

MIGRAINE: DIAGNOSIS, TREATMENT AND UNDERSTANDING c.1960–2010

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary, University of London, on 28 May 2013

Edited by C Overy and E M Tansey

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WHAT IS A WITNESS SEMINAR?

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

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

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

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

¹ See pages 137–142 for a full list of Witness Seminars held, details of the published volumes and other related publications.

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

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

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

² See our Group’s website at <http://www.history.qmul.ac.uk/research/modbiomed> (visited 8 April 2014).

ACKNOWLEDGEMENTS

The topic of 'Migraine: Diagnosis, treatment and understanding c.1960–2010' follows on from a Witness Seminar held in December 2012 on 'Drugs affecting 5-HT systems'. We are very grateful to Dr Mark Weatherall for his help in the planning of this meeting and for his excellent chairing of the occasion. We also thank Dr Giles Elrington for writing the introduction to the volume, and Dr Patrick Humphrey and Dr Alec Oxford for providing images and documents to illustrate the proceedings. Our gratitude also goes to the Wellcome Library, London, for permission to use photographs from the meeting.

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

Tilli Tansey

Caroline Overy

School of History, Queen Mary, University of London

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ABBREVIATIONS AND ANCILLARY GUIDES

| | |
|--------------|---|
| 5-HT | 5-hydroxytryptamine |
| BASH | British Association for the Study of Headache |
| CGRP | Calcitonin gene related peptide |
| fMRI | Functional magnetic resonance imaging |
| IHS | International Headache Society |
| MR | Magnetic resonance |
| NGF | Nerve growth factor |
| NICE | National Institute for Health and Care Excellence |
| NIH | National Institutes of Health |
| NIHR | National Institute for Health Research |
| NSAID | Non-steroidal anti-inflammatory drug |
| PET | Positron emission tomography |

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

The DrugBank database

www.drugbank.ca/ (visited 8 April 2014)

Medicines Information from NICE

www.evidence.nhs.uk/about-evidence-services/content-and-sources/medicines-information (visited 8 April 2014)

The PubChem project

<http://pubchem.ncbi.nlm.nih.gov/> (visited 8 April 2014)

The IUPHAR/ BPS Guide to Pharmacology

www.guidetopharmacology.org/ (visited 8 April 2014)

Glossary of Terms and Symbols Used in Pharmacology (Boston University School of Medicine: Pharmacology and Experimental Therapeutics)

www.bumc.bu.edu/busm-pm/academics/resources/glossary (visited 8 April 2014)

INTRODUCTION

Fifty years of migraine

My first memory of migraine is from the 1970s. My childhood friend's mother would simply disappear for a couple of days at a time, and I was told this was because she had migraine. I wondered what on earth could do this to a person. But attempts at treatment came before understanding when as a newly qualified doctor in 1981, I saw a young woman with migraine who had quite a taste for chocolate and the treatment seemed so obvious to me. Later I learned that pizotifen could be used and as this was the only treatment I knew, other than analgesia, I was stumped when a patient had already tried pizotifen. CT scans were new then and offered a way of appearing to do something, though now simply imaging the patient is a strategy I disparage. Around that time, a leaflet from the City of London Migraine Clinic advised regular naproxen in place of as-required frequent analgesia, a strategy I still use. As a neurology registrar in the early 1980s I recall a patient who appeared to be describing a condition I'd only ever read about: cluster headache. I asked my boss who told me he had never seen a case! The next decade brought two great advances: firstly attending the International Headache Society Meeting and beginning to understand Medication Overuse Headache; secondly, triptans were discovered and licensed. Suddenly we had a specific and highly effective acute rescue, and prophylaxis seemed very out of date. I had written my thesis on a rare disorder of neuromuscular transmission (the Lambert Eaton Myasthenic Syndrome) and then realised I needed to be expert in a common disease, so chose headache as my sub-specialty. To my great surprise, in the last couple of years, the use of Botox as prophylaxis for chronic migraine has brought me back to synaptic transmission, in the context of headache. Moving forward, triptans are coming off patent and it is increasingly clear that their overuse is as harmful as overuse of any other short-term rescue medication. The new therapies now are devices to alter nerve function in the head. If we can find a device that aborts headache, will overuse bring the same difficulties of rebound and tolerance, as with medications? We have treatment, but do we have understanding?

The concept of 'hemicrania', that is half head pain, gives us the word migraine; yet nowadays we have a separate group of disorders in which a pure hemicrania, such as cluster headache, is considered by most to be separate from migraine.

Can we now be sure whether migraine is one disease or many? If we start from a position of existing knowledge and travel a line of enquiry in migraine, we tend to return to the starting point, but facing in a different direction.

Over the last half-century the genesis of migraine knowledge and therapeutics is a microcosm of medicine. In 1960 the leading academic neurology unit in the UK would study disorders only of the peripheral nervous system, because only when those could be understood, can one move to a more complex area such as the central nervous system.¹ Then, migraine was a psychoneurotic disorder with predisposition arising from lack of a Y chromosome. Establishment of migraine as an organic disorder arose from understanding migraine aura. Thereafter it becomes clear that the absence of aura does not deny the organic nature of the disease. Once we are sure that migraine is ‘real’, it becomes worthy of scientific study.

Next, we need a definition. In the absence of a verifiable organic substrate that can be demonstrated independently of history (examination and investigation being normal), definition is operational rather than pathological. Meaningful definition is the essential prerequisite for scientific study. Therefore the classification of migraine and of other headache disorders has been the catalyst for the therapeutic advances in migraine over the last 50 years.² This Witness Seminar shows how in fact these moved hand-in-hand, rather than stepwise, with the development of specific effective migraine therapeutics.

The location of migraine’s molecular pathology has had a long journey around the body – in blood platelets, female pelvic organs, lung, heart, neck, immune system, psyche, arteries, or nerves. The strong consensus is now that migraine is a disorder of the nerves; within the central nervous system. That’s agreed, but where, within the central nervous system? The strongest contender is the trigeminal nucleus in the brainstem, though there remains a school of thought that the cerebral cortex contains the underlying migraine generator.

Migraine is a disorder of the central nervous system, and relates closely to under-activity of the neurotransmitter 5-HT (serotonin).³ The development of 5-HT agonists, that is triptan drugs, has revolutionized the management of migraine.⁴

¹ ie the Institute of Neurology, Queen Square.

² For discussion on the classification of headaches, see pages 11–15.

³ For consistency the term ‘5-HT’ has been used throughout and in most cases the term ‘serotonin’ has been changed to 5-HT.

⁴ See pages 33–8 and 42–5.

The specificity of triptans for migraine therapy provides support for the headache classification, because triptan response is highly specific for migraine compared with other headaches. Just don't mention the fact that cluster headache, one of the hemicranias, responds very well to triptans, as does tension type headache (in people who also have migraine). But the classification tells us that cluster and tension type headache are different disorders from migraine; or could it be that migraine is in fact a spectrum disorder, rather than a single illness, in which a person with the underlying predisposition to migraine is vulnerable also to other types of headache? Still, we have a unifying hypothesis: 5-HT deficiency. Yet the cause of that deficiency remains elusive, appearing to result from a range of genetic triggers that may act through ion channel dysfunction. And are we sure that this is truly a disorder of the central nervous system and not the peripheral nervous system?

The advances of the last half-century have led to many effective therapies, the very large majority being 5-HT drugs.⁵ This Witness Seminar describes how the older agents, nowadays considered by many to be archaic, actually work quite well but the key point was being very careful in how to use these agents correctly. Current migraine practitioners still struggle with encouraging patients to use the new drugs at the right time and at the right dose. We hear from those active in the field decades ago, about the difficulties of delivering drugs through the stomach at a time of migraine-related gastric stasis. As triptans go off patent and over-the-counter migraine treatment moves away from systemic oral medications towards 'treating the head', so we start to think about Botox injections in and around the head which may provide the same step change in therapy for the current decade, as triptans did 20 years ago. The consensus view appears to be that Botox is a treatment for peripheral, not central, nociceptors.⁶

Fifty years of science has established migraine as an organic disease of the nervous system. Those who have achieved this can agree about much, but not about everything. To the outsider, much of what has been achieved might seem obvious. Trying to define migraine is like trying to define a dog: it's so obvious when you see it, do you really need a definition? But once the definition is agreed, can we be sure it is not self-fulfilling? Do we really know that the migraine definition has excluded wolves and foxes that corrupt the purity of the concept? Having established a hard-core of patients whom all experts would

⁵ For further discussion on 5-HT drugs, see the Witness Seminar 'Drugs affecting 5-HT systems', (Overy and Tansey (eds) (2013)).

⁶ For discussions on the use of Botox, see pages 48 and 57.

agree have migraine, we see that these patients have a range of other sorts of headache, including tension type headache and primary stabbing headache, which by definition are different from migraine. The Witness Seminar draws appropriate attention to the great advances in therapeutics of migraine, and to the key importance of treatment specificity. Yet what has become clear in recent years, as we swing from enthusiasm for acute rescue away from prophylaxis, and then back again, is that the biggest problem with migraine treatment is that frequent use of short-term medications tends to make migraine attacks occur more often. Arguably the key biological difference between migraine and the hemicranias, including cluster headache, is that the former are worsened by frequent medication, whereas the latter are not.

This Witness Seminar takes us through half a century of clinical science and therapeutics that have beyond doubt changed the lives of many people for the better; though there have been steps both forwards and backwards, there are fortunately more of the former. We hear from those who were there at the start, and others who joined later, enthusiastic to take further forward both knowledge and palliation. Those of us who aspire to stand on the shoulders of giants should try to do so without causing too many headaches.



Figure A: Dr Giles Elrington

MIGRAINE: DIAGNOSIS, TREATMENT AND UNDERSTANDING c.1960–2010

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Edited by C Overy and E M Tansey

MIGRAINE: DIAGNOSIS, TREATMENT AND UNDERSTANDING c.1960–2010

Participants*

| | |
|--------------------------|----------------------------|
| Dr Jeffrey Aronson | Dr Alec Oxford |
| Mrs Mary Ayres | Dr Richard Peatfield |
| Dr Tom Blackburn | Mrs Vicky Quarshie |
| Dr Katherine Foxhall | Professor Merton Sandler |
| Dr Patrick Humphrey | Professor Pramod Saxena |
| Professor Brian Hurwitz | Professor Tilli Tansey |
| Professor Trevor Jones | Mrs Wendy Thomas |
| Professor Anne MacGregor | Dr Glyn Volans |
| Dr Michael O'Brien | Dr Mark Weatherall (Chair) |
| Professor Jes Olesen | |

Also present: Professor Inger Olesen

Apologies include: Professor Paul Andrews, Dr Helen Connor, Dr Desmond Carroll, Dr Giles Elrington, Dr Wasyl Feniuk, Professor Gavin Giovannoni, Dr Peter Goadsby, Professor Jim Lance, Dr Graeme Martin, Dr Aarno Palotie, Dr John Pearce, Dr Tim Steiner, Dr Malcolm Thomas, Lord Walton

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



Figure 1: Dr Mark Weatherall and Professor Tilli Tansey

Professor Tilli Tansey: Welcome everyone to this Witness Seminar on migraine over the past 40 or 50 years. Let me begin by telling you what a Witness Seminar is although I know there are quite a few people who have been to previous meetings. What we hope to do at these meetings is to get stories from those of you who were there at the time, about what happened or perhaps sometimes what didn't happen, who the supporters were, what the drivers were, what the brakes were in the process of improvements in treatment, diagnosis, and understanding of migraine. Everyone is free to contribute as and when they feel able to. We record the meetings and then we publish them with suitable footnotes and bibliographies. You will be asked to assign copyright to the Wellcome Trust but nothing you say will be published without your permission. This meeting on migraine came about largely because we had a meeting on drugs affecting 5-HT systems a few months ago.¹ That in itself had come about because we'd had a meeting on platinum compounds in chemotherapy, which finished off with the development of the 5-HT receptor antagonists.² We had so much on 5-HT and the different drugs affecting 5-HT systems that we didn't have the proper place or time to develop the story of the triptans or to put that development into the wider context of clinical, especially neurological, research. So we hope to correct that deficiency today. As with any of our meetings it depends a great deal on who will attend and our chairman. We're delighted that you've all accepted our invitation and particularly pleased that Mark Weatherall has accepted the invitation to chair this meeting. I'm sure most of you know Mark, he's a Consultant Neurologist at

¹ Overy and Tansey (eds) (2013).

