for something else?

WM: This was a huge shock to me. I flew into Munich and I expected everybody to speak perfect English like they do in the movies [laughter]. It was just total ignorance on my part. I got into Munich and stayed there for a little while. Then I bought myself a Volkswagen car and then went south through Austria, then Italy, Genoa for just a little while, and had a friend who was studying music in Aix en Provence just above Marseille, so I drove through Nice and Monaco and ended up staying with him in Aix en Provence for a few months. Then I headed north, made it through France, and came over on the ferry. This would have been 1972/73. I got in about 10 o'clock at night and I figured I'd drive a little bit further north. So I'm driving further north out of London and I'm thinking, 'I've got to find a hotel.' I kept looking at these hotels and they all had signs out front and it said, 'Residents Only' and I thought, 'Gee, I'm not a resident of the country' [laughter]. Finally, I found a motel that didn't have 'Residents Only.' I kept heading north, and ultimately made it up to Scotland. To cut a long story short, I met my future wife there and we went back to the

States, to Detroit. I started going back to junior college and I started taking a few courses in physiology and getting the science back up, but my wife really didn't like it. We decided to come back to Scotland and we were living in Perth where her family was located. My first son was born, and I decided I want to go to university, I want to get into some form of medical science, physiology, pharmacology. It dawned on me that I had to go back and get O grades and Higher grades in science to be able to get to university.

TT: This is a bit daunting because you're in your mid 20s by then?

WM: I'm 25 and living in Perth, and so I got a job working nights, go into work at 10 o'clock work until six o'clock in the morning, come home, get about two hours sleep and then go to all my classes. I did that for about three years, but managed to come out with Higher grades in physics, chemistry, mathematics and biology. I really put in a bit of effort so I got straight As and applied to universities, and Edinburgh was my first choice.

I started looking into seeing the reputations of the universities and I looked at biological sciences at Edinburgh and they had exactly what I was looking for because I could see that I could sort of get into chemistry, pharmacology and physiology and got accepted at Edinburgh. I thought I was going to have to work the whole time to put myself through but by the time I applied I'd been a resident for three years and the government paid for it all. Phenomenal system. I was absolutely astounded. They paid all my tuition and we got an allowance and stuff like that.

TT: You did physiology from the start?

WM: You had to start out in biological sciences. You do three years and come out with a BSc, then your fourth year you're allowed to specialise if you've done well enough during your three years.

WM: Physiology just really struck me as, 'Boy, that's really what I want to do.' The whole Department was very good, got my interest really going in physiology, kinda fed my interest in the neurosciences which I thought was very interesting. So was working with Paul Andrews though I can't remember a lot about what Paul taught us actually [laughs]. I just don't remember doing the GI system with him and I say that for a reason because ultimately it was the GI that really caught my interest once I got into industry, and we got back in touch when I was at Beecham.

TT: At the end of your degree, did you thinking of carrying on?

WM: I had three kids, and thought 'Got to get a job.' I applied for anything and everything: British Rail, to be an accountant, to all the pharmaceutical companies and ultimately got a job with a contract research organisation: Inveresk Research International (IRI).

The wonderful thing about Edinburgh was we were all licensed by the Home Office in our final year and we were doing experiments, on rats, on ferrets. I came out of the university with a pretty good *in vivo* experience which meant that when this job came up I was able to slot right in.

TT: Inveresk wasn't very far away, was it?

WM: In Musselburgh. I got myself a bicycle and I used to cycle out to work every day and I got very fit, got very fit, heart rate went down to about 45 beats a minute [laughs]. I picked up on experience particularly recovery, surgical experience. What they were looking for was to develop models in non-human primates. There weren't many places using non-human primates and I wouldn't want to do it anymore, but at that time it was quite a selling point because you could develop models in the non-human primates of drug dependency.

TT: What kind of animals were you doing recovery surgery on?

WM: Baboons *Papio papio* and macaques. Allowing them to self-administer drugs to see what they would substitute: if you started them out on cocaine, you could see what drugs would substitute by the various tobacco companies.

TT: What monitoring were you doing? Physiological or behavioural?

WM: Pretty much behavioural. You had a whole list and you would watch them and tick off on that. So that certainly got me into those type of skills too.

TT: Did you have any say in the kind of projects you were involved with?

WM: With contract research you have a client comes in and they go, 'We'd like this study done and here's what we're interested in.' I can remember sitting around the table with my supervisor and the client telling us, 'This is what we need done' and kinda looking over at my supervisor and, 'Can you do that?' 'Yes, of course we can do that, no problem.' We had no idea how to do it but you couldn't turn down the business. This is one of the things that drove me out of contract research because it became what I started calling the instant expert syndrome.

TT: Who were your customers mainly?

WM: Mainly the pharmaceutical companies. It wasn't just the science side, you had to meet the clients, you had to sell, which wasn't something that I really wanted to do.

TT: You were there for two years? You developed new skills, enhanced your repertoire of practical skills and had your eyes open for something else?

WM: You've got to remember I'm 10 years behind in age than everybody else. So I figured I'd better get out and see what I can find in "Big Pharma" at that point, and that struck me as where it was going to be most likely that I was going to find a position. Back then you used to look at *New Scientist*, the classified section, and they were packed with job adverts. I got two interviews. The first one was with Wyeth in Maidenhead and was a cardiovascular job. Exactly at the same time I went down for a Beecham interview, and it was going to be in GI motility: Wyeth didn't make me an offer and Beecham did. That would have been 1982 and I moved down to Harlow.

The Beecham Harlow research site, it wasn't a big site. It had Gastric Motility, Gastric Ulcer, Cardiovascular Department, the Arthritis Department and there were two CNS Departments. Each project area maybe only had about 20 to 25 people in it. The research building had a surgical suite with an X-ray suite with a full fluoroscopy unit. You had two full surgical areas where you could do clean surgery, and this fluoroscopy suite right off it. It was quite astounding what they had. The fluoroscopy area nobody used, it was just sitting there. The whole structure at Beecham at the time was amazingly horizontal. We were in Gastric Motility and there was Gareth Sanger, Christine McClelland, Mike Kelly, Brian McRitchie, myself, Steve Cooper and a couple of technicians. I started on investigating lower oesophageal sphincter pressure, which I knew nothing about [laughs]. The model was fairly straightforward to set up but there were a lot of problems as it had been set up. I went right back to square one on the literature. Our poor librarian, her workload must have gone up tenfold because I wanted to know everything I could about this lower oesophageal sphincter and the measurement.

TT: This was a dog model, Wes? Why the dog?

WM: Probably because they had the colony. They were looking at gastric motility (GM) a lot and so a lot of these animals had Heidenhain pouches and also gastric fistula. So it made use of what we had there already surgically with the dogs. This is where the X-ray suite came in because we were looking to work out a non-invasive method to measure gastric emptying. Gastric emptying is

extraordinarily difficult to figure out how you are actually going to measure it. We were taking the dogs, giving them a radio-opaque meal and using the fluoroscopy to look at them about every half hour. That's fine but how do you quantify it? So we figured, 'We'll take the dogs and we'll feed them a radio opaque meal and we'll put in 50 little radio opaque glass pellets, only three millimetres in diameter. I used to make this stuff up in the morning and I'd take about a half a tin of regular dog food, put in the little pellets and then mix in this radio opaque medium, which had a vanilla flavour. It sounds terrible and the dogs absolutely loved it.

We figured 'Then we'll get them onto the fluoroscopy table and we'll just watch and count how fast the little glass spheres empty and that will give us a wonderful quantification method for seeing how they go out. And then if you give a drug that increases the GM and gastric emptying, well the pellets are going to go out faster, aren't they?' Great in theory [laughs]. It doesn't work that way at all. First time we did this, we can see the radio opaque meal, starting to empty. You can start to see it outlining the intestines. However, the stomach, not a single pellet comes out. We go on. After four hours the meal's almost completely emptied out of the stomach, but not a single pellet out of the stomach. To cut a long story short, 10 hours later all of a sudden they all go out at once. There's a phenomena of the gut that's called a migrating myoelectric complex. The GI tract is marvellous and this is one of the things that started really getting me interested in GI. How on earth does the stomach know, to keep these things in and then to get rid of them like that? How does it do that? If you think of dogs and even people 10, 15 to 20,000 years ago, we ate a lot of garbage. Probably a lot of bone and bits of gravel and everything in there. And so that would all obviously go into our digestive system. At some point the stomach needs to clear all this stuff out and keep it going and that's what this migrating myoelectric complex does, it starts at the oesophagus and it's this little wave of muscular and electrical activity that works its way down through the whole intestine and it will only start once the meal is almost down to the colon. Everything has got to get all the way through the system and then finally this complex comes in, says 'Stomach is empty for the most part, let's get rid of any garbage that's in there.' That's what happens, and that's what we saw. This was kinda wow! What's going on here? What's the coordination, the neurology that's going on to actually do something like that?