² Christie and Tansey (eds) (2007).

Charing Cross. What many of you may not know is he's also a medical historian (see Appendix 1); he intercalated to do a BSc and then a PhD in the history of medicine when he was a medical student at Cambridge so he's doubly qualified and very welcome to chair this meeting. Thank you very much Mark.

Dr Mark Weatherall: Thank you very much, Tilli, and a very belated thank you for being so kind to me in my PhD viva all those years ago. [Laughter] So, yes, it's a real pleasure to see you all here. Some of you I know personally and those whom I don't know personally I know by reputation, so it's an honour and a delight to be able to chair this meeting. Migraine is a common, important neurological disorder. I don't think anyone in this room would quarrel with that statement. But had that statement been made 50 years ago then there might have been quite a number of people that would have been prepared to put their hand up and disagree with me, quite forcefully. I'm sure there are still a few who would be prepared to do that now. One of the things we'd really like to explore today is how migraine has come to take its place alongside other common important neurological disorders in the worlds of science and of clinical medicine (Table 1). We're going to do that by going back to the period at which some of those present started to work in the field to talk about what it was like to be interested in migraine, maybe to have migraine, in the 1960s and early 1970s, and then, as Tilli said, to set into that context some of the work that was done at the time, both around acute treatments like the triptans and also other treatments such as methysergide, pizotifen and so on. I warned Michael O'Brien that I might come to him first: Michael, would you be able to start us off? You entered the field in the mid to late 1960s – what was the attraction of migraine at the time?

| |
|--|
| Pre 1990s Migraine pre 1970s From ergotamine etc. to the triptans Discovery & impact of the triptans |
| 1990s and beyond Growth of a sub-specialty: specialized clinics : training and networks Funding research and treatment New therapeutics |

Table 1: Outline programme for Migraine: Diagnosis, Treatment and Understanding c.1960–2010



Figure 2: Dr Michael O'Brien

Dr Michael O'Brien: My interest was in the pathophysiology of cerebral circulation, cerebral haemodynamics, cerebral blood flow and metabolism, and migraine was one of a number of topics that lent itself to this. It wasn't migraine itself which was my prime interest, it was the measurement of brain circulation and I started doing that in 1966. I published a paper in 1967, which I think was the first ever report of a measurement of cerebral blood flow in a migraine attack.³ At that time migraine was thought to be a biphasic vascular event and it was thought that that could explain nearly everything. So the idea was that the aura stage was associated with vasoconstriction, which caused the aura, or at least triggered it, because Leão's spreading depression had been reported in 1944.⁴ So people knew about it and although it had been demonstrated in experimental animals like rabbits, it had never been shown in man. It is only very recently that the work of Professor Anthony Strong has shown spreading depression in man, particularly in relation to stroke.⁵ Anyway, at that time it was possible that vasoconstriction in some way triggered a Leão-type spreading depression. Then the question was 'what happened in the headache stage?' That was thought to be vasodilation, particularly in the non-cerebral cranial circulation, which includes the intracranial non-cerebral circulation. One of

³ O'Brien (1967).

⁴ Leão (1944, 1947).

⁵ See, for example, Woitzik *et al.* (2013).

the big problems with that, of course, was the pallor that most people have in the headache stage and, if this was vasodilation, why weren't they flushed? There was quite a lot of speculation as to why that might be.

Weatherall: One thing you said quite early on was that as a neurologist you were, of course, interested in migraine. Do you think neurologists really were all that interested in migraine?

O'Brien: Well, I think they were because that was one of the commonest forms of headache; in fact, I think for many neurologists it's the commonest outpatient referral. So, along with MS and epilepsy and so on, headache jumps out at the top of most people's lists.

Weatherall: In terms of someone training in neurology in the 1960s, did it seem to be an exciting field, an interesting field, to be entering?

O'Brien: No. [Laughter]

Weatherall: By way of comparison, what might have been the sort of exciting fields to have chosen at that stage?

O'Brien: I think Parkinson's disease, for instance, hadn't really taken off at that point and become a major interest. MS of course was, epilepsy to some extent was, but it's interesting that at that time there was no epilepsy service at Queen Square in the 1960s. There was no headache service at Queen Square in the 1960s. The domination there by Gilliatt was on peripheral nerves.⁶

Weatherall: Pramod Saxena, you were laughing at Michael's comment – would you like to expand on that for us?

Professor Pramod Saxena: I was not laughing at Michael, no, no, no; I wouldn't dare do that. No, I just think that in neurology in those days, there was not much available as drug treatment. You could diagnose very well, beautifully in fact, and part of that's even true now, but you could not do very much for the patient. But things have developed since then, also thanks to our neurologist friends.

Professor Jes Olesen: I entered the field in the late 1960s and early 1970s and I believe that there was extremely little interest in migraine and that continues almost to this day, despite the fact that it's so common and a big thing in neurology practice. It was completely common not to learn anything about

⁶ See, for example, Gilliatt (1961); Gilliatt and Willison (1963). Professor Roger Gilliatt (1922–1991) held the Chair of Clinical Neurology at the Institute of Neurology, Queen Square, London, from 1962 to 1987.



Figure 3: Professor Jes Olesen

migraine or other headaches right up until the 1980s. But also I have to disagree with Pramod Saxena, they were not able to make the diagnosis very precisely because the classification was extremely poor, the definition of the disorder was very poor, and the other thing that made neurologists stay away from headache and migraine was the fact that the neurological examination is normal. It's a real nuisance for a neurologist to look at people with a normal neurological examination. Furthermore, all our wonderful X-rays, angiograms, and, at that time, pneumoencephalographies, and later on scans, all of these are normal. So it is for all these reasons that neurologists have been very reluctant to go into headache and even today it's still a much understudied condition. The resources spent are completely out of proportion to the socio-economic cost of migraine, which we have estimated very precisely within the last ten years.⁷

Dr Patrick Humphrey: I just want to make a short response to Michael's comments, which I recognise very much but he didn't mention the work of Harold Wolff.⁸ Having read all his papers, I'm a tremendous admirer because he was a brilliant medical scientist. I can only tell you that we would never have discovered the triptans if Wolff hadn't written those very elegant papers, if he hadn't pointed to blood vessels and particularly obviously blood vessels

⁷ See, for example, Gustavsson *et al.* (2011); Bloudek *et al.* (2012); Steiner (2010). See also Steiner *et al.* (2003).

⁸ Harold Wolff (1898–1962) was Professor of Medicine (Neurology and Psychiatry) at Cornell University Medical College and Director of the Neurological Service of the New York Hospital, New York; for further biographical details see page 109.



Figure 4: Dr Patrick Humphrey

in the head.⁹ It just so happened that the 5-HT receptor that we discovered at which triptans are agonists are mainly found in certain cranial blood vessels. So I think we mustn't forget Harold Wolff who was brilliant and his papers are still worth reading as exemplars of how to write good medical science papers that illuminate; for example, Graham and Wolff (1938).¹⁰ Do go and read them; that's how papers should be written.

Weatherall: We'll come back to Wolff.

Professor Merton Sandler: I wrote a paper 41 years ago, that was before Pat was born, I think, [laughter] entitled 'Migraine: a pulmonary disease?'¹¹ This came about because John Vane had invited me to examine one of his PhD students at that time, a girl called Valerie Alabaster, who was working with Mick Bakhle.¹² A good PhD thesis.¹³ And it suddenly struck me that what they did was perfuse rabbit heart, rabbit atrium with 5-HT or tryptamine and found what

⁹ See, for example, Wolff, Marcussen and Kunkle (1948); Marcussen and Wolff (1949).

¹⁰ Graham and Wolff (1938).

¹¹ Sandler (1972).

¹² Sir John Vane was Professor of Experimental Pharmacology at the Royal College of Surgeons. He was jointly awarded (with Sune K. Bergström and Bengt I. Samuelsson) the 1984 Nobel Prize in Physiology or Medicine for 'discoveries concerning prostaglandins and related biologically active substances'. Dr Y S (Mick) Bakhle joined the Department of Pharmacology at the Royal College of Surgeons in 1965 where he remained for nearly 30 years. He was a participant at the Witness Seminar on drugs affecting 5-HT systems (Overy and Tansey (eds) (2013)).

¹³ Alabaster (1971).



Figure 5: Professor Merton Sandler

the effluent was on the other side. The effluent was a funny mixture of all sorts of things, very few of which they could actually identify. So I started thinking and published this airy-fairy paper in the *Lancet*, which you know was obviously looking for rubbish to pad it out with in those days. Anyway that was one of the things that I started. We'd started a year or two before with monoamines when Edda Hanington – oh she was lovely, wasn't she, those who remember her – had put tyramine on the map, so we had been thinking about tyramine in any case at that time.¹⁴ I mustn't ramble on like this at this stage of the game, but the monoamines had come on the scene and funny, possible things had emerged at the end of it. One of them I got a bit of a bee in my bonnet about, and I think it could even be that it has a real role and that's nerve growth factor (NGF). I consider that NGF has all the qualities of a substance that might produce pain. It is, when injected, a profoundly potent pain-producing substance and I think we should be aware of it, Mr Chairman.

Dr Richard Peatfield: Just one thought going back to Michael's comments: we haven't accounted for the feud between Lord Brain and the rest of British neurology.¹⁵ Lord Brain was the founding father of the Migraine Trust. He thought migraine was really quite important but he'd fallen out quite catastrophically with the rest of the Queen Square establishment who, I think,

¹⁴ See, for example, Hanington (1967); Smith, Kellow and Hanington (1970). See also comments by Professor Anne MacGregor on pages 10–11 and note 18.

¹⁵ Walter Russell Brain, 1st Baron Brain (1895–1966) was Consulting Physician to the London Hospital and to Maida Vale Hospital for Nervous Diseases. For further biographical details see R A H (1982).



Figure 6: Mrs Mary Ayres, Professor Anne MacGregor and Professor Merton Sandler

almost to a man, decided migraine was not important largely because Lord Brain thought it was, and not for any other better reason. Lord Brain, I think, had written a textbook while a senior registrar, which was rather better than anyone else had ever written and he was never spoken to again.¹⁶ I exaggerate slightly but I think only slightly.

Weatherall: Whereabouts did Macdonald Critchley sit in that particular feud?

Peatfield: Others might know that better than me.

Professor Anne MacGregor: I don't know where he sat but I think it's worthwhile noting that he did set up a migraine clinic in 1955 as one of the first migraine clinics, which means that somebody must have considered it to be interesting at that time.¹⁷ However, I'm assuming that was purely clinical with little research being done. There is one question I would like to ask my colleagues who were doing research during the 1970s and 1980s. I went to visit Edda Hanington in the 1980s after she'd retired and she said that much of the

¹⁶ Brain and Strauss (1929).

¹⁷ Macdonald Critchley (1900–1997) set up the first headache clinic in Britain in 1955 at King's College Hospital where he was Consulting Neurologist, and the National Hospital, Queen Square where he was Consulting Physician. For further biographical details, see page 100.

research that they did and published on migraine was actually migraine with aura and they didn't include migraine without aura because it wasn't so easily diagnosable.¹⁸ I am interested to know whether that was true, since that would have quite an impact on understanding of migraine from that time.

Dr Glyn Volans: My comment is linked to Lord Brain I think. I'm the only person so far who is not a neurologist. I came not studying neurology but as a clinical pharmacologist when that had only just about been invented.¹⁹ What I found was an opening to work at Barts with Paul Turner and with Marcia Wilkinson who was heading the migraine clinic, and it was Marcia I think who came from the Lord Brain side of things if my memory is correct.²⁰ In fact, I saw only a few weeks ago that Marcia died recently, well into her 90s and still apparently very active towards the end.²¹

What we had available as I came to Barts in 1972 was, firstly, an up-to-date, comprehensive international classification for migraine that the clinic was working to, and the ability to see the patients acutely at the clinic as well as patients referred in the more normal ways.²² So we really had a good place to be studying the condition.