At that point I started talking with Gareth saying, 'Man, there's a whole lot more to the GI tract than I ever thought, with the whole enteric nervous system and what was going on.' We'd started talking with our clinicians and it dawned on me that these are the things that drive people to the doctor, the problems with their GI tract, problems with their urinary tract. The unglamorous little things. From there I was pretty well hooked, and boy this is really one interesting area.

TT: How much independence then did you have to develop a project?

WM: I was pretty independent. I became pretty good friends with a guy who actually knew how to operate all the X-ray equipment, Geoff Heald. He and I worked out a system where we weren't going to use these little spheres because they were kinda useless anyway in quantifying just how fast things happen. We could actually look at a dog's stomach and produce a contour map of the radio opaque meal that was in it, to get an idea of how much was going down. I got to a point where I just didn't even want to go home at night, and over the one year we were working on it, I don't think I took more than two days' holiday. I just wanted to keep going on the thing the whole time it was that exciting and nobody else had done anything like that.

We were producing results and certainly we were taking the compounds at the time BRL 24924. As an aside, I have to say, I still remember all the numbers. I've got this horrible feeling that when we're all going senile and living in a home together we'll go, 'Do you remember old BRL 24924, boy that was a heck of a compound!' [Laughs] You get all these numbers. People are going to look at us and go, 'What are you talking about?' At that time were looking for a GM stimulant which did not have dopamine antagonist activity, as this is what was causing the problems with metoclopramide. This is the work that Gareth Sanger was pulled in to do. So we put in the BRL 24924 which was a benzamide, it had no dopamine antagonist activity, and were able to show quite marked effects in the dog.

TT: Were you able to publish this?

WM: It was a little tricky. We were able to put out abstracts on BRL 24924 and at the Gordon Research Conference. The GM side of it we were able to get going, we could put out a certain amount.

TT: That's the constant conflict of people in the industry, isn't it?

WM: If you want to publish, it's the icing on the cake. I have to give Gareth Sanger a phenomenal amount of credit because Gareth was publishing three to four papers a year as an industrial scientist. It was almost unheard of to be able to do that.

TT: Clearly Beecham were tolerating you doing all of this and allowing you quite a lot of leeway.

WM: It was. I think I have to say that's kinda down to my immediate boss David Turner and probably the head of the site at the time, Bob Poyser. Bob was encouraged by our work. He saw it, he got it. Once Bob was kinda bumped upstairs, Tony Ainsworth came on over as head of the site and he encouraged our work too but I don't know if I would be given that sort of leeway anymore. I think we were actually producing enough things and it was novel enough that Bob had enough insight to say, 'Okay, yes, this is novel stuff.' I made a comment about him in your 5-HT Witness Seminar, I remember him at meeting, he got up and he said, 'Things like this just don't come along. I don't know what we're going to do with it but we're not going to forget it.'

TT: Did you have interactions with people from other companies?

WM: We certainly got out to meetings, the BPS meetings, which were very good. There was a different attitude then and okay, nobody was giving away any big secrets, but we talked to each other. We'd say, yes, okay, this is what we're doing. And the other big thing was, and it just got so difficult later on, people were pretty free with their compounds.

TT: That comes across remarkably in the 5-HT Witness Seminar, how you all exchanged compounds and gave compounds to academics.

WM: Yes, and without the clause written in that 'anything discovered has got to go…' and the involvement of big management and the lawyers like now, and yes, people gave out the compounds. That was certainly the key to the anti-emetic work Gareth and I did because John Fozard gave us the MDL 72222 and he gave it to us quite freely.

TT: At what point did you get back in touch with Paul Andrews? Was it during that motility work or was it later?

WM: I had been working in the motility side, and then David Turner, our head of project, said, 'What would you think about doing work with emesis because we know metoclopramide is an anti-emetic, we're not sure what the dopamine

side of it is doing, but, let's have a look at developing emetic models.' At first it was just David Turner and myself and we got hold of ferrets, the animal model for emesis. I was really good friends with the supervisor of the animal house, Bob Collie and we got our vet, and we started working how we were going to do all the surgery on the ferrets. Because if you wanted to dose a ferret intravenously [laughs] you ain't going to put it in their little legs, I can tell you.

We got the vets out to show us how to do clean surgery, and we got our own little dedicated operating theatre. And that's where it all started out. We started, knowing from the literature from the Bristol-Myers group that they actually developed the whole idea using the ferret in emesis. In conjunction with that of course Paul Andrews was using the ferret for a lot of his GI work.

TT: And motility, not secretion, because so many people worked on secretion.

WM: Exactly. We got the ferrets and set up the surgical procedures, the whole surgery was actually implanting intravenous cannulae. We had to cannulate the jugular vein but with the ferret you had to exteriorise it at the back of the neck so you could actually do something with it or they bite you. We started looking at metoclopramide in the ferret model, using cisplatin to induce emesis. We got a very nice consistent response, and in fact it's probably why the whole 5-HT_3 area worked as well as it did because we actually had a model, a model, not an assay. We had an assay that mimicked the clinical situation fairly closely. And that's a problem today, you get so many people today that say, 'We've got a model' and so many of the models are not models, they're assays. But to actually mimic the clinical situation with the model, it's very difficult. And that's where we had a terrific advantage because we could model it.

We started looking at the cisplatin and we worked away at it and we got a pretty decent response to the cisplatin. In fact, I say decent, if you gave the animal cisplatin, they vomited. No question about it, 100%, which was another big thing. We used to have eight animals on the go, so what we used to do is we used to spend a day and a half or two days of surgery. We'd start about eight or nine o'clock in the morning cannulating these ferrets and we'd get through about four a day. We used to get out by the second day, we were pretty tired, just straight surgery for two days solid. We never lost a single ferret surgically and that was pretty reasonable. They were all pretty comfortable, they were all given analgesics, to tide them over the period of the surgery and the other thing with the ferret, is the back of the neck, the skin on the back of the neck is roughly one centimetre, one and a half centimetres of solid, thick, durable tissue and when

ferrets fight, especially the males, they latch onto the back of the necks. And you look at the backs of the neck of some of these things when they've been housed together and compared to the surgery we did, it was nothing compared to what they did to each other. They just used to tear their necks apart when they were together so we used to have to keep them all separated. Then we'd give them a three-day recovery period – this was all set out by the Home Office and that's when we would do the cisplatin on the third day so they'd recovered.

We started looking at dopamine antagonists because the competitor compound, domperidone, was a Janssen compound. The whole issue with the cisplatin-induced vomiting, it's just horrendous for the patients. People were actually refusing cancer treatments that potentially were curative with cisplatin because they didn't want to go through this vomiting. So there was a huge problem there. There were a number of claims that the domperidone actually worked pretty well, at least had some efficacy against the cisplatin induced vomiting.

I looked in the ferret with domperidone against the cisplatin induced emesis and everything I could see, the dopamine antagonist actually made it worse. Then we had this compound, BRL 24924. This was developed specifically as a GM stimulant void of dopamine antagonists, and this was going to be a big compound for the company. Ultimately it became Renzapride, a kinda competitor to Cisapride although it never made it to market. I can remember somebody gave me the compound, Renzapride, and said, 'Okay, test this in the cisplatin model and let's see what it does. It doesn't have any dopamine antagonism, it's a benzamide.' So I put it in the ferret and lo and behold it worked.

So now we knew that it wasn't dopamine antagonism that was stopping the cisplatin induced emesis. We knew metoclopramide had whatever it was and we knew BRL 24924 Renzapride had it. Gareth had been working *in vitro* with all the compounds and he really understood the pharmacology of what was going on. He had a real good idea. He looked at the compounds and he looked at the 24924, and I have to admit I'd never even heard of 5-HT receptors at this point [laughter], never in my life, I didn't know anything about 5-HT other than it existed. And Gareth is looking at this thing and he just makes this absolute quantum jump and he goes, 'It's 5-HT M-receptor antagonism.' Couldn't believe it. Gareth had known that John Fozard was working on this 5-HT. This is the old classic Gaddum classification of 5-HT as "D" and "M" back then. Even in our first paper we call it "5-HT M".

So Gareth looks at it and says, 'It's 5-HT M, that's what it is,' goes to John and gets the compound, MDL 72222 and says, 'Okay, come on, let's test it.' And I think, 'Okay, that sounds a good idea'. I put it in the ferrets and it just stopped the cisplatin induced vomiting cold. Absolutely cold. It was just absolutely astounding because I hadn't even seen that from the metoclopramide or the 24924. And the animals just looked perfect, it's like they never even had the cisplatin. What made it so powerful because (a) the cisplatin always caused the animals to vomit; and (b) this stopped it completely. It was right about that time I got a hold of Paul Andrews because we started having a difficult time getting our ferrets. I got a hold of Paul on the phone, 'Paul, where do you get your ferrets from?' He goes, 'Why are you looking for a supply of ferrets?' 'Well, because we're looking at cisplatin induced emesis.' 'Well, I think we might have a common interest here.' Because he was obviously getting into it quite a bit at that point too. So that's how we got together.

TT: This is when you're still at Beecham?

WM: Yes. It was amazing, and again I just got so into the work, I just didn't even want to go home. I just wanted to keep doing it. Well this problem was so significant in cancer patients.

TT: You've had this amazing eureka moment seeing this cisplatin induced emesis stop just like that and you start talking to Paul Andrews and you're developing it in the company. At what point do you go public?

WM: It was 1986 and the first abstract on cisplatin in the ferret was presented at the BPS. At the time we put out the abstract we knew exactly what was happening. We actually knew all the way back around 1984. So we knew it all the way back then and of course we couldn't publish. We did know that the Bradford group…

TT: Bob Naylor and Brenda Costall?

WM: Yes, they were working in the 5-HT M-receptor area. I don't know if we knew they were actually involved in anti-emetic work at that time but they were. I think they were already onto things by then themselves but I know they had a real close look at that abstract, and in the abstract we actually say that what's happened is either down to 5-HT M-receptor antagonism or GM. Now we knew it wasn't GM changes, but Gareth is so conservative, he couldn't state it because we hadn't ruled it out formally but we knew it wasn't. So we put that in, Gareth put that extra little line in, and of course the Bradford group

came along and they were having a real good look at this, and then they had a number of studies down themselves. But I've talked with Bob any number of times and gone over what happened, and we published our first paper in *BJP,* and, if you look at the title of our first paper, *BJP* came out roughly I think about four weeks before Bob Naylor's group published their paper. If you look at the title in the papers, it's about a 10 or 12-word title and there's about two words difference. It's one of these things, a parallel discovery. It's absolutely astounding. But what Bob didn't tell me until I just actually read it in your Witness Seminar, *Drugs Affecting 5-HT Systems*, was that he didn't believe it was going to work [laughter]. I've tried to look back and trace it, who came up with that at what point and all of that, and as far as I can figure, Gareth was really the first one by several months to actually put this together and say, 'Yes, this is actually what's going on'.

From there on we had a heck of a time with Beechams, they didn't want to know it as an anti-emetic. The problem was they had been in the area before and they'd been looking at cannabinoids and these things probably stopped forms of nausea and vomiting but they did it in dogs. And the poor dogs, they couldn't even stand up, they were knocked right off their feet, so they probably couldn't vomit even if they wanted to, and had such high side effects. Gareth and I had a meeting with senior management at the time they just said, 'No way! No way are we going into anti-emetics!' Gareth and I was just got up and I even pointed at one chap and said, 'If your child was vomiting, would you refuse them this anti-emetic?' We came out of the meeting and one of our colleagues, Christine McClelland, looked at me and said, 'Jeez, I thought you were going to get fired right there.' I was probably just so naïve that I assumed it was going to do something for people too, and no one would actually turn it down.

TT: So how did you react? That must have been such a massive bucket of cold water over you.

WM: I just wouldn't allow it. I said, 'We're going to do it'. Gareth was really into it too. So what happened was management said no but we'd not only developed the cisplatin work, but I'd gone ahead and developed a model of a cytotoxic drug using doxorubicin and cyclophosphamide, which caused a vomiting response even worse than the cisplatin in the ferret. The 5-HT_3 receptor antagonist worked even better against it. Then we did a radiation model of vomiting. Geoff Heald worked out how to do this. We put the ferrets in a Perspex cage, and ferrets love little enclosed spaces, they'd curl up, and we'd put them under the X-ray machine and we'd irradiate them.

The first one we put in, we didn't know what to expect, and 21 minutes later bang, he goes on, the complete vomiting response. That went on for 30 minutes and after that period of time the animal looked right as rain – he'd got the vomiting done. We did five animals and out of those five animals the first one started at about 21 minutes, the longest was 21 minutes when it started vomiting and the shortest was 19½ minutes.

So then we did the 5-HT_3 antagonist against the radiation and it worked even better. So we had the cisplatin, the doxorubicin and cyclophosphamide and we had the radiation models, all pretty big ones in anti-cancer therapy. And that's when we got called in by Keith Mansford, the Head of Research. What happened was, I dosing animals with, I think it was cisplatin, and I used to have to do this control animal that wouldn't get the 5-HT_3 antagonist. So they'd all get their cisplatin and they'd all vomit, and then they didn't if they had the 5-HT_3. I had this little control animal that didn't get the 5-HT_3 antagonist. I was thinking, 'Oh Jeez, I can't just let the little guy just keep vomiting like this' and that's when I sort of worked out, while he was actually vomiting he just wouldn't be looking at me: what if I gave him the 5-HT_3 antagonist? I fastened this little connector on really fast into the cannula at the back of his neck and just within five seconds I wacked this 5-HT_3 antagonist in, I mean that went in fast. And the animal, I remember the first one I did, he was retching and vomiting, it was kinda right in the middle of the retches, and he just shook his head and then he looked up and that was it. He just completely stopped vomiting. He was absolutely perfect, and then I couldn't get the connector off him, could I? [Laughter].

TT: Because he was fine by then. He would have bitten you?

WM: That's what I was saying, in the 5-HT Witness Seminar. I knew they loved milk so I had to get him a little bowl of milk and he ran over and got his milk and that's when he was distracted, I could get the connector off the thing. And we videoed that, again Geoff Heald again did this for me. He was great with all this equipment and everything so he actually, he and I got in there and did the whole thing and we videoed it. And Keith Mansford saw the video.

TT: So Beechams was having a change of mind?

WM: I think Keith was fairly well convinced that in fact, yes, there was something there and everything sort of changed. At that point, 1986, I moved to Pfizer. It was right at that point. The experimental work had been done.

TT: What was the set up? You handing the compound over because you were leaving but even if you'd stayed there it would have moved into clinical trials. And you'd have lost touch with it anyway?

WM: Yes. It moved very fast. By the time I left I think we'd only put out a couple of abstracts and the initial paper, the cisplatin-induced emesis M receptor one. Then there were three more papers. Gareth Sanger made sure my name went on all those when I was at Pfizer. Now that's quite exceptional. I know what industry's like and once you leave somewhere, you are left. Even though you put work in on it. But Gareth made sure that whoever did the work always got credit for it. He was quite exceptional in that way.

TT: Why did you leave?

WM: I was still interested in the GM side and Pfizer was just starting to get into IBS. I figured we pretty well had the emesis down the line, and the next big steps were going to be in IBS. It looked like an interesting time to get in at the bottom again and see what could be done on the IBS side. But it never really took off. Well it did in a way, we ended up looking at a gut selective calcium antagonist. Pfizer, at Sandwich at the time, were huge in cardiovascular, and had a calcium antagonist programme and somebody made an observation that it looked like you could get some sort of GI selectivity with the calcium antagonist without affecting the cardiovascular system. That became the basis of the project - to look for a calcium antagonist that would slow down GM. Of course it was a load of rubbish, because nobody really knows where the symptoms are coming from with IBS. This is the real problem in the area.