¹⁸ See further comments by Professor Anne MacGregor on page 57. Dr Edda Hanington wrote widely on migraine and headache; see, for example, Hanington (1974, 1980). She reported on the relationship of tyramine to the migraine attack; see comments by Professor Merton Sandler on page 9.

¹⁹ For a discussion of the term 'clinical pharmacology', see the Witness Seminar on clinical pharmacology in the UK, pages 6–8 (Reynolds and Tansey (eds) (2008a)).

²⁰ Professor Paul Turner (1933–1994) was a Professor of Clinical Pharmacology and Consultant Physician at St Bartholomew's Hospital from 1972 until his retirement in 1993; see Richens (1995). Dr Marcia Wilkinson (1919–2013) was a Consultant Neurologist at the Elizabeth Garrett Anderson Hospital in London from 1953 until 1984 and was the first Medical Director of the City Migraine Clinic from 1970. See comments by Professor Anne MacGregor on pages 15–16 and page 109 for further biographical details.

²¹ See MacGregor (2013).

²² The definitions of a migraine had been agreed in 1969 at a meeting of the Research Group on Migraine and Headache of the World Federation of Neurology, of which Dr Macdonald Critchley was the President. Migraine was defined as 'A familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting. In some cases they are preceded by, or associated with, neurological and mood disturbances.' The classification was then divided into those conditions that fall within the above definition (either classical migraine or non-classical migraine) and conditions which may fall within the category of migraine (cluster headaches, facial 'migraine', ophthalmoplegic 'migraine' and 'hemiplegic migraine'). World Federation of Neurology (1970).



Figure 7: Dr Glyn Volans and Dr Richard Peatfield

Weatherall: Leading on both from Glyn’s and Anne’s comments, one question that I want to ask: in 1962 the American Headache Society Ad Hoc Classification Committee came up with a classification for headache disorders (Table 2).²³ Was this something that people were using at the time, or was it really tangential to clinical practice?

| | |
|------|---|
| 1 | Vascular headache of the migraine type ‘Classic’ migraine ‘Common’ migraine ‘Cluster’ headache Hemiplegic and ophthalmoplegic migraine Lower-half headache |
| 2 | Muscle-contraction headache |
| 3 | Combined headache: vascular and muscle-contraction |
| 4 | Headache of nasal vasomotor reaction |
| 5 | Headache of delusional, conversion, or hypochondriacal states |
| 6 | Nonmigrainous vascular headaches |
| 7 | Traction headache |
| 8 | Headache due to overt cranial inflammation |
| 9–13 | Headache due to disease of ocular, aural, nasal and sinus, dental, or other cranial or neck structures |
| 14 | Cranial neuritides |
| 15 | Cranial neuralgias |

Table 2: The classification of headaches (The Ad Hoc Committee on Classification of Headache, 1962)

²³ The Ad Hoc Committee on Classification of Headache (1962).

Olesen: There was this National Institutes of Health (NIH) classification but there was also a classification of the World Federation of Neurology, actually spearheaded by I don't remember who but it was a Brit, and they were quite similar but not completely similar.²⁴ I think they were widely used but the problem was, of course, that they were completely non-operational, they were completely ambiguous if you wish. You could diagnose any kind of headache as migraine according to those criteria if you wanted to. That was the reason why we had to make the international headache classification much later. In the meantime, I think patients were diagnosed according to good clinical practice in the place where they came from and not really according to these so-called definitions because they were useless.

Humphrey: When Jes got involved in the international headache classification I was so excited and pleased. When we started trying to do clinical trials with certainly the forerunner of sumatriptan, which I think was AH25086, the methodology for such trials had not been worked out. Initially we had about eight patients who had what they thought was severe migraine and seven of them were just miraculously cured, or rather the symptoms went. And the last one no joy at all, and it turned out later he had a broken jaw, not migraine. That just typifies the problems that were around at the time trying to do any proper clinical trials, so when we wanted to get into big, credible trials with sumatriptan it was imperative that people knew what they were doing. I think Jes led the way in doing good clinical trials in this field, with proper diagnosis at the forefront.

Weatherall: Yes, that's the importance of the final section of all the operational criteria, isn't it – not attributable to any other disorder.²⁵ While we're talking about classification, I think it would be very helpful if Jes would tell us a little bit about the background to the IHS, the first iteration of the IHS criteria, because I think again it does form a context for the triptan story.²⁶

Olesen: Yes, I'm happy to. I went into migraine headache research from studies of brain blood flow and had a thorough physiological schooling. I was used to thinking in rather scientific ways about things and that didn't seem to be the

²⁴ See note 22. Dr Richard Peatfield wrote: 'The other attempt at a diagnostic definition was by Vahlquist (1955).' Note on draft transcript 24 June 2013.

²⁵ The final section (section 14) of the IHS Criteria is 'Other headache disorders', comprising 14.1 Headache not elsewhere classified and 14.2 Headache unspecified. (Headache Classification Committee of the International Headache Society (IHS) (2013), page 787).

²⁶ For the development and pharmacology of the triptans, see Humphrey, Ferrari and Olesen (eds) (2001).

case for most of the physicians who practised headache at the time. When I started to do clinical work I realised that these criteria were useless because you could interpret them in any way you wanted. They were full of words like ‘usual’ and ‘sometimes’ and ‘often’ and so on. So I made up my own criteria based on the large amount of clinical material we had in Copenhagen. They were more unambiguous and we used them for our own research but then I realised this is never going anywhere; we have to do it in an international organization and almost at the same time the International Headache Society (IHS) had been formed.²⁷

I was organizing the second congress of the International Headache Society in Copenhagen in 1985, and so at that congress and during the business meeting of the International Headache Society, I suggested that the Society should take an initiative to form a classification committee and come up with a more unambiguous set of diagnostic criteria and so on. Of course, they immediately appointed me chairman of the initiative and gave me a free hand. That’s when I started to build up the organization behind the first edition of the International Headache Society classification. I don’t know how much you want to know but I studied all kinds of disease classifications at that time; I realised that the most advanced and the most suitable for the headache field was the psychiatric DSM-III classification where they had this system of criteria a, b, c, and d and so on you should fulfil.²⁸ It was really very operational. Then we put together a committee with the leading scientists from all over the world and started the work. We quickly reached a decision about the number of chapters and distributed the chairmanship of each chapter. We recruited many more people because one of the big tasks from the beginning was clearly the problem of acceptance throughout the world by headache experts. That was why I wanted to involve as many people as possible because if you’ve been part of the work you can’t possibly afterwards say it was bad. We had more than 100 people working on this over three years and published the

²⁷ The IHS is an international charitable organization, set up in 1982 ‘for the benefit of people affected by headache disorders. The purpose of IHS is to advance headache science, education, and management, and promote headache awareness worldwide.’ See their website at www.ihs-headache.org (visited 28 January 2014).

²⁸ *The Diagnostic and Statistical Manual of Mental Disorders* (DSM) was first published in 1952 by the American Psychiatric Association. It is the standard classification for mental disorders. DSM-III was published in 1980.

first edition in 1988.²⁹ And very unlike, for example, epilepsy classifications, the headache classification met no opposition and was just widely accepted throughout the world and translated into many languages.³⁰ So that was very, very positive.

Saxena: I don't know whether I should bring it up or not but earlier, Mark, you asked what one remembers about Macdonald Critchley. What I remember, which perhaps I should not say, is a meeting organized by Professor Sicuteri, perhaps Jes Olesen was there too, to discuss the formation of the European and International Headache Societies.³¹ This idea was vehemently opposed by Macdonald Critchley, so much so that he at the time said, 'That man Saxena, now he's the ringleader!' He was right perhaps, perhaps not, but other people actually joined hands and they eventually founded the European as well as the International Headache Societies.³² This I wanted to say. I thought, well this is a meeting where you have got to be candid. So I thought I would be.

Weatherall: Thank you very much. I want to move on to talk about treatment options. Pramod said quite early on that actually there weren't that many treatment options, but the late 1960s, early 1970s is a period at which some of the medications that we still use today, or are about to stop being able to use, like methysergide, were available or about to become so. So I wanted to ask, having made a diagnosis of migraine, what treatment options were available?

MacGregor: Having written Marcia Wilkinson's obituary recently and gone back through her entire life, which was absolutely fascinating as a history in itself, she set up the migraine clinic at the Elizabeth Garrett Anderson Hospital

²⁹ Headache Classification Committee of the International Headache Society (1988); the second edition was published in 2004 (Headache Classification Subcommittee of the International Headache Society (2004)), and online two years later: <http://ihs-classification.org/en/> (visited 8 January 2014). The beta version of the third edition was published in 2013 (Headache Classification Committee of the International Headache Society (IHS) (2013)).

³⁰ For the background to epilepsy classification see the introduction to Engel (2013); see also Berg and Scheffer (2011).

³¹ Professor Federigo Sicuteri (1920–2003) was Professor of Clinical Pharmacology and later Internal Medicine at Florence University. In 1976 he founded the Italian Headache Society for the Study of Headache; he was a member of the Steering Committee of the International Headache Society and became President of the Society from 1991 to 1993.

³² The International Headache Society was founded in 1982 and the European Headache Federation was founded in 1992.



Figure 8: left to right: Dr Jeffrey Aronson, Mrs Mary Ayres, Professor Pramod Saxena (speaking), Professor Anne MacGregor, Dr Alec Oxford, Dr Tom Blackburn

in the 1960s.³³ Her main line of treatment was based on the thesis of Elizabeth Garrett Anderson, who had not been able to take her thesis in the UK because she was a woman, so she'd gone to Paris and wrote her thesis on migraine.³⁴ Marcia Wilkinson had then translated it and used it as her premise for treatment at the Elizabeth Garrett Anderson Hospital. So it goes back a long way but the premise was keeping to a routine: sleep, regular meals, not getting dehydrated, and buckets of sweet tea, I think, came into it somewhere along the line.³⁵ Aspirin was another strategy. This was something Wilkinson was then still following through when she was working at the City Migraine Clinics. Then the aspirin studies that Glyn Volans did, very elegant ones, brought aspirin through.³⁶ Just to put it into perspective in 1989, she gave a talk to the American Headache Society, as it was then, on management of migraine in Britain entitled 'Three aspirin and a sweet cup of tea'.³⁷ So I think from that, you can start talking about the rest of the science.

³³ MacGregor (2013).

³⁴ Garrett (1870). See Wilkinson and Isler (1999).

³⁵ According to Wilkinson's translation 'a small cup of tea towards four or five o'clock in the afternoon is beneficial' (Wilkinson and Isler (1999), page 12).

³⁶ See, for example, Volans (1974, 1975).

³⁷ Professor Anne MacGregor wrote: 'The actual publication was less provocative – 'Treatment of acute migraine: the British experience' (Wilkinson (1990)). I had a copy of the typewritten script which she read out, so I know what the presentation title and content were.' Email to Ms Caroline Overy, 19 December 2013.

Weatherall: Glyn Volans, since we're talking about aspirin: aspirin was the great invention of Bayer at the beginning of the twentieth century, used very widely for a number of pain conditions.³⁸ Tell us a bit about how you got involved in looking at aspirin and other substances and where that took you.

Volans: At that time we had two general purpose analgesics, aspirin and paracetamol, which were very effective for headaches in most people. I reviewed the literature around both, and found that paracetamol was clinically a little more difficult because if you ever have to taste the stuff it's nauseating in its own right. However, the key driving factor as to why I studied the absorption of aspirin and not paracetamol was because I could measure it. We had a fluorimeter in the department with which I could measure aspirin levels with great accuracy, whereas if I had wanted to measure paracetamol at that time I had to go to the real experts in the School of Pharmacy. They had these impressive machines for high-performance liquid chromatography techniques, with which you could measure paracetamol levels if you worked on it with great skill for a day or two to get a single result. So it was very clear for me that I should put paracetamol out of the picture for the studies on drug absorption.

We later found that if you work hard enough at paracetamol you can make it more acceptable to the patient, and the French pharmaceutical industry, for instance, was very capable of producing of pleasant tasting soluble formulations. In fact, the aspirin formulation which we gave our patients was advertised on TV as a lady drinking it out of a champagne glass saying, 'It may not be champagne but it is good for my headache.' The same company could make paracetamol drinkable; I'm not sure how much that kind of product is used now but it can be done.

Once I had demonstrated the ability to study aspirin absorption accurately in volunteers, the other key factor then was the migraine clinic where I was able to get patients suffering from acute migraine to volunteer as they came in through the door. I could then study them not only in the migraine attacks but also when they would come back for their follow-up visits, at which time they also agreed to the control studies.³⁹

³⁸ Acetyl salicylic acid, or aspirin, was synthesized by the German chemist Felix Hoffman, possibly under the direction of Arthur Eichengrün, in the laboratories of the German dye manufacturer, Friedrich Bayer and Co. in 1897, and was launched following clinical trials from 1899. See Sneader (2000).

³⁹ See Volans (1978), also Volans (1974, 1975).

That's how aspirin came to the fore at that time. A question I would ask now, and I certainly have the beginnings of an answer, is where does the other major non-prescription analgesic fit into current treatment? Is ibuprofen, which has been available without prescription since the mid 1980s, just as good as the other two drugs or is it just possible it could be even better?⁴⁰

Weatherall: Can I ask specifically about aspirin and metoclopramide? I believe you studied that combination of an analgesic and an antiemetic. Was that combination in widespread use at that stage?

Volans: I don't think it was used widely, but it must be possible that people in emergency departments who were looking after patients who were vomiting all over the place would have used injectable metoclopramide as a symptomatic treatment.

In the migraine clinic, at that time, the intramuscular preparation of metoclopramide was easy to give and, by the time that we got to that phase, we'd pretty well convinced ourselves that what was causing the poor absorption was delayed gastric emptying and that metoclopramide, from everything we knew about its mechanism of action, sounded the right antiemetic to use.⁴¹

In contrast, all of the other antiemetics, which worked essentially by anticholinergic mechanisms, were very likely to cause gastric stasis or to make it worse. Indeed, one of the final drug absorption studies in which I participated, was led by a colleague, Gillian Wainscott.⁴² There we used what was then the most popular injectable antiemetic, i.e. prochlorperazine (then called thiethylperazine) trade name Stemetil. When we gave that to patients they were certainly made no better and just possibly they felt worse.⁴³

Dr Jeffrey Aronson: I can add a comment on the clinical pharmacology of metoclopramide and its use in migraine because of course vomiting is a very prominent part. As a sufferer, I find that the intensity of the vomiting is proportional to the intensity of the headache, and you can use antiemetics to relieve that. But an important factor in the use of a drug like metoclopramide is that its action is

⁴⁰ Dr Glyn Volans wrote: 'This question was not answered directly, at that time, but from the later discussions it is clear that nonsteroidal anti-inflammatory drugs (NSAIDs) are now recommended in current guidelines.' Note on draft transcript, 2 July 2013. See pages 48–9.

⁴¹ Volans (1975).

⁴² See page 20 and note 47.

⁴³ Wainscott, Kaspi and Volans (1976).

through increasing the speed of gastric emptying, which should also improve the rate of absorption of the analgesic that you're giving, and if you don't take the analgesic soon enough then the reduced speed of absorption means that the drug fails. So there is an extra twist to metoclopramide, apart from its native antiemetic effect, in enhancing the rate of absorption. I'm not sure, Glyn, if you were on that paper that Laurie Prescott published in the *BMJ* in the 1970s showing the curves of absorption of paracetamol with and without metoclopramide?⁴⁴

Volans: No, I was not involved in that later work but I was aware of the major advances, which gave them the ability to measure paracetamol accurately and efficiently. I don't remember whether they were giving the metoclopramide intramuscularly like we were or if they had moved onto studying the oral formulation.⁴⁵

Aronson: That raises another very interesting point about treatment that you're asking, Mark, and that is that drugs are absorbed primarily in the small bowel, not in the stomach, so the speed of gastric emptying is important to deliver the drug to the site of absorption. If you give the metoclopramide intramuscularly, then you will enhance the rate of contraction of the stomach and thus deliver the oral aspirin or paracetamol to the small bowel. But I don't know what happens if you give oral metoclopramide, because that should be subject to the same delay in absorption if it's not absorbed in the stomach. Yet the drug companies subsequently issued combinations, oral combinations, Paramax for example, which is paracetamol plus Maxolon (metoclopramide), and an equivalent one with aspirin and metoclopramide (Migravess). I've no idea, if anybody has any idea here about trials carried out with those sorts of formulations, whether oral metoclopramide is effective? I don't know.⁴⁶

⁴⁴ Nimmo *et al.* (1973). Professor Laurie Prescott was Professor of Clinical Pharmacology at the University of Edinburgh and was a participant at the Witness Seminar on clinical pharmacology (Reynolds and Tansey (eds) (2008a)). Dr Jeffrey Aronson added: 'Glyn Volans also subsequently showed that intramuscular metoclopramide increased the speed of absorption of aspirin in migraine (Volans G N (1975)).' Note on draft transcript, 30 July 2013.

⁴⁵ In the study by Nimmo *et al.* (see note 44) the absorption of paracetamol in healthy volunteers was accelerated by intravenous injection of 10mg of metoclopramide.

⁴⁶ Dr Jeffrey Aronson wrote: 'There is a systematic review by Andrew Moore and my erstwhile colleague Sheena Derry, showing that oral paracetamol plus metoclopramide is as effective as sumatriptan (Derry and Moore (2013)). In one careful study, oral metoclopramide increased the speed and extent of absorption of aspirin in subjects with migraine and intramuscular metoclopramide had a bigger effect, but neither completely restored the absorption to normal (Ross-Lee *et al.* (1983)).' Note on draft transcript, 30 July 2013.

Volans: I'd have to do a literature search but I think there was marginal evidence that the oral formulations may have improved things and certainly that they were not making things any worse. The aforementioned Gill Wainscott, in fact, moved from the migraine clinic to work with one of the drug companies at that stage in her career, although she subsequently had the sense to leave and become a psychiatrist.⁴⁷

Peatfield: A bit later domperidone came in and I do know there is a trial showing the action of paracetamol is enhanced by oral domperidone, which we like in preference to metoclopramide because of the risk of involuntary facial movements in young women.⁴⁸

Weatherall: Michael, can I just go back to you? Working as a general neurologist in the 1970s, what might you be advising your patients with migraine to do or take?

O'Brien: Even earlier in the 1960s, there were thought to be three arms really: the first was to try and establish whether there were any aggravating or precipitating factors because, obviously, if somebody was getting their migraine because of red wine or something, if they could avoid it then they did better than anything any physician could do. The yield from that is not very great but it's still worth attempting. And the second arm was to treat the acute attack when it happens – nobody's mentioned the ergotamines at this point but we had ergotamine by mouth, by injection, and by suppository. We also had dihydroergotamine and obviously aspirin and paracetamol but nobody's mentioned codeine, which we also had. So we had a number of preparations for the acute event and, of course, we knew at that stage in the 1960s that if you didn't start treatment right at the beginning of the attack, as early as possible, it didn't work. I'm not sure we knew why, until Glyn's work emerged, but we certainly knew it. And then the third possibility was prophylaxis and prophylaxis was just extremely limited. Dihydroergotamine was used as prophylaxis. Some people used aspirin as prophylaxis, small doses of aspirin (I think that actually came in rather later), but the effective prophylaxis didn't come along until later. I don't think we even used beta blockers at that stage, those came in later as well. So those were the three ways in which you tackled patients with migraine.

⁴⁷ See page 18. Dr Gillian Wainscott is a Consultant Psychiatrist and Clinical Director at Birmingham and Solihull Mental Health NHS Foundation Trust.

⁴⁸ MacGregor, Wilkinson and Bancroft (1993). For the use of metoclopramide and involuntary facial movements, see, for example, Melmed and Bank (1975).

Weatherall: Merton, could I ask you specifically in terms of advising people in how to manage migraine, what sort of things would you be saying to people at that time?

Sandler: Well, I'm not a neurologist; that was not my forte. In fact, can I say at this stage that about ten years ago I got fed up with migraine completely but before I decided to pass to somewhere else or whatever, I put my thoughts down on paper. One or two interesting things emerged at that time as you have been talking about. It was my complete conviction that the aura of migraine was just another triggering event which was active like any other triggering event that we know about. Nobody has cottoned onto this. I published that article, all I knew about migraine really, ten years ago in a volume entitled *Wine*.⁴⁹ That was the wrong place to do it; it just happened to be that Roger Pinder and I were publishing this book so it was a convenient place to put it. I'm quite sure that it fell completely flat, nobody else has read that article ever since, and that it remains in the literature.

Humphrey: Can I just make a few comments because obviously I'm not a clinician, but when I was asked to work on migraine by David Jack at Ware I had an empty lab and a young lady (Eira Apperley) that I worked with, and was left to 'get on with it.'⁵⁰ So the first good thing was that I heard a programme on Radio 4 on the trials and tribulations of migraine sufferers, around the time that my friends had been saying: 'Don't waste time working on migraine, it's just something neurotic women complain about, it's not a real disease.' And it was neurologists saying that, but I realised it was a real disease and thought I'd better go and find out about it. I was lucky enough to talk to Marcia Wilkinson and spent quite a lot of time with her and she was a lovely lady, she knew how to treat her patients. What did I learn from it? Well, we've heard how she treated her patients and she treated them as best she could with bed rest and keeping them in a dark room and so on and so on. But what she actually made me realise was that there were no good treatments for migraine, so it was another reason for working on it because it was a serious disease that needed a new medicine. The other thing she confirmed to me, which was reassuring, was that

⁴⁹ Sandler (2003).

⁵⁰ Sir David Jack was Head of Research, later Research and Development Director, at the pharmaceutical manufacturers Allen & Hanburys (now part of GlaxoSmithKline) in Ware, Hertfordshire. See page 103 for further biographical details.

ergotamine did work.⁵¹ It was not a nice drug, she didn't want to particularly use it, but it actually worked in some patients.⁵² So we had a drug that worked – that was another starting point. The other thing that she was not overly keen on using were prophylactics because she didn't think they really worked. I'm just amazed that people sell them today and make money out of them because if you look at them, every single prophylactic drug for migraine then and now gives you a 50 per cent reduction in severity of headache, and 50 per cent reduction in number of attacks at best. Okay, if you're having eight attacks a month maybe that helps, but not much. The key there, though, was looking at the prophylactics for migraine and trying to understand what they may be doing to provide their limited effects. I got much of this from Jim Lance, who was another clinician who provided a lot of important information to me. He published a paper in the 1970s with Anthony and Somerville, where they looked at all the prophylactics that were available then.⁵³ A lot of them were 5-HT receptor antagonists, dirty ones like cyproheptadine and later on pizotifen came along. But they all provided this less than 50 per cent reduction and were all similar, but one stood out a little bit and that was methysergide. Methysergide seemed to be slightly better, again as a prophylactic, but there were reasons for not taking it, retroperitoneal fibrosis kicking in if using it for too long and so on. But again it was another clue. So I had two clues, methysergide and ergotamine, and I can tell you a lot more about that later. I was really just making the point about what was available in the 1970s: not much.

Weatherall: We'll come back to where you took that patent in a little while if we may.

Dr Tom Blackburn: Can I just ask my clinical colleagues: with regard to trying to provoke migraine attacks and the amount of work that went on in the 1960s and 1970s with compounds like reserpine, fenfluramine, zimelidine, all agents that were able to provoke migraine attacks. How important were they to the clinicians with regard to developing the hypothesis that 5-HT was important?

⁵¹ See, for example, Wilkinson (1971).

⁵² For a discussion of a randomized trial of ergotamine in 1970, see Ness, Reynolds and Tansey (eds) (2002), pages 72–3.