By then I was transitioning anyway from GI to the urogenital side and bladder problems and it was reasonably well known that you could use anticholinergics in urinary urge incontinence. So these selective M_3 selective muscarinic antagonists are actually pretty effective in urinary urge incontinence.

TT: How soon did this come into your career at Pfizer?

WM: I was there for about 23 years. I started out in the GI area and then after I'd been in the GI area for a little while I ended up going over into pulmonary. What I found was I was actually able to lead a team. I found that when you're leading a team, everybody is looking for is just somebody to make a decision. I realised it didn't make any difference if my decision was right or wrong, I just had to make that decision and say, 'That's what we're going to do.' If you get down that one and it's the wrong decision, you can always come back. But you

have to have somebody who is making the decision and that's what I could do. So I could make these decisions, yes okay, and we actually got down the line where we had what was a PAF [platelet activating factor] and also a histamine receptor 1 (H_1) antagonist. That was challenging but fun, but it never worked out in the clinic. It was one of these things that sounded a good idea to begin, it was not a bad something for allergies but it wasn't something that was going to cure asthma or something like that.

TT: You then moved into the urinary side?

WM: Again it sort of played to my strengths because it was *in vivo* work and very fine surgical work. I was able to set up a model ultimately in a guinea pig. I was able to actually look at the bladder as it was functioning and you think the bladder is just a little bag, don't you, it just kinda sits there and it fills up. I'm looking at this guinea pig bladder and the thing is twitching all over the place, it's going like that the whole time.

TT: I get the impression, because you're very, very animated about those four magic years at Beechams that Pfizer didn't quite match up?

WM: Pfizer was interesting. At the time it was very pharmacokinetic oriented and I didn't have a particular good grounding in pharmacokinetics. I always had the kinda feeling, 'Let's understand what we're doing physiologically.' If we can't understand the normal physiology how can we ever hope to understand the pathophysiology? Pfizer was, as most companies were, very much involved in absolute chemistry-led projects. The ratio of chemist to biologist at Pfizer at the time was about one to one, which is pretty high. So there's this constant drive to keep this pipeline filled and hence, 'Oh well, let's try this.' But you end up in a situation where you're taking stuff into the clinic and that's when things get expensive. And the attitude, and again this isn't just Pfizer, the attitude of clinicians within Big Pharma, 'Kill the compound as fast as you can.' So clinicians, they got a compound coming in, their whole goal was to kill that compound as fast as they could so that money wasn't spent on it. The problem was nothing was making it through.

There's been a huge shift now because as far as I know, the big pharmaceutical companies aren't doing a lot of research. This has all been contracted out and the whole idea is for the smaller companies to come up with the goods, do the work, and then when it gets a certain way down the line, it looks promising, then they will virtually sell the company to "Big Pharma". And I think that's the way it's got to go.

TT: You've often gone into things and thought, 'Well, I don't understand that; I'll try to understand it.' You're not going in preloaded with all these ideas of 'can't do that'. Is that a fair assessment?

WM: Yes, it probably is. It probably goes back to what catches my interest but yes it was just naïve in the sense of not understanding that I couldn't do it, and thinking, 'of course I can do it'. Why not? This is one of the problems I have with a number of pharmacologists. You get some very high powered pharmacologists who have done a lot of really top notch experimental work but if you look for pharmacologists who put the meat on the table and said, 'Here's a discovery that has actually gone forward to make money or help people, improve conditions' then there's a lot of pharmacologists out there that have not been able to do that.

TT: I wonder about something else in your career because you are very, very unusual to have got to your position and had your career without a PhD. Would a PhD have knocked the ignorance and naïveté out of you in a way?

WM: It may very well have. I suppose you can end up in a situation I did avoid as you go down the PhD line, you become very specialised and very focused in a particular area. This is one of the things I've found disconcerting with the BPS. When I first started going to them back in the 1980s and you'd go around to all the different posters and you'd talk to almost everybody, and you'd go, 'Oh, that's really interesting.' And now if you go, and I'm sure it's in the other societies too, don't get me wrong, I'm not singling out the BPS, it's so very focused in a particular area.

TT: Yes, 5-HT_3 people talk to 5-HT_3 people.

WM: And that's all they want to hear about, rather than going around and talking other people. I don't go to the BPSs anymore, I find it is so focussed on stuff I've lost touch with anyway. I do wish they could instil that feeling of 'let's go around and look at all the posters. One of the other things I found quite frightening was I went to a BPS meeting last year, Gareth was giving a presentation. There was a whole section on pain research, and I went into this, there were about seven presentations, and about halfway through the second or third presentation I'm thinking, 'Crikey, this is what we were talking about 30 years ago!' You've got to move on; particularly with pain. I've always held that, the Holy Grail of Pharmacology is a truly broad spectrum, non-opioid analgesic. I would say this is where research should be aimed. But the stuff I heard that day, doesn't seem to have moved on. I could understand what they were saying. Now if I could understand what they were saying from stuff I'd

picked up 30 years ago and saw the same stuff coming up, then I think, 'They're not approaching it the right way.' You get so many mechanisms. 'Oh yes, here's the mechanism.'

We used to run into this problem at clinical meetings, I don't know if you ever went to those meetings? Terrific meetings. I loved the hospitality suites.

TT: Some great people used to go to those, I haven't been for years.

WM: We used to get up there this is going back about 20 years, I suppose, and you'd get a lot of the clinicians in and we were looking at IBS at the time. The clinicians would go, 'Here's a patient population of irritable bowel syndromers and they have raised levels of such and such. Therefore, such and such must be the cause.' And you're thinking, 'No, you've got correlation, you don't have causation!'

TT: Compared with somebody like say Gareth, or Pat Humphrey, although it could be said they haven't been honoured sufficiently, you sort of missed out on awards and honours.

WM: [Laughs] I've got no problem with that one at all. The reward is actually seeing the drug go into the clinic. I often look at that first paper that Gareth and I put out, the inhibition of cisplatin-induced emesis and you could come up to me and you could say, 'Look, I would give you a 100 other papers, publications for that one,' and I wouldn't trade anything for that one paper. It means that much to me. There's nothing that can reward me more than actually knowing and hearing the stories of the people, patients, who have actually benefitted from the work. Chris Davis, wrote a book on the 5-HT book and right at the end he does a quick review of history of nausea and vomiting because the whole 5-HT_3 area had stimulated the thing at that time. He goes on about how the discovery of the 5-HT_3 antagonists were made and he refers to it as 'seminal paper by Miner and Sanger' and his very last sentence is something along the line of 'for this breakthrough, for it can be justifiably called that, has in some instances meant an improvement in the quality of life and I'm sure in some cases life itself.' How can you get a better reward than that? [Laughs]

TT: Wes, thanks so much for such for giving me your time today, and for the great stories.

Figure 10: Professor Gareth Sanger

Professor Gareth Sanger BSc PhD DSc FBPhS FRSB (b. 1953) received his first two degrees in physiology from the Universities of Newcastle and Manchester (1974 and 1977), returning to Manchester to be awarded his DSc in 1998. He was a postdoctoral fellow at King's College Hospital Medical School, London, examining the functions of some of the newly discovered prostanoids on the human isolated gut. Moving to industrial research he identified 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 held various roles within the 'discovery science' arm of the business, exploring multiple research areas and new drug targets, placing several novel compounds into development. In 2008 he was elected Fellow of the BPS (FBPhS), and in 2009 joined QMUL as Professor of Neuropharmacology. He was elected Fellow of the Royal Society of Biology (FRSB) in 2013. His research focus is on using human GI tissues for translational neuropharmacology, the consequences and mechanisms of advanced age on human bowel functions and on the mechanisms of disordered gastric movements during nausea. He has published more than 150 peer-reviewed manuscripts, served on editorial boards, teaches on BSc, MSc and MBBS courses and sits on advisory boards for GI research within the pharmaceutical industry.

10 Sanger, Gareth*

Tilli Tansey: To begin with, Gareth, how did you become a scientist? Were you particularly influenced from your family or school? What did you enjoy doing as a little boy?

Gareth Sanger: I've no idea why I became a scientist. I lived in a little village called Heacham in Norfolk and as a boy I spent most of my free time on the beach with great friends swimming, fishing, throwing people off rubber dinghies, and enjoying it all. I passed the 11+ and went to the Grammar School in King's Lynn, which was about a 30- or 40-minute bus journey away. At school I always thought my best subjects were biology, history and art. I loved being on the coast, I did biology A level projects on the mussel beds and the sewerage output and how things grew, and my father helped me, getting the local tidal charts and the current flows from the local Council, where he worked. It seemed natural to try for a career in marine zoology.

It was a village life, a little isolated. Going to university I suddenly realised that I'd actually had a life that was different. The newly-discovered discos, parties and drinking were activities that all my new friends had had in their later school years, whereas I never had. So I kind of felt grateful I'd had a different life, how lucky we were to have that slightly isolated country life and then to do all the fun things associated with going to university, rather than have the same experience all of the time.

TT: You mentioned your father helping your projects. Did you have any family background of science?

GS: No, I was the first to go to university. My father was the child of a boot mender who believed in education and saved all his pennies to make sure his two sons got an education. My father originally wanted to be a woodwork teacher. Then the War happened and after serving in Europe and Asia, he realised there was no money in woodwork, so he retrained as a "sanitary" or public health

* Edited passages from the interview conducted by Professor Tilli Tansey, 8 December 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

inspector. He eventually became a Local Government Manager and looked after the whole of King's Lynn. I used to go with him in the evenings, if I was lucky, to inspect the meat at the local slaughter house. We'd go in and he'd show me where the tuberculosis was on the lungs, and I'd watch the pigs being brought in and shot. That was good fun for a kid!

TT: Did you have any particular teacher who inspired you?

GS: No, I was a very average student. By the time A levels came, I knew I had to do some "sciencey" things so I ended up doing physics. I'm terrible at maths, and with hindsight perhaps that wasn't the best choice.

TT: You did the traditional three?

GS: Biology, chemistry, physics, yes. I had a very naïve, unstructured mind at that time. I just enjoyed life and did things without really thinking. University happened because it just did. Even though I was the first to go from my family, and not everybody did those days, it was the kind of thing my friends did.

So I went to Newcastle to do zoology because they had a good marine zoology station, Cullercoats. It was liberating. I could do what I enjoyed, I could do it at my pace, which was either faster or slower. I could dig into things that were fun, I could stay in one area and dig around. I knew nothing of the word 'physiology', which was the degree I finally took. I'd never heard of 'pharmacology', I'd never heard of 'biomedicine' or any of the terms now. You had to do three subjects in your first year. You had to do physical sciences, which was for biologists. I had to do zoology and I chose physiology which I'd never heard as my third option. Zoology, I loved. It was around the time that coelacanths were rediscovered, a resurrected fossilised fish. We spent the entire year examining and classifying the entire animal kingdom; I loved it, it was great. But at the end of it, I felt that physiology was offering me a slightly harder science and a slightly more purposeful direction. My zoology tutor, Dr Panchen said, 'Whatever you choose will be right, because you'll never know what you missed,' which was some of the best advice I've ever had. So I went and did physiology.

TT: Was there any particular course or system that especially interested you?

GS: There were bits that were tough, bits that were difficult and bits that were great fun. There were good lecturers. David Horrobin I remember very well, he went on to do Evening Primrose Oil. Professor Harper was the Head of the Department of Physiology, and he wouldn't let anybody transfer to physiology if your first year option was psychology, because he regarded that as a weak

option. He retired and Eric Blair took over. They were both gastro-intestinal, GI, people, and there were a lot of the other GI scientists in the department, and that somehow must have seeped in and made me interested in the whole area.

TT: You got your degree and then you decided to do a PhD?

GS: I didn't know what to do, my mind was still open and drifting. I found this PhD position in Manchester and I thought, 'Well, I'll have that, thank you', and got it. I turned up and I often say that the only thing I learned from my supervisor was where the good pubs were in Manchester. He was Andrew Watt, who had been Hans Kosterlitz's PhD-student. A really nice chap, but taught me almost nothing. My PhD was on the effects of prostaglandins on intestinal sympathetic activity. I did a lot of tissue bath work, I did a lot of radio-labelled transmitters, all of which I picked up from different people and developed the techniques. At the end of my PhD, I knew I needed training, which is why I picked up on the enjoyment I had from papers written by a certain Alan Bennett, was then Professor of Pharmacology at KCLMedical School in London. He seemed to write in a way that didn't just record the results, but pushed the boundaries a bit and speculated on where that might lead to. My PhD was unproductive, I didn't know how to write papers, I wrote one that was rejected immediately, which I've always regretted because I think it was a good piece of work.

TT: What was it about and who rejected it?

GS: It was just radio-labelled choline release (acetylcholine release) from cholinergic nerves in guinea pig ileum. I used C^{14}-labelled choline to incubate the tissues during electrical stimulation, so it would be taken up in the right receptor pools and then measured the radio-label in fractions as it came off, having subsequently washed and stimulated. No one had done that before – in gut at least – so that was the paper, and I was quite proud of it, but then it got bounced, I think, by the *BJP*. My supervisor did nothing, didn't teach me, didn't help me, and say, 'Never mind, let's go for some other journal.' It lay fallow and nothing happened, and a few years later people at the Karolinska published the method.

So I approached Alan Bennett who said, 'Yes, I will take you on if you pass your PhD.' I then made him my external examiner, and passed, and went down to work with him. My PhD was 1977.

TT: Who was funding your post-doc?

GS: It was a mixture of money that Alan put together from various drug industries, so it wasn't a regular fellowship from SRC [Science Research Council] or MRC.

I was a bit overawed; I was only a student, well only a post-doc, but still learning how to open my mouth in public. Various people used to pop in: John Vane along with Harry Collier and Salvador Moncada, various other people whose names I don't remember would pop in and out.

TT: You were at King's?

GS: King's Hospital down on Denmark Hill. We were based in the Surgery Department at the Hospital.

TT: From your PhD in prostaglandins and then continuing to Alan Bennett's lab, you're really becoming a pharmacologist?

GS: Yes, my PhD was in a Physiology Department. I knew no pharmacology, although Andrew Watt encouraged me to do my two presentations to the BPS. I knew I needed training. Alan knew that and took me under his wing. I went through periods of time when I would come into work and sneak past his office and he would jump out at me and say, 'Define a pA_2!' And the first time I mumbled, but hadn't got a clue what it was. Eventually I learnt it and I could say, 'pA_2 is the negative log…' and so on. So I could sneak past his office without having to give the definition of a pA_2. Then I had to define pD_2, and that's how he started to teach me pharmacology. He would train me in the presentations, so if I had a ten minutes' presentation to make at a BPS meeting then to begin with we would spend a large part of the day rehearsing. So I would start, and he'd say, 'No, no, no, no, you've got to learn your first line.' I'd learn my line, then the second sentence, 'No! You cannot do that, start again.' And we'd get through about the third line, 'No, no, no! Not right. Start again.' 'No, you're waving your hands about too much, keep them to your side. Start again.' That was how I was trained.

For manuscripts, I wrote the first draft, he would then tear it apart, usually in red ink. There were no word processors, it was then given to typists to retype. When I went to Alan's memorial I was editing a manuscript that we were writing together in the lab and I was inking it, with suggested corrections. I said 'Hello' to Alan's wife and his daughter, and told them 'Look, I'm doing the same. Here

is a manuscript and I've got red ink all over it, just like your dad did to me.' And they laughed and his daughters said, 'Oh yes, he used to do that to our homework as well.' [Laughter].

But, anyway, being in the Surgery Department, Alan Bennett used human tissue. That's where I was introduced to it. The then Head of Surgery was Mr Murrey. He helped to pioneer vagotomy surgery for treatment of ulcer. I've still got some of his papers. Also popping in and out was a guy who worked with Hans Kosterlitz.

TT: John Hughes?

GS: Yes, he was a post-doc there before my time. Anyway, we worked in the Surgery Department and got human tissue without consent or anything in those days.

TT: It was very different then.

GS: Yes. We used human gut, human uterus and other tissues. It was standard practice, coming into work, to swing by the theatre list, and see if there was anything to collect that day.

TT: What was the main focus of your project?

GS: The different prostanoids were being discovered, prostacyclin, 6-keto-$PGF_1\alpha$, leukotrienes, they were all new. I spent a lot of time just dropping them on human gut to see what they did, because no one knew. We started doing the same in human myometrium as well, and then we linked up with a guy who could do mass spectrometry and we published a couple of good papers on that. We published quite a bit.

TT: It sounds as if almost everything you did turned into a paper at that time.