⁵³ Lance, Anthony and Somerville (1970). James Lance was Professor of Neurology at the University of New South Wales from 1975 to 1992 and since then, Professor Emeritus. He has published widely on headaches and migraine.



Figure 9: Dr Patrick Humphrey and Dr Tom Blackburn

O'Brien: The answer is 'not very' because there was always the concern that a provoked attack wasn't quite the same thing as the naturally occurring attacks; that was the big difficulty. Anne asked why these studies, or most of the studies, were done in migraine with aura.⁵⁴ The answer is because then you really knew it was migraine and there wasn't going to be any confusion about any other sort of headache. I think that the view was, certainly my view at the time was, that probably there was a vasoconstrictive phase in the brain and that probably everybody had it, but not in all of them was it eloquent. Then, as I said, even if you could measure cerebral blood flow (CBF) before a headache in patients without a prodrome they would probably still show some vasoconstriction and that was the conclusion that I reached in the 1960s.⁵⁵

Professor Trevor Jones: To return to ergotamine for a while. Before I became R&D director at Wellcome I was responsible for Development, and Migril (ergotamine) was one of our tablet products (Figure 11). In Dartford, where our production factories were, they had planted fields of rye grass and had these incredibly large tractors, about ten feet high, that went through the rye fields and impregnated the rye ears with ergot (I think there are pictures in the museum). The problem with the formulation of Migril – cyclizine, caffeine, and ergotamine – was to maintain stability during its shelf life otherwise it would degrade to

⁵⁴ See pages 10–11.

⁵⁵ See, for example, O'Brien (1967), see page 5.



Figure 10: Professor Trevor Jones

lysergic acid (LSD) and although you might feel better, it's not a good therapy! The wheel has turned full circle because I am now on the Board of Allergan in the USA and we are just about to launch a product called Levadex, which is dihydroergotamine as a unique, breath-actuated aerosol spray with very, very fine particles, so you don't get the side effects that we saw in the early days of Migril.⁵⁶

MacGregor: Just going back to ergotamine. I think it's actually very interesting because it was the only treatment that was available at that level when I first came into managing migraine in the late 1980s. If you got the dose right and the absorption right, patients really got on with it very well. It's a shame now that these drugs that are still effective are becoming no longer available. You can no longer get hold of Cafergot in the UK; methysergide may disappear. Migril is still available.⁵⁷ So there is a return but it doesn't necessarily mean to say that drugs like the ergotamine inhalers should have disappeared just because they became too expensive to make because of concerns about chlorofluorocarbons (CFCs). So these things do change over time. But ergotamine was a very useful drug.

⁵⁶ Levadex was rejected by the FDA in April 2013 due to concerns about manufacturing. Professor Trevor Jones wrote: 'There were one or two manufacturing issues raised by the US FDA that are now resolved so we anticipate final review by US FDA this year.' Email to Ms Caroline Overy, 5 February 2014.

⁵⁷ Cafergot, a compound of ergotamine tartrate and caffeine made by Alliance Pharmaceuticals, was discontinued in the UK in November 2012. Methysergide, marketed as Deseril, was discontinued in the UK in May 2013. Migril, manufactured by Wockhardt, is the brand name of ergotamine tartrate, cyclizine hydrochloride, and caffeine hydrate.

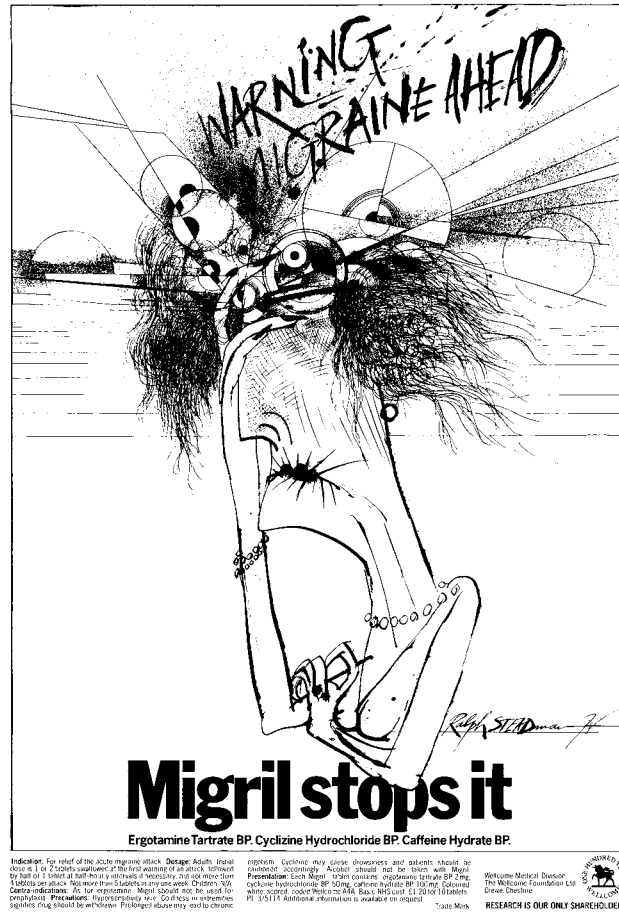


Figure 11: Wellcome Foundation Ltd advertisement proof: Ralph Steadman cartoon for Migril, c.1979.

Humphrey: I agree with you, Anne; you know obviously it works in certain people and you have to be clever about how you use it, but I would ask why would you use it because I know lots of friends, some pharmacologists, who've got migraine, and in those days they were using bigger and bigger doses and what happened? They got sick. They were violently sick because ergotamine is a dopamine agonist. Ergotamine is a potent agonist at a number of different receptor types. It's got lots of other effects and it's a potent coronary vasoconstrictor. I spent ten years of my life trying to defend sumatriptan for its relative safety because we did a huge amount of work on coronary vessels and cardiac blood flow; and now sumatriptan is available over the counter and yet people are trying to bring back ergotamine. It doesn't make any sense whatsoever.

Sandler: The question of what were the first indications of whether 5-HT was working in migraine or not arose several speakers back. I always remember an absolutely fascinating case in the literature of a patient with migraine who developed carcinoid tumour and once his tumour started to pump 5-HT into his circulation he was right as rain, his migraine was gone.⁵⁸

Saxena: I recall that paper as well, so Merton I will support you. A couple of points, well more than a couple of points, I'd like to make, if I may? I started with 5-HT in 1962, when I passed medicine and joined the Pharmacology Department at King George's Medical College, Lucknow. Lucknow perhaps may be known to you in England – it was the place where, according to you, the Indian Mutiny took place.

Jones: Birthplace of Cliff Richard. [Laughter]

Saxena: Indeed, and that's where I come from, Lucknow. We call your 'Indian Mutiny' the first war of independence, but that's an aside. [Laughter] I landed up working there with 5-HT during my MD after my MBBS. Then, in 1966, when I joined Organon International at Oss in the Netherlands, they were trying to develop mianserin, a 5-HT antagonist, as an anti-migraine drug. Why? Because, like methysergide, mianserin was able to block the rat uterus contraction elicited by 5-HT and we all know now that this is a 5-HT₂ receptor-mediated response. In those days, the 5-HT₂ receptor used to be called the D receptor. So I was asked by the management: 'Okay, here is mianserin; prove in your animal experiments whether it would work in migraine.' So in 1966 I thought: 'Well, what is migraine?' The first paper, as Pat said earlier, that came to my mind, and I was most impressed, was by Graham and Wolff, published in 1938.⁵⁹ It reached India in 1939, I think; I was *in utero*. During the headache, temporal artery pulsations are high and when you give ergotamine both headache and pulsations decrease at the same time. So I thought that firstly, there is definitely involvement of head blood vessels here, and secondly, I knew that the effective drugs at that time were ergotamine, dihydroergotamine, methysergide, pizotifen, and they all had something to do with 5-HT, so that said to me also: 'Yes, 5-HT is important'. Thirdly, a report in 1960 by Kimball, Freidman, and Vallejo mentioned that if you give reserpine you can elicit migraine-like attacks in migraine patients, and when you give 5-HT intravenously, of course, because it's not absorbed, you can abort those migraine

⁵⁸ Hopf, Johnson and Gutmann (1992).

⁵⁹ Graham and Wolff (1938).

attacks.⁶⁰ Lastly, Sicuteri, Testi, and Anselmi had shown that there is an increase in the excretion of a 5-HT metabolite, 5-hydroxyindole acetic acid, in the urine during the headache phase.⁶¹ This all fitted very, very nicely. So it came to me: ‘Okay, we’ll record carotid blood flow in our animal experiment’; those were the early days of the electromagnetic blood flow meter. Not only that, we also recorded blood flow in the mesenteric artery, femoral artery, and many other blood vessels. To my surprise, in the very first experiment, I saw that when I gave ergotamine, I think 1 or 2µg per kg doses, nothing happened to blood flow in any of the other blood vessels, except that carotid artery blood flow decreased enormously. There was no, or very little, increase in blood pressure with those doses.⁶² So this was surprising; why was this happening? And it happened also with methysergide.⁶³ It didn’t happen with pizotifen⁶⁴ and unfortunately it didn’t happen with mianserin, which was an Organon compound.⁶⁵ So I said to the management that mianserin was perhaps not a good compound for migraine. It turned out to be effective as an anti-depressive agent. In 1974, we published that methysergide was acting like 5-HT, so I compared it with 5-HT and it also decreased blood flow in the carotid artery and I said, ‘Why? This is interesting.’ So methysergide is in fact an antagonist at what we now call the 5-HT₂ receptor, or the D receptor at that time, but an agonist at what I termed the atypical receptors in our publication of 1974.⁶⁶ And so, this is where one should look for an anti-migraine drug.

Around that time, the head of department of Organon pharmacology, Ivan Bonta, was appointed Professor of Pharmacology at Rotterdam and I thought, ‘Oh, perhaps I want to be called a Professor’, which was very high sounding in those days. So I said: ‘Well, I’d like to go back to academia’ and I moved with him to Rotterdam. But I tried to persuade Organon that this was the line they should go down and this was where perhaps the future lay.

⁶⁰ Kimball, Freidman and Vallejo (1960).

⁶¹ Sicuteri, Testi and Anselmi (1961).

⁶² Saxena (1972).

⁶³ Saxena (1972, 1974).

⁶⁴ Saxena (1972).

⁶⁵ Saxena, van Houwelingen and Bonta (1971).

⁶⁶ Saxena (1974).

The next important thing was that I came here to London for the first time, to one of the Migraine Trust meetings; I think it was the second or third meeting in 1971/1972 or around that time. There I met Hartwig Heyck, and I think Michael O'Brien was saying, 'Look, patients are pale when they are having a migraine attack'.⁶⁷ I heard Hartwig Heyck, a neurologist at that time in Berlin, talk about so-called arteriovenous anastomoses. I had never heard of them. I thought: 'What are these? I don't know.' But, he explained that these are the direct communication between arteries and vein. When they open up all the blood is shunted to the venous side, causing 'dancing' arteries.⁶⁸ I said: 'Well, that's very fascinating. I'd like to have a model in animals so that we can record blood flow across arteriovenous anastomoses.' So, with the help of our friend from San Francisco, Ralph Forsyth, who came to us for about a year and a half, I established the radioactive microsphere technique and we were able to show that 5-HT decreases arteriovenous shunting, but conspicuously increases blood flow in the skin.⁶⁹ When I infused 5-HT on one side, half of the pig head turned red, but the arteriovenous shunting went down to nearly zero.⁷⁰ Well, that's very fascinating. Exactly the same thing was happening with ergotamine minus the dilation part, so no redness, no nothing.⁷¹ The same happened with methysergide.⁷² Later on, of course, more drugs were available to block the 5-HT receptors, so we were able to say, 'Okay, arteriovenous constriction is mediated by the atypical 5-HT receptor.' With Pat Humphrey and others, we were able to classify and name the 5-HT receptors and we said, 'Well, this atypical 5-HT receptor is 5-HT₁-like', later called 5-HT_{1B}.⁷³ If I remember correctly, it was at Pat's insistence that we initially called it '5-HT₁-like'; he wanted to be vague.

⁶⁷ See, for example, Lance and Anthony (1971).