GS: Absolutely, yes. But it was characterisation of the new prostanoids that were being discovered by the minute at the time; that was mostly what we did.

TT: Towards the end of your three year post-doc, did you deliberately think about going into the drug industry?

GS: Yes. I didn't know what to do and had no idea what an academic life would be, and met somebody who said, 'It's better in industry, because you haven't got to spend all your time applying for money.' Alan talked to John Flack who was then Director of one of the sites of Beecham Pharmaceuticals. He interviewed me and gave me a job in the GI therapeutic area.

TT: Which Beechams site were you on? And what was your project?

GS: I was at the Harlow site. I was almost literally shown a desk in a small room that was a lab. They cleared out a bit of space for me and found a table and a chair and I can't remember the words exactly, but it was something like, 'Find something to do.' I spent quite a lot of time writing up my old papers, reading new papers, trying to think of experiments to do. Some worked, some of them quite complex, and some led to a good direction of research.

TT: You were in GI, there must have been some indication what sort of things you were looking at?

GS: The area of GI I was in was tasked with finding a better metoclopramide, that retained its beneficial activity, but without the extra pyramidal side effects. What I ended up doing was trying to understand how metoclopramide worked.

TT: You were very, very fortunate having that freedom. It must have been quite daunting at the time.

GS: At the time. But with hindsight, what a gift, yes. I gravitated to thinking, 'How does metoclopramide work?' I'd worked out that it stimulates gut movement, and so it would involve nerves in some way. I'd picked up a technique from my time in Alan Bennett's on how to stimulate nerves; what I wanted was a stimulator that gave me biphasic square wave pulses, so they built one for me. Great! So I stimulated the nerves in rat stomach. Rat stomach, because metoclopramide was meant to be a stimulant of stomach emptying, and with hindsight I have lived with that technique almost all my life, and I think I actually changed how GI biology *in vitro* has been done. It's very simple for people to take a bit of gut out, put it in the tissue bath and throw something at it and stand back and look. It's still done by, dare I say it, molecular biologists who really have no idea of the physiology, and will drop it on and say, 'Oh, it does something.' I've got examples that make me cross even now. That's been with me all the time, and it's not novel – far from it – but it's been a very important tool and continues to be. When I arrived at Beecham it was normal to do tissue bath work with one tissue bath. I was used to working with Alan who dictated that you would use four at the very minimum, and if you could grab somebody else's kit when you had valuable human tissue, then you did eight, and that was hard work. But four at least. So I came in and set four up and I remember people coming, 'You can't do that, it's not possible.' Now people who work with me, standard, you do eight. And if you've got available tissue, you do 16.

Anyway, I found responses to metoclopramide that made sense. I worked out that the only thing that mimicked it was 5-HT, and there were certain hints in the literature that suggested that was a good direction to go. I couldn't block it, I couldn't modify it, I talked to chemists and after getting permission, I ended up probably with the world's first 5-HT_4 receptor antagonist, but didn't know it was 5-HT_4.

TT: What date would that have been?

GS: In the 1980s. But the whole focus of the Department was to get rid of the CNS dopamine effect of metoclopramide. By default it produced molecules that still stimulated gut movements, but the dogma at the time was that this was still mediated by dopamine receptors. There was a CNS department next door that were trying to produce CNS-active dopamine D_2 antagonists. Eventually, I was able to show that firstly, dopamine wasn't involved in this GI action. There was a lot going on at the time, but basically by doing this work what I was doing was overcoming the dogma of the time. It caused a lot of difficulty which was quite fractious at the time, quite difficult. It wasn't popular: basically, saying dopamine was not the mechanism.

TT: How did your bosses at Beechams take this?

GS: I think I was a slightly bad boy. I remember getting a bad pay rise because it was deemed I couldn't get on with everybody. In those days, inflation was about 20%, so just to keep up with inflation you got a ridiculous pay rise. About two years later I became Head of the Department, so it was a very strange environment; topsy-turvy. I had to turn it around. I thought it was 5-HT, so I was testing drugs like methysergide that would block, but I didn't know why. I found my own molecules that would block, but I didn't know what to do with them. I started proposing that we had to go for these, because they might be a good therapeutics and we did run a programme in the end and found, many years later, good 5-HT_4 receptor antagonists.

TT: There was much doubt at the time about 5-HT as a neurotransmitter.

GS: There was. There was a group within Beechams who at the time were working on a drug that had just been in-licensed called "paroxetine". The SSRI that became the world-wide success known as Paxil, for treatment of depression! No one quite believed in it then. So there was no real 5-HT interest, there was no real basic research and certainly no drive to work on 5-HT within Beecham at the time.

TT: I don't think that was unusual. I think that's why there was a group of believers, and you all suddenly found each other.

GS: Yes. I was aware of the 5-HT_M receptor, subsequently called 5-HT_3. I wrote to John Fozard at Merrill Dow in France: 'Could I get a sample of your molecule MDL72222 to test?' I tried to block metoclopramide with that and I couldn't, yet I could block other things with it. By reading the literature, I finally figured out that metoclopramide could stimulate gut movements through this mechanism that I'd uncovered, now known as 5-HT_4, and I could see that it also antagonised 5-HT_3.

Wes (Miner) would be in the corner working with his little ferrets, trying to use dopamine receptor antagonists to block the severe form of vomiting caused by the anti-cancer drug cisplatin – but not successfully. I asked him to test the compound now known as renzapride and it blocked. This did not block the dopamine receptor, but it did stimulate GM. I asked Wes to test renzapride because by then I knew it would also block the actions of 5-HT at the 5-$HT_{M/3}$ receptor. This would have been in the early 1980s. All of a sudden the penny drops. I went back to Wes and said, 'I know how this works, will you test this?' I gave him a sample of the selective 5-HT_3 receptor antagonist MDL72222. It worked, and suddenly we had the whole thing.

TT: I think suddenly 'having the whole thing' is a bit glib, isn't it? You'd spent a lot of time thinking this through.

GS: Yes, I did. I knew the literature. Those of us who have got one or two grey hairs now, including Paul Andrews, sometimes do the old war horse stuff, 'Why don't the younger people know the literature? Why don't they write papers?' We've speculated that in those days you had your little card index file – I see you've got one on your shelf. You had little notes on everything. Now, it's not so necessary, you just go into PubMed, get out what you want, as I do. I wonder if that has had some impact on not really knowing the literature, I knew every paper at the time. Metoclopramide had been linked to 5-HT, and I had every reference in which it had been tested using isolated gut. I knew all the good and the bad, I knew it all. I was moving to 5-HT, but my pharmacology wasn't good enough to do the receptor blocking experiments David Clarke subsequently did in order to prove that the ability of metoclopramide and renzapride to stimulate intestinal motility was because it could activate the newly-characterised 5-HT_4 receptor.

However, before this definition I was doing an experiment in the lab, and I got a phone call, a man with a very thick French accent. It was Joel Bockaert who said 'We found your receptor. We've done mouse collicular neurons, we've found it in the CNS.' I went, 'Wow! Really?' And that became 5-HT_4.

TT: You'd obviously been publishing your ideas – were there any constraints on publishing?

GS: I was allowed to publish, most of it anyway. Because I was overturning the dogma within the Department, I would sometimes come out of a meeting thoroughly pissed off, so I invented a behaviour which I've subsequently had to use. Sometimes the only way to get people to believe you is to publish: 'My boss won't believe me so I'm going to get my peers to believe me.' So yes, it caught the attention of Joel Bockaert who had read my papers and replicated and extended the data in his model. That's when he phoned me up and said, 'We've just found your receptor, but in the brain.'

TT: How did you know him? Through the Serotonin Club, or Pharm Soc?

GS: I didn't. I'd never heard of him before. 5-HT hadn't really broken through yet, so I don't think there was a Serotonin Club then. I didn't know Joel at all, and he phoned me up – which was lovely of him – to say that he'd just replicated my data, but in the brain. And then he named it 5-HT_4.

TT: That's even more astonishing.

GS: I was in the middle of an experiment at the time and I just said, 'Stunning, thank you! Can you send me the paper?'

TT: So you had a receptor and you had a name for it. What did your bosses at Beechams think about that?