⁶⁸ Heyck (1969). Professor Hartwig Heyck (1912–1982) was Chief Physician of the Neurological Department of Rudolf Virchow Hospital in Berlin.

⁶⁹ Saxena and Verdouw (1982).

⁷⁰ Professor Pramod Saxena wrote: 'By the way, infusion of 5-HT in the human brachial artery also decreases arteriovenous shunting and causes skin redness (Blauw *et al.* (1991)).' Note on draft transcript, 1 August 2013.

⁷¹ Johnston and Saxena (1978).

⁷² Forsyth and Saxena (1978).

⁷³ Bradley *et al.* (1986).

Humphrey: I think people just need to realise this was in the pre-molecular era. These receptors hadn't been cloned and I was very worried about being too dogmatic about what it was, so '5-HT₁-like' was right, I think, because in the end 5-HT_{1B} and 5-HT_{1D} are almost undifferentiable pharmacologically anyway, even molecularly they're incredibly similar.

Saxena: Absolutely correct. So the pharmacologists were ahead of the molecular biologists in this respect. And there were not many pharmacologists in those days – I think you could count them on one hand – I think four or five pharmacologists were working in the field of migraine. This was an area which was depleted. I thought, 'Oh okay, not many people are following this.' Later on, of course, with the discovery of sumatriptan everything changed. Just to round off: 5-HT and methysergide and ergotamine are very selective in constricting carotid blood vessels and this selectivity extends exclusively to arteriovenous anastomoses, emphasizing the work of Heyck. I was very excited and, I think, Pat, it was 1975 or 1976 that we met in London. I had been invited to give a talk at, I believe, a British Pharmacological Society meeting, and Pat happened to be there as well. He said: 'Well, do visit us' and 'very nice meeting you' etc. etc. I thought, 'Well, this young man is very dashing' but I didn't know him at that time. So, I went to his office at Allen & Hanburys, if I recall correctly, at Ware. We had a talk and some years later, 1980/1981, before sumatriptan was synthesized, at least as far as I know, he came along with Wasyl Feniuk to Rotterdam with two compounds and tested them in our arteriovenous anastomoses model. I have the experiments somewhere still on my computer. They didn't tell me, of course, what compounds they tested, but these were effective in decreasing arteriovenous shunting. Pat and Wasyl were very happy and they went back extremely satisfied.

O'Brien: I just wanted to comment on Heyck's experiments. He published his paper in 1970 and the suggestion was there were shunts both in the scalp and in the brain and the shunts opened up in the brain, thereby causing cortical ischemia, which thereby caused the aura.⁷⁴ That was his theory. And, in fact, although shunts do exist in the skin they've never been demonstrated in the brain. His experiments were basically to inject a tracer into the carotid artery and measure jugular venous concentrations and he found that migraine patients, when they didn't have a headache, and control patients had the same arteriovenous difference. But the arteriovenous difference dropped considerably during the headache stage, suggesting shunt flow. Unfortunately, it doesn't

⁷⁴ Heyck (1970).

really match with Elkind's experiments in which he injected a tracer, sodium unfortunately, which is diffusion, not perfusion, dependent, and he showed an increased clearance which is not shunt flow because shunt flow is not perfusion dependent.⁷⁵ So you wouldn't measure it. And Elkind's experiments, which were very elegant really at the time, showed faster clearance from the scalp, implying increased blood flow.

Volans: Could I add to the list of drugs that was in use for prevention? Clonidine. I can't remember the exact mechanism of action but in contrast to its original use for treating hypertension it was thought to be quite different. The dose that was developed for migraine was very much lower than the one used to lower blood pressure and this avoided many of the side effects. It was marketed as something called Dixarit. But what happened to that? I don't see it on any present-day lists of preventative treatments.

Peatfield: There was very little evidence that it worked at all. I drafted a review for the *Drug and Therapeutics Bulletin* after Andrew Herxheimer and I hatched a plot to get rid of the stuff on the grounds that it didn't work.⁷⁶ [Laughter] My friend John Fozard said it had no pharmacological effect at the doses used in man in any animal model whatever.⁷⁷

Olesen: Just a last thing about ergotamine. It was actually a very effective drug but people didn't quite know how to use it and there were very, very poor studies of the pharmacology of ergotamine available at that time. Actually my first PhD student was Peer Tfelt-Hansen and he studied the pharmacology of ergotamine. We wrote four or five papers about it because I thought that a compound that has no general analgesic effect but nevertheless works for migraine is a very interesting substance and might lead us on the way to understand migraine mechanisms.⁷⁸ But it turned out that the drug was too dirty; it works on too many receptors and it wasn't possible to use the mechanisms of the drug to understand migraine, and it was shown that bioavailability is very, very variable. The dose had to be titrated in every single patient and the dose needed can vary up to a factor of ten between patients. The route of administration was

⁷⁵ Elkind, Friedman and Grossman (1964).

⁷⁶ [Peatfield] (1990).

⁷⁷ Peatfield, Fozard and Rose (1986). For biographical information on John Fozard see page 101.

⁷⁸ Tfelt-Hansen, Eickhoff and Olesen (1980, 1982a, 1982b); Tfelt-Hansen and Olesen (1981).

extremely important, oral bioavailability being very, very low. The rectal route was popular on the continent and still is and ergotamine is somewhat better absorbed rectally. Using the full potential of ergotamine would actually have made it a much better drug but it wasn't really realised how to do that until the triptans came around.

Humphrey: I just wanted to respond to Michael actually but having heard what Jes has just said, I think he's brilliantly clear as usual. Listen to him. Because there is that amazing finding, as you said, that it's not an analgesic and it works in migraine so there's a clue there, a very important clue. But the dirtiness of the drug has to be recorded. We know it's an alpha agonist, we know it's a dopamine agonist, we know it interacts with a lot of the 5-HT receptors, so it's not a clean drug. And in this day and age, 2013, we should be using cleaner and cleaner drugs. That should be the aim of all drug development. The triptans are actually selective and clean, we'll come onto it at some stage, just activating the receptor through which ergotamine, and through which methysergide, were working, without activating all the other receptors. Can I just respond to Michael about the arteriovenous anastomoses? I think Heyck, a bit like I feel about Wolff's work, did work on arteriovenous anastomoses that was incredibly important and yet, nowadays, most don't believe in them in regard to the aetiology of migraine, and possibly I don't either, but it was again a very important way forward because we learnt so much about things that were going on in the head.⁷⁹ The mere fact that he could measure these AV differences on the side of the headache means there's some pathological event on the headache side that's going on, possibly related to disruptions of cranial blood flow, which are very, very local. So if you're talking about shunts we're not talking about massive shunts, we're talking about local shunts. I did actually find a paper, I don't know how good it is and I have not seen the work reproduced, but the authors actually found evidence of dural shunts in the meninges.⁸⁰ If we believe that that is where the vascular changes are taking place, then we should debate their significance if there are shunts there apparently.

Olesen: I too really must say that there aren't any functioning shunts in human beings and there aren't any functioning shunts during migraine attacks. We have studied this many, many times with much, much better techniques than those which Heyck and others used in the old days, and the way I look at this is

⁷⁹ Heyck (1969).

⁸⁰ Kerber and Newton (1973).

that sometimes a false positive finding can be extremely stimulating to science. Science moves on and later on you realise it was actually wrong but it was very productive. It set a lot of thought into motion and a lot of development and that's how we should look at shunts today. They do not exist in the human situation, not even during a migraine attack, but the results at the time were extremely interesting. The model that Pramod Saxena developed was extremely good and extremely important in predicting efficacy of future migraine drugs, but not because it exists in humans.

Saxena: Jes and I have been friends for, I don't know, 45–50 years nearly, but this is one point which we have not been able to resolve. Pat said: 'Well, I believe that the shunts are not important.' There's nothing to 'believe' in science; you either show it or put it on the shelf until somebody else proves it right or wrong. Whatever experiments Jes has done, which have been plenty and beautiful, it has not yet been ruled out whether the shunts are involved or not involved in migraine. It is not true that shunts are not there in humans. Going back many years, Rowbotham and Little and Kerber and Newton, I believe, showed very, very clearly that shunts are, of course, in the human skin but also in dura mater.⁸¹ So, we have got a challenge actually for the neurologists to take up experiments, which they can today. Peer Tfelt-Hansen did make an attempt, but he used normal volunteers. I challenge neurologists to have patients under attack and have a jugular venous catheter, which these days is not that difficult, and measure what Heyck did, all those years ago and prove him right or wrong. Do those same experiments first. And, Jes, saying that the science moves on. Yes, of course, in many cases it moves on, but I can give you examples where science comes back to the same old point. For example, Lauder Brunton proposed that amyl nitrite decreases the load on the heart by a vasodilator action and relieves angina pectoris attack. Again, more than a hundred years later we are back to the same theory.⁸² So that's not the point that the science moves on; sometimes science comes back.

Olesen: Pharmacological models can be extremely good and predictive even if they do not reflect the human situation, that's the case with your model. I mean you have not studied human beings. I have studied human beings for 30 years, during and outside of migraine attacks, and when we inject radioactive xenon

⁸¹ Rowbotham and Little (1965); Kerber and Newton (1973).

⁸² Brunton (1867). Sir Thomas Lauder Brunton (1844–1916) was a physiologist and physician at Edinburgh Infirmary and later St Bartholomew's Hospital, London, where he remained for 33 years. See also Fye (1986).

into carotid artery we could see clearly, for example in brain tumours, there was shunting because you see a peak in the clearance curve. But we've never seen anything like it in migraine during or outside of attacks. So I think it's really a fruitless thing to continue to discuss. Those people who study it have not seen it; those people who don't study it believe that it must be there because they have a very good animal model.

Saxena: Well, what do I say? [Laughter] I'll shorten the debate and say, 'Look, do the experiments that Heyck did at that time with the better techniques and better reliability in migraine patients under attack and prove us wrong.' I wouldn't care tuppence about it.

Weatherall: I'm going to invoke the Chairman's privilege to move on, if I may. I'm sure that you'll be very happy to carry on that particular conversation afterwards. I'd like really to move on to talk about the triptans and maybe I could come back to Pat Humphrey. You've already told us a little bit about the circumstances in which you came to be asked to work on migraine. Take us back to that point and tell us about where you decided to take that particular request.

Humphrey: Yes, okay. I was at St Mary's Hospital Medical School where I was teaching physiology and had done a PhD in pharmacology there. I didn't really want to remain a teacher, I wanted to discover a drug, so I was very delighted when David Jack asked me to come to Ware and start on a migraine project.⁸³ Why did he want somebody to work on a migraine project? Well, his daughter had migraine and he also believed in working on common diseases that were poorly treated, and, boy, was that the case. It is very common and it was very poorly treated, as Marcia Wilkinson, and other clinicians I went to talk to about it, made clear to me. So I thought it very important to start with the medical understanding first and I spent three months talking to people all over the world and reading all the medical literature.

I think the seminal points were firstly, Wolff's work. I never knew Wolff, obviously he preceded me in years and everything else, but his papers were brilliant, they put me onto a vascular focus. Secondly, talking to clinicians, it was clear that ergotamine worked. Again, I think Jes has very elegantly made the point – it's not an analgesic but it works in migraine; it's doing something but where? Thirdly, Lance's work was very instructive as well, seminal in the sense that methysergide seemed to be doing something the other 5-HT antagonists

⁸³ See page 21 and note 50.

didn't,⁸⁴ and it turned out of course later we found out it's an agonist at a novel previously unidentified receptor. Also, the whole 5-HT story that Lance had followed up on from other people, like Sicuteri, who showed indole acetic acid coming out in the urine during a migraine attack, so it looks as though 5-HT is depleted from platelets and then it comes out in the urine as its metabolite.⁸⁵ So, 5-HT is involved, ergotamine is a 5-HT agonist, and methysergide might have serotonergic properties – at the time we didn't know that it was a 5-HT agonist, but it was an ergot alkaloid type of molecule. We were looking at these concepts, which led to my view that we've got to find out what's special about methysergide because why is it different to all the other 5-HT receptor antagonists but yet it's doing something not dissimilar to ergotamine. I say that because, again, in talking to Lance in detail about his patients he told me, and this was the most seminal observation, that occasionally he gave methysergide to a patient in his office. They'd come in, they were having a terrible migraine attack and he would prescribe methysergide for prophylaxis but he said: 'Take your first tablet now.' And they took their first tablet in the office and it fixed the migraine in front of him. Now it didn't happen very often but he was sharp enough to make the observation and tell me about it; that was the critical thing. So the whole thing was, what was unique about methysergide? Possibly an action shared with ergotamine, but that's too dirty a drug to work out the amine receptor that might be involved because it activates so many different receptor types.

Of course, the next seminal thing, the last bit of the jigsaw, was Pramod's work because he was looking at carotid shunts. The thing about shunts that appealed to me was that they provided a hypothesis you could hang your hat on about what causes migraine. So the Heyck hypothesis around the pathophysiological role of shunts was the best we had at the time and there's Pramod showing that the methysergide actively constricted these shunts whereas the other 5-HT antagonists didn't. And so that was very appealing. Now that wasn't how we got to sumatriptan specifically because, as Pramod has inferred, we'd already started looking at cranial blood vessels. We were trying to work out what was going on in terms of the receptors because at the time we only knew of two different 5-HT receptor types, the 5-HT₂ receptor and the 5-HT₃ receptor, which Gaddum called 'D' and 'M'.⁸⁶ We started looking at this and, funnily enough, one of the

⁸⁴ See, for example, Curran and Lance (1964); Lance, Anthony and Somerville (1970).

⁸⁵ Sicuteri, Testi and Anselmi (1961).

⁸⁶ Gaddum and Picarelli (1957).

preparations we used early on as a sort of marker for peripheral blood vessels was the canine saphenous vein. And it turns out that that was selectively constricted by methysergide. We couldn't believe it; what's happening here? That's how we discovered sumatriptan really, by looking at blood vessels, looking at dog saphenous vein and suddenly finding out methysergide was an antagonist in every blood vessel we looked at except the dog saphenous vein, where it constricted.⁸⁷ So then we went looking in cranial blood vessels and there we found some, but not all, cranial blood vessels would constrict to methysergide. We were really onto what we thought was a third 5-HT receptor type, and it eventually turned out to be the 5-HT_{1B} receptor. The other thing is we also found that the same or similar receptor was on sympathetic nerves innervating certain blood vessels where it was inhibitory, so that was probably the 5-HT_{1D} receptor but at the time we weren't sure. Every single compound we ever made activated both receptors so that's why I was quite happy to lump them together for a very long time. But, having found a compound that was selective for the dog saphenous vein receptor, we wanted to go to Pramod's laboratories and find out whether it constricted carotid shunts selectively, and it was brilliant on shunts. They were about the only vessels it constricted *in vivo* that you could measure. It didn't affect cerebral blood flow or anything else, just constricted carotid shunt flow in an extraordinarily selective way and potently.

Weatherall: Can you just tell us a little bit about the process of how these molecules were made and constructed?

Humphrey: The other thing is that when I arrived at this empty lab and the Head of the department, Roy Brittain,⁸⁸ said to me: 'Well look, here are some lab notebooks of what we've been doing' because apparently they'd had a project five years earlier and they had been synthesizing all these massive great ergot alkaloid molecules. One of the reasons ergotamine doesn't work for lots of people is that it's not absorbed. You know people who have taken it orally and it doesn't even get into the blood stream, there's virtually zero ergotamine in the blood. So I wasn't going to make large molecules. Well, what would you make – 5-HT-like molecules. The 5-HT hypothesis was such that 5-HT was involved, so we were making very simple molecules, which were just simple indolic variants on 5-HT. Now I say that, I'm slightly embarrassed because I've

⁸⁷ Apperley *et al.* (1980).

⁸⁸ Dr Roy Brittain (1930–2013) was appointed Head of the Pharmacology Department at Allen & Hanburys Laboratories at Ware in 1962, becoming Research Director in 1979 and Head of Glaxo Group Research from 1983 until his retirement in 1992; see Drew and Humphrey (2013).



Figure 12: Dr Alec Oxford

got the chemist who made them all sitting next to me [Alec Oxford] and I say 'simple molecules'. Well, at that time making 5-HT analogues was not easy. There was quite a long run in period until we got going. But that's what we did. We made simple analogues of 5-HT.

Weatherall: Maybe Alec Oxford, would you like to tell us a little bit about that side of things?

Dr Alec Oxford: Our target was an orally acting selective full agonist mediating contraction of the dog isolated saphenous vein. The strategy was to start with 5-HT and identify the key features that gave the affinity and selectivity for this 5-HT receptor. We assumed that the hydroxyl group would be very important and we spent a long time studying the properties of this substituent by replacing it with other groups such as a hydrogen atom, alkyl group, methoxy group or chlorine atom, usually with loss of activity and selectivity, but eventually we found that a carboxamide function gave rise to a potent agonist at this 5-HT receptor (AH21467, 5-CT). However, when this compound was injected into animals it caused a profound fall in blood pressure. This then led to the discovery that it was acting at a vasodilator receptor, now known as the 5-HT₇ receptor, as well as the dog saphenous vein receptor. But we found that if we introduced another methylene group between the carboxamide and the indole ring we got rid of the activity at the vasodilator receptor, and this gave rise to a selective agonist at the 5-HT₁ receptor on dog saphenous vein (AH22800). A more

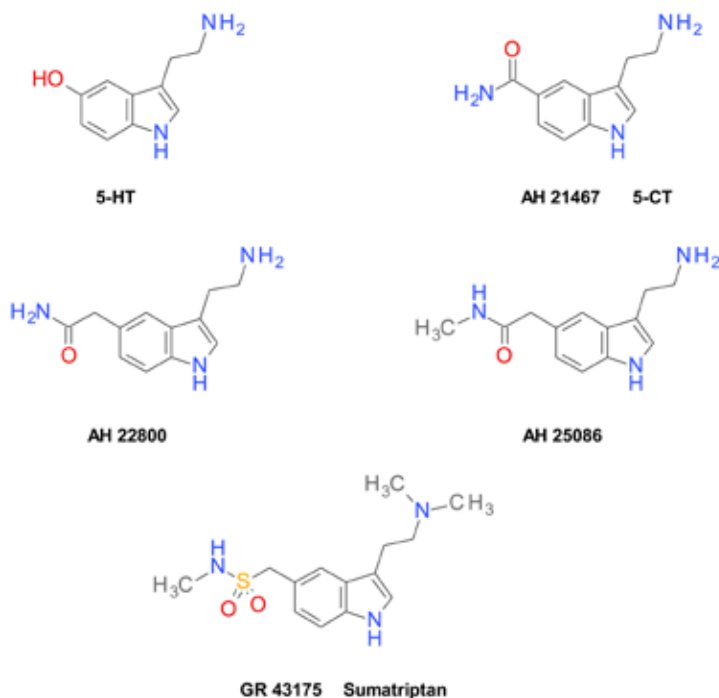


Figure 13: Chemical structure of some 5-HT agonists

potent and selective analogue (AH25086) was found to be an effective anti-migraine agent but only by i.v. administration.⁸⁹ Further analogues eventually gave rise to the orally acting compound sumatriptan only after several hundred tryptamine derivatives had been synthesized.⁹⁰

Humphrey: Just to add to that, the whole hypothesis within the project which I was running at the time was to make a selective compound for this dog saphenous vein receptor and when we put it *in vivo* it should constrict the carotid shunts and it would not have any effect on blood pressure because it would not have any effect on any other blood vessels. When we put our lead compound (AH21467) into an anaesthetized dog, the blood pressure fell right down into its boots to everyone's surprise and amazement. The project team was deflated and disappointed but I went to David Jack and said: 'This has happened but I think we have probably found another 5-HT receptor, it's the

⁸⁹ Doenicke *et al.* (1987).

⁹⁰ For an overview of the clinical studies with GR43175 see Perrin *et al.* (1989). For the development of sumatriptan see Humphrey *et al.* (1990); Humphrey (2001).

only way I can explain it.’ He said: ‘Well, go away for 12 months and come back when you’ve proved it.’ That was the amazing thing because today that would never happen. It would be ‘hard luck, your hypothesis is wrong, go away.’ But he didn’t say that and luckily the chemists stuck with us too, because they were very disappointed that the hypothesis I had put together was possibly wrong. But they stuck through it and when we proved it, or had better evidence for it, we went away and started the chemistry again.

Blackburn: I think this addresses my question earlier with regard to how important some of these agonists were in our early understanding of migraine. This is classic Sir Jim Black’s work, where he used agonists to tease out receptor function.⁹¹ That is what pharmacology is all about, developing 5-HT-like agonist compounds to understand receptor subtypes and their function.⁹²

Saxena: Absolutely. And Glaxo had experience in that because they had synthesized the anti-asthma drug salbutamol on the same basis, modifying the isoprenaline molecule to obtain a more selective compound.⁹³ May I ask a question to Pat or Alec? Would they today reveal which were the compounds they tested at my lab in about 1981? They have never done it so perhaps today might be the day!

Humphrey: Well, the problem is it’s so long ago I’ve forgotten, Pramod. [Pat smiling – laughter]

Jones: The fortunate thing about drug discovery and development is that if you’ve got pioneers like Pat and Alec, the ‘follower’ can actually benefit from all of their knowledge and experience – and that’s what happened in my time at Wellcome. By that time it was established that sumatriptan was effective, we

⁹¹ Professor Sir James Black (1924–2010) was Professor of Analytical Pharmacology at King’s College Hospital Medical School, London, from 1984 to 1993. His work at ICI in the 1960s led to the development of the first beta blocker, propranolol. He was jointly awarded the 1988 Nobel Prize for Physiology or Medicine (with George Hitchings and Gertrude Elion) for ‘discoveries of important principles for drug treatment’. See the special issue of the *British Journal of Pharmacology* celebrating his life and work (McGrath, Bond and MacKie (eds) (2010)).

⁹² For discussion on 5-HT receptor subtypes, see the Witness Seminar on drugs affecting 5-HT systems (Overy and Tansey (eds) (2013)).

⁹³ The Allen & Hanburys research laboratories at Ware (absorbed into Glaxo in 1958) had developed the anti-asthma drug salbutamol in 1966, which was marketed in 1969 as the Ventolin inhaler; Sir David Jack (see page 21, note 50) discusses its development at the Witness Seminar on childhood asthma (Reynolds and Tansey E M. (eds) (2001)).

knew its possible mode of action and, with very good medicinal chemistry, we decided to make the molecule more lipophilic so that we could get the drug into the central space – across the blood–brain barrier – because sumatriptan was relatively poor in that regard; in fact it probably doesn't penetrate the blood–brain barrier at all. So that led us to a rather simple, but very elegant, piece of medicinal chemistry that resulted in zolmitriptan. As you say, the word 'simple' is a comparative term and the absorption of zolmitriptan was 64 per cent against the 4 per cent of sumatriptan.

Humphrey: 14–15 per cent of sumatriptan.

Jones: Oh, I beg your pardon, 14–15 per cent. Interestingly, the Phase I study, as it was called in those days (nowadays we prefer to divide drug development into two steps, 'Learn' and 'Confirm'), was conducted in a clinic in Amsterdam. I remember my Medical Director coming to my office and saying: 'I think we've got a problem.' The study was in a very small number of migraineur⁹⁴ volunteers, the statistical analysis of the results showed that the efficacy was equivocal. In fact, as we discovered, there was one patient who had just taken a dose of the experimental medicine and suddenly realised that her car was parked outside and she hadn't paid the parking fee. She looked out the window to see it being towed away and flipped into a major migraine crisis. Analysis without that patient did show adequate significance and allowed us to carry on and do the next study in a broader population. Had we not known about that volunteer incident we probably would have killed the project! As it turned out the compound was never launched by Wellcome because we were then taken over by Glaxo who couldn't take it on because of the monopoly potential with sumatriptan, so zolmitriptan became the property of Astra Zeneca.⁹⁵

MacGregor: I was actually going to slightly change tack with the fact that the development of sumatriptan and the development of the IHS diagnostic criteria led to a complete change in the way that clinical trials for migraine were undertaken. I think that if we just had the classification and we hadn't had the development of sumatriptan, or the other way around, then the development of clinical trial programmes in migraine and research would be very different. But having the two together meant that the whole way we approached clinical trials

⁹⁴ Dr Jeffrey Aronson wrote: 'I can think of only two conditions whose sufferers are denoted by a French word in English: migraineurs and ticeurs (sufferers from Tourette's syndrome).' Note on draft transcript, 30 July 2013.