GS: At that time, I was also doing 5-HT_3, which was even more contentious because I really was now unashamedly overturning the dopamine dogma. I would be so fed up I would go in to meetings and say, 'Well, here's the molecules you wanted me to test, here's the data. Right, now I want to talk about this.' We'd go off on some tangent and it would upset everybody, because I was never keeping to the agenda. I understand that, but in my non-politically trained youth, that was what I did.

TT: But you were clearly tolerated. They didn't sack you.

GS: Well, they downgraded my pay rise once. But I would go in and they still wouldn't believe this stuff. I was then onto 5-HT_3, and I remember working out a marketing size by figuring out how many cancer patients there were, how many got treated, how many would therefore receive an anti-emetic, and I presented this to try and turn it around and say, 'Look, this is worth doing. Forget the science, surely this has to be worth some money. The then Director of Research told me something like, 'How dare you present this when we've got salesmen out there in the North of England trying to sell bloody Lucozade to people who can't afford it, just to pay your salary so you can deliver this crap.' We had our programmes, we knew what we wanted, but the company didn't want that, thank you very much.

TT: It's quite astonishing to think that you were allowed to continue. Did you have an advocate at a higher level or were you just so far out, it was a case of 'Okay, let's just see what he comes up with'?

GS: It wasn't the days when they just hired and fired. And they weren't lean and mean in terms of staff. It was clear that I was a bit unusual, in the sense that I was trying to change things. The story developed further. We had a new Clinical Director: Garth Rapaport came in, and I started talking with him, and said, 'This is what we've got.' Garth was a clinician and he must have treated these patients, and he went to Keith Mansford – Chairman of R&D at Beechams – and Keith said, 'We want this,' and it all changed. Then I was flavour of the month.

TT: What was your precise role at the time?

GS: We were in self-contained Therapeutic Groups with chemistry, biochemistry, pharmacology and *in vivo* biology. About 30 to 40 people but mostly chemists, and I knew no chemistry so I relied on the Head of Chemistry there. We prosecuted the 5-HT_3 receptor, we went back to 5-HT_4 and developed antagonists. Then we decided we didn't want an agonist. It didn't all pan out, and certain other programmes of work were started, which in the normal way of things, didn't work.

TT: That must be part of just a normal cycle: evolution, continuity, change.

GS: Yes, absolutely. Most ideas in industry don't work. Then we merged with Smith, Kline & French and I ran the team that was trying to put the GI interest together, so I was backwards and forwards on an aeroplane trying to put that together. Great experience, but I probably wasn't ready for it.

TT: Can you say a little bit more about this merger: you're becoming more of a manager rather than a hands on person? How did you feel about that?

GS: Very strange. Almost emotional handing my experimental rig over – it took a little while to learn how to enjoy science through other people. I got to the stage where I was getting bored with it and wanted something bigger.

TT: Bigger in terms of management or science or both?

GS: I wanted something more stimulating; something bigger and better, and I was getting interested in the next level. That was never going to happen, because we merged with Smith, Kline & French. My opposite number was Mike Parsons, so we became equal partners. I was charged with putting everything together in the GI section, into the new SB.

TT: You were doing motility, and Mike secretion?

GS: Yes, I was in charge of the motility. Mike was in charge of the secretion side. There had to be some strategic plan to say what we were going to do in the whole GI area for this new company SB. In the first several months' loads of us were flying backwards and forwards presenting plans, getting it all ready to get these companies together. I was running the merger team that put all GI together for the new company.

TT: What kind of constraints or brief did you have for that? The whole SWOT analysis?

GS: Yes, all that stuff. It was finding what have we had, what are they aiming for, is it worth continuing it or killing it, what opportunities have we got tucked away? W gathered all the opportunities, put them together, and presented what they were, what the likelihood for success was, what the marketing opportunities were, could we do it, or couldn't we? What should die, what should live? All merger activities were ultimately in the presence of McKinseys, the management consultants, who were in my view absolute rubbish. I went through many of those meetings where, effectively, we ended up telling them what we'd do, so what was the point?

TT: This is very different from your life as a research scientist.

GS: Yes, I probably wasn't ready for it but it was good experience. I did all that and then settled down with Mike and myself running GI until the next therapeutic area review when GI was killed, Mike was paid off with a lot of money to go and work at the University of Hertfordshire, and I ended up in neuroscience.

TT: On your CV there's this very interesting expression, '…following a business-related withdrawal from GI research.' Is that a standard expression?

GS: Yes, it is. I went for a job interview at the time, wanting to get out, and with hindsight it was obvious, but the first thing they said, 'You've got this gap in your CV, explain it. Why have you suddenly switched?' So I thought, 'Yes, you're right'. So GI was killed, and it was my first experience of redundancy. I now know what it's like to experience 'survivor's guilt'; most of my team were made redundant. There were tears and it was a terrible day. I stayed behind in the lab unable to confront them, even though it wasn't my choice. Then I just stormed into the general meeting absolutely furious, and I sat down and listened to this crap that I was now being given. Anyway, I survived, but clearly I wasn't running things anymore, because I didn't know any neuroscience. I ended up in a group which ended up going outside, getting external money from Europe, a Framework [Programme] 4 [FP4] collaboration, to stitch together a consortium of people studying the role of long-term potentiation in cognition. We got a lot of money and didn't produce a damn thing in terms of drugs, but that's what you had to do at the time.

TT: This was the mid-to-late 1990s. Were you tempted to leave?

GS: Yes, I did go for different interviews but I was swimming against the world tide; GI wasn't popular. I slogged it out. I set up other collaborations in neuropathic pain, got money for that, got external money for long-term depression and potentiation, but I was drowning definitely, definitely.

TT: How usual was getting external money in your company?

GS: It was unusual, but it was the way the company wanted to go. The human genome had been discovered, nobody knew anything about it, and you just had to start collaborating and getting external money to try and exploit the new knowledge. When I got the FP4 grant it was touted as a big success, because I'd just effectively added something like ten full-time employees to the company's payroll, and XX million pounds, or whatever it was, into the company research.

TT: You had a gun to your head. Can you reflect a little on the challenges of being forced out of GI into CNS?

GS: I was drowning, and it was hard.

TT: Are there advantages coming from a different field – do you see things differently? You've already talked about overturning the dopamine dogma, you've fought against the tide a lot already.

GS: Yes. I talked to Pat Humphrey a little while after that, when he'd left Glaxo for Cambridge. I was surprised to hear him voice my experience, which was fear that you were going to screw things up, because you'd been shifted from an area in which you were effectively a world leader, into another area you didn't know. It was really having the rug pulled out from under your feet. It was real fear that you couldn't do it anymore. I was surprised to hear him say that, because I thought he'd kind of gone into the same thing, but it was real fear that you couldn't hack it.

TT: And that was the same for you?

GS: Yes, absolutely, and for Pat to say exactly the same words, surprised me. So real fear. I didn't know how I could hack this having come from effectively being a world expert in one area to being a child among world experts in a different area. How do I survive and conduct myself?

TT: How did you get the ideas, the confidence, to pick up the long-term potentiation (LTP) stuff?

GS: I went and talked to Tim Bliss at Mill Hill. We spotted the opportunity to get European money. Tim got all his friends together and I brought the industrial bit in, and we came up with a consortium and got the money.

TT: Did that make you feel more confident within the company?

GS: Yes, I suppose so, but I was still in an area that I knew nothing or very little about. So kind of disembodied from it all really, you're a manager. It wasn't my science; I was doing the coordinating managing job then. I tried to get involved but you can't compete with people who have done their PhDs and post-docs in the same area. What can you bring? Not a lot. So you have to just try and find ways of coordinating it, take the money and go home.

TT: And not get too frustrated? For seven, eight years?

GS: Yes, and then we merged again and became GSK, and Tachii Yamada took over as Head of R&D, and he was a big GI man. So GI came back again. I got back into GI. Not to run it, it was deemed they wanted fresh blood. Somebody was recruited who was utterly, utterly abysmal; just awful, awful.

In the end, I wrote my personal appraisal 'I think I've had a good year, I've achieved it against difficult odds, in the face of opposition, without any support and indeed hindrance from my line management.' You don't normally write that type of thing if you value your job. I included examples where I was about to start a programme, which subsequently went all the way to Phase 2B. I was about to go on and propose this whole programme of work. Five minutes before my meeting, my manager comes into my office and says, 'You've got to cancel. We're not ready. You can't do this.' I said, 'I'm sorry, I'm going to do this,' went in and it was accepted. We ended up with the longest surviving molecule from that group. By that time I thought, 'I'm just going to go back to science, publish and enjoy,' which is what I've done ever since. About two years before I left, GI was killed again and I went into immuno-inflammation. By which time I'd given up.