⁹⁵ Glaxo and the Wellcome Foundation merged in 1995 to form Glaxo Wellcome.

at that time became much more rigid. The follow up with patients was much better and it led to a whole change in the way that we did research, not just the new drugs. Really incredible.

Blackburn: One of the things we've discussed with Pat's work and with sumatriptan was the focus on intervention therapy. I think it was you, Richard, and Tim Steiner, who worked with the ICI 5-HT receptor antagonists at the time, in particular ICI 169,369. It was around this time that ICI Pharmaceuticals were trying to develop a prophylactic treatment for migraine acting at the 5-HT₂ receptor as we knew it then. Interestingly, methysergide is also very potent at the 5-HT_{2A} receptor and we were trying to develop a selective 5-HT_{2A} receptor antagonist compound and we showed in a migraine study significant clinical efficacy. We also looked at it in anxiety, depression, and in schizophrenia. Unfortunately, the clinical signals in those studies were compromised by the clinical design and the number of patients, but ICI felt at that time that the prophylactic market was not a good market as we would be totally overwhelmed by Glaxo's intervention therapy with sumatriptan.

Peatfield: Weren't we all?

Blackburn: Yes, exactly. [Laughter] It even came to pass at one of the British Pharmacological Society meetings that there was some criticism of Glaxo in their marketing strategy and the way they went about it. But that's by the by. It worked. It is an excellent drug. I also took part in a Migraine Trust meeting in London that Pat and I often talk about, where Barry Cox and I (ICI) presented the rationale for the prophylactic treatment of migraine with ICI 169,369 and Pat and Glaxo were marketing sumatriptan for intervention therapy and did a fantastic job! After which the ICI marketing boys said: 'There's no way that our prophylactic treatment would be useful in the treatment of migraine.'⁹⁶ The ICI marketing boys won and the project was terminated.

However, today prophylactic treatment is still of great interest. And, interestingly, at that time I worked with a young lady in Lund in Sweden (Inger Jansen, now Inger Olesen, whom I'm delighted is with us today) with Lars Edvinsson, where we looked at the compound on human temporal artery and pial artery. If I'm

⁹⁶ Dr Tom Blackburn wrote: '... although it showed efficacy in one study at Charing Cross with Richard Peatfield.' Email to Ms Caroline Overy, 18 December 2013. Dr Richard Peatfield added that there was 'a small open study (10 patients) of ICI 169,369 done by my Charing Cross colleagues Paul Davies and Tim Steiner (while I was away as Senior Registrar in Leeds). This speaks of "some beneficial effect", though it was "not marked" (Davies and Steiner (1990))'. Email to Ms Caroline Overy, 22 January 2014.

correct, we observed antagonist activity on temporal and pial vessels, which was unlike the findings with ketanserin or methysergide.⁹⁷ ICI 169,369 was active on both vessels and the interesting thing we found out much later, was that ICI 169,369 had activity at the 5-HT_{1C} receptor subtype, which subsequently became known as the 5-HT_{2C} receptor, which is found in the choroid plexus and has been implicated in the pathophysiology of migraine. At this time, I was developing these ideas, but unfortunately the interest and CNS research moved over to the US and the programme was closed down.

Weatherall: What happened to the compound?

Blackburn: It never made it, it just lost its way. It died and some would argue that compounds die in drug development either due to toxicity, safety, drug metabolism and pharmacokinetics, or lack of efficacy. But, in this case, and as we know today, 33 per cent of the attrition rate associated with drug development is down to marketing or management prejudice. Unfortunately, that was the case with the ICI compounds.

Peatfield: I should say as a little aside there was a Migraine Trust symposium, it must have been 1990, when I think there were a thousand delegates and I think 900 of them were paid for by Glaxo. It was a magnificent sales propaganda exercise and it carried the day.⁹⁸

Blackburn: This was the Migraine Trust meeting I think I went to that the Patron Princess Margaret attended. I think it was the one where Princess Margaret came in with her entourage and, getting back to the comment about champagne,⁹⁹ the first thing she was given as a migraineur was a large gin and tonic as she walked in. [Laughter] So whether that cured her migraine or not, I don't know.

Olesen: You bring up a very important point. Many possibly effective prophylactic drugs are not developed because people feel that the triptans solve all problems. I meet with many drug companies with several interesting compounds showing promise of prophylactic activity in animal models but they all get killed because so-called marketing research – which actually has nothing to do with research, it's just prejudice – also says there's a very small

⁹⁷ Jansen *et al.* (1991).

⁹⁸ Some of the papers from this meeting were published in a special issue of *European Neurology*, entitled *Sumatriptan. From molecule to man* (Anon (1991)).

⁹⁹ See page 17.

prophylactic market. This is because all drugs are off-patent. Marketing people also think that the triptans can do everything we need. This, we know of course today, is far from true. Talking about the triptans, they were an enormous breakthrough, it was a change of paradigm of the whole scene for migraine and their importance cannot be over-emphasized.¹⁰⁰ For many years we have known, however, that they are far from the final answer that we need to the migraine problem. We are now actually in a situation where their success is blocking further drug development.

Weatherall: Thank you, Jes, I think that's a very, very interesting point from a historical point of view. I'd like to just take the story back a little bit because we took it through with Pat Humphrey to the point at which they developed a compound and you trialled it in Pramod's model and that it seemed to be effective. I just wondered if you could speak a little bit more about how that compound actually became the drug?

Humphrey: Obviously we got excited because we could then elucidate within the company, an idea of how this compound would work clinically. You know we had the carotid shunts hypothesis, this compound worked on the shunts. Obviously one of the more challenging points that was an issue for me was that we had a vasoconstrictor agent – what's it going to do? We went on to do some extensive microsphere studies which we'd learnt in Pramod's lab, and I'll be eternally grateful to him for that, where we could show that this compound didn't affect coronary blood flow, didn't affect cerebral blood flow, it didn't affect blood flow in the limbs, and it was very different to ergotamine in terms of its vascular profile. All it did was constrict these shunts. So we had Heyck's carotid shunt hypothesis of the aetiology of migraine, we had a compound that worked on it, so let's get in a clinic and find out. The problem was that nobody was very interested in the idea. You went to talk to clinicians about this idea but none was interested. I'm not going to name names, but they weren't. We ended up having a couple of anaesthetists in Germany who were prepared to do the study and that paper was published in 1988.¹⁰¹

The other problem, of course, is how do you do such a clinical study properly and this is why I was so excited by Jes Olesen's work, his thinking, and his drive. But, to be fair, there was a lot of push from Glaxo in terms of wanting that done. I think there was quite a bit of funding, wasn't there, Jes? Through Glaxo's support

¹⁰⁰ See Humphrey, Ferrari and Olesen (eds) (2001).

¹⁰¹ Doenicke, Brand and Perrin (1988).

12/04/2012

Dear Dr. Humphrey,

I write to you personally to thank you for your part in developing sumatriptan, but I hope you will share these words with other pharmacologists you may know and work with.

I can't express what an amazing gift you have given me with sumatriptan. I'm currently pursuing a PhD—something that would be near impossible with the incredible days-long (and drug-resistant) migraines I used to get. Freedom from migraines means I'm more productive, active, social, and all-around happier.

Thank you for the years of work you put into developing this drug, and for your continuing dedication to making normal life accessible to people like me. You may not often get to meet the people you touch; you may rarely get thanks for your work... But know that everytime I take that little pill, I send warm thoughts your way. Best, [REDACTED]

Figure 14: Letter to Dr Patrick Humphrey thanking him for his part in the development of sumatriptan

things got going internationally. And it was for the good of everybody. People knock the pharmaceutical industry and I'm not going to defend the marketing boys but at the end of the day this was a potentially exciting compound. If we could do the right studies and show it worked, we could then market it and we could go on and find other drugs. This drug, at the end of the day, didn't need marketing because it worked. I've got a letter in my pocket (Figure 14), which is one of many that I still receive from women, saying, 'You've changed my life', which is extraordinary; 20 years on you still get letters like that.¹⁰²

So it must work. It didn't necessarily need marketing but you do, in the modern era, need structured support and funding. When we started trying to develop sumatriptan in a new therapeutic area, without experience, we did not have an understanding of how to conduct proper clinical trials and unfortunately our German friends, who, though competent, were not proper neurologists. It needed people like Jes Olesen and Jim Lance and other people around the

¹⁰² At a Witness Seminar on platinum salts, Robert Naylor, Professor of Pharmacology and Neuropharmacology at the University of Bradford (1998–2011), refers to receiving similar letters of thanks from patients, following the introduction of ondansetron as an antiemetic in cancer treatment. See Christie and Tansy (eds) (2007), page 59.

world to say: ‘This drug works’, before others would believe in it. When I heard people like Jes saying, ‘Yes, this is a good drug’, you knew it was a good drug that could benefit migraineurs. Then the issues really were more around the safety issues.

But I’ve probably gone off a little bit from what you asked me to talk about because the original compound worked really well in these German trials. We got very excited about it but for various reasons we didn’t want to develop it, there was an issue around oral bioavailability. Trevor’s already alluded to the bioavailability of sumatriptan,¹⁰³ which was the follow-up compound from AH25086, but I was very happy with it because it actually was absorbed very well, because that 14 to 15 per cent was absolutely reliable, it wasn’t variable as you often get with a 15 per cent bioavailability compound.¹⁰⁴ I didn’t want it to get in the brain. I still don’t think sumatriptan gets in the brain to any significant degree – a lot of the other triptans do, and they’re no better clinically.¹⁰⁵ But at the time I thought: ‘This is going to be bad news if we get a compound like this into the brain, we don’t want it in the brain.’ So 14 per cent was great by me and sumatriptan was the development compound, and it was patented in 1984. By then, all this work that Jes and all the international people he’d pulled in had done, had led us to be able to do some really good trials, and it all came together. Sumatriptan Trial 1, well it’s all out there in the literature, you can see it, but it was just literally amazing, particularly by the subcutaneous route.¹⁰⁶ But around the corner was the other issue about safety and we were initially using sumatriptan intravenously in our experimental trials. We did have one woman who had an ECG event but we argued that we were not going to use this drug intravenously; a great big bolus of any drug will create very high local concentrations. We knew it was safe in all the animal studies we had done. We had given it to animals for months; we had given it by every route you can think of. We argued that it was just a question of dose. But, as it turned out, we found that there were some 5-HT_{1B} receptors in human coronary arteries and that led to a lot of work looking at isolated coronary arteries and so on. In the end we concluded that this drug was safe providing you weren’t going to give

¹⁰³ See page 39.

¹⁰⁴ Fowler *et al.* (1988).

¹⁰⁵ Dr Patrick Humphrey wrote: ‘This refers to other triptans thereby making an important point about a predominantly peripheral action for them all, see Humphrey, Ferrari and Olesen (eds) (2001).’ Email to Ms Caroline Overy, 19 December 2013.

¹⁰⁶ See, for example, the Sumatriptan Auto-Injector Study Group (1991).



Figure 15: The sumatriptan discovery team c. 1984. Pictured left to right: Martin Owen, Helen Connor, Patrick Humphrey, Darko Butina, Wasyl Feniuk, Marion Perren, Alec Oxford, Pam Gaskin, Ian Coates

it to people with severe arteriosclerosis, you weren't going to give it to people who were in the middle of a stroke or other such cardiovascular risk scenarios.¹⁰⁷ Again, diagnosis is absolutely imperative. There's a big story there but I won't go on about it, but that was my biggest worry for a number of years, and I spent a lot of time talking to cardiovascular experts and trying to do studies to show this drug's safe. Ironically, it