TT: This would be about 2000?

GS: Something like that. I just thought, 'Right. I've got children to support. I'm just going to put my head down and do a job, and I'm going to publish and enjoy myself as a scientist and do whatever they want, but I'm going to enjoy the science bit.' I've done that ever since. It was a way of doing the job in a good way. By then I knew the business.

TT: This is when you finally left? The MRC Skills Gap Award.

GS: Yes. Jackie Hunter told me about a grant opportunity which was joint MRC and BBSRC, which I applied for and I got two years' salary.

TT: This was for you to fulfil a gap in an existing programme?

GS: Yes, a gap in university skills, which from industry I had certain skills and I could move those over to university and grow and develop things.

TT: Why did you choose QMUL?

GS: There were no other GI Units within commuting distance, so I didn't have to move home as well; it was an obvious place to have a go. I had a clear mission to set my own lab up. I had no authority for anybody else. Once again I was given a room that was not fit for purpose. My first task was to clear all the junk

out, so I dumped it in another unused room. I wasn't liked, but it was fine. I went back to my primary skills from a long time ago, which was functional translation. Only now I was using different words to describe the same job.

TT: This goes back to your King's College days?

GS: Yes. I'd done human in my post-doc. When I went to Beechams, I started doing human which set a slight precedent, and other people started using human tissues. And in my industrial career, it was important to establish confidence that your drug would translate to humans, so I would contract work out. I always did human tissue work a little bit.

TT: To the general public at least, that's what drug companies should be working with.

GS: Yes. You have to translate to human. I've got a history of this, and that was the skills gap that I tried to fill. It didn't really matter what you did within that, but that was the gap.

TT: Which you've continued since then. You've had some very impressive honours. Which do you value the most, or has given you most satisfaction?

GS: At the time 5-HT_3 came out and was being worked on, there was an economic depression, and I didn't really see the patients. What I saw was the numbers of jobs I'd created. So what I, at that time, was most proud of, was the fact that I'd created quite a lot of skilled jobs, and I was really proud of that in the middle of a depression. So that was a feeling I strongly had: I felt proud I'd created jobs.

I would have loved to have had some recognition from the cancer community, because I think we changed the whole landscape. I've had personal experience, when my late partner was dying with cancer, I was able to get the right anti-emetic medication for her. It was an emotional experience for different reasons. Sitting in the outpatient treatment ward, watching the chemo going online, but it was a family ward. And one of the nurses came up and offered her a sandwich. There were children coming in and there were several people there, and you just laid back under treatment and took your medicine and ate a sandwich. Our work helped make that possible.

I was just thinking of another story based on 5-HT_3 and anti-emetics. I was asked by Robert Twycross of Oxford Palliative Medicine, to give a talk at one of his hospice care meetings. It was a round table workshop and I went in, there's a

talk going on and I sat at the back. As it progressed I realised these guys had no idea of what to do. I then became quite noisy and said, 'No, no, no, you can't do that! Why not use this drug?' Robert was great, explaining the realities patiently: 'These people cannot take oral medications, Gareth. We have to give it by, intravenously.' So, suddenly, I realised that I was in a different clinical world – palliative medicine – but I was still appalled at the level of ignorance. So I made a big fuss and I kept getting invited back. For many years I would give lectures at the hospice down at south London. Eventually, that became outdated and I don't do any of that now, because they have caught up. I thoroughly enjoyed it; the people there were lovely people. Very caring, very gentle. All of them, all of the clinicians, and that was an eye opener.

TT: As a drug discoverer and developer, given the kind of career you've had, do you feel possessive about the molecules? Are they your children in some way?

GS: Yes, I had to hand over granisetron. It was deemed I was a good drug discoverer and it would be a waste to keep me linked to the molecule for its development.

TT: I want to ask you about the role of scientific societies like the Pharm Soc. How important have they been in your career?

GS: Pharm Soc in particular, going back to Alan Bennett, who taught me how to present and that discipline of getting it all in within ten minutes. The Pharm Soc when I joined was a place of really good science. You were questioned on your science. The abstracts you submitted had to be changed according to the questions. At the end of the session, the Chair of the session asked all the Members to vote on whether they wanted to accept it or not, and some weren't. It was hard, it was scary, but serious training. I then was lucky enough to get into the 5-HT area, and the basic discovery of science came largely from industry. And a lot of that activity took place at the Pharm Soc. It was a serious hotbed to be at, and you had to be there. I have mostly worked in GI research and I never attended the GI meetings, like the British Gastroenterology Society and Digestive Diseases Week and others. I never attended them because I didn't see the kind of science there that I wanted to do; the new ideas, the discoveries. So I always attended the BPS for the buzz of discovery, the discussion that you could learn from, the ability to rub shoulders with the great and the good, and do things. As years have gone by, I think the BPS has dropped off as the molecular and therapeutic areas have ascended. That's been good in many ways, and molecular certainly had to ascend, but there's also been a loss of that core

understanding of the basic discipline. Obviously in the industry there are times when, for your job, you have to go to the GI meetings, and I used to go. Now I'm back in academia, I've been to some of them and realise I don't get anything out of them. I always go to the annual BPS meeting, and it's lovely to see old colleagues, it's good to be there, talk science, etc. But it's not as demanding as it used to be. It's not as creative as I knew it. And that leaves me with a dilemma. I don't know where my scientific home is anymore. Yes to pharmacology always, but where do I go to get maximum benefit now? It's not to the therapeutic areas, you only go there if you've got a drug and you want to sell something to a clinician. Where do I go now? I'm not sure.

TT: I know lots of homeless pharmacologists, physiologists, biochemists, all wandering around. Were you at the famous BPS meeting at Birmingham when Philip Bradley organised a 5-HT meeting?

GS: I was doing a lot of work on 5-HT, but to begin with, wasn't part of the club. I became part of it, but I wasn't initially.

TT: An important part of academic life is work on editing and advisory committees; you did an awful lot of these whilst you were still in industry. Was that quite well accepted?

GS: I don't know; I just did it. I don't think the powers that be in industry were aware I did it, or cared, as long as I did my job. Now you'd probably have to have it as a metric somewhere, then no-one really cared as long as you did your job. The first time I was asked, I was absolutely flattered. It was, for me, an achievement to edit the *BJP*; I did that for seven years. Eventually, I was asked to do it again, by which time I was getting a bit jaded with it. Also with the career changes in industry, I just couldn't keep it up. At times I had to dedicate myself to just surviving, so I dropped some of those things. I know there was discussion about inviting me back for the third time, and I winced when I heard it. It hasn't happened, so it's fine and I'm not editing at all. I kind of think that I did my bit. I was asked to start *Frontiers in Pharmacology (Gastrointestinal and Hepatic Pharmacology)* off, and I did. Then my partner died and I just, emotionally, couldn't do it anymore, so I gave up.

TT: One final question. In describing creativity, Pasteur said that 'fortune favours the prepared mind'. Is your creativity like thinking outside the box, or thinking a little bit further ahead than the box almost? You said you were good at art at school. When you're thinking about molecules and receptors, do you have a visualisation of them?

GS: I think I probably collect bits of information and then synthesize that into a story. I've got those bits of information in my head. They've got to connect somehow. What's the story? I probably do that. A bit of a collector, I think.

TT: Did you have a favourite toy as a child?

GS: A favourite toy as a child? [Laughs]. I was into jigsaws, which I loved. My father made me a little jigsaw board, and off I went. I always loved jigsaws – I still do, but it's not something I do. But when I'm ancient and bedridden, perhaps. How would I start doing a jigsaw? It would be sorting all the pieces out, collecting, organising and synthesizing. My mother gave me a jigsaw, which I didn't do for a long time, of an apple, a red apple, so it was about 80% red. There's another jigsaw even worse than that that she gave me too. That you can't do by vision. Well, you can't do it by colour vision, you do it by shape vision.

TT: Seeing patterns. That's almost what you do with drugs and receptors.

GS: It is that, yes.

TT: At that happy juncture, I think we have to stop. Thank you so much for your time Gareth.

Related resources

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Names in **bold** refer to interviewees

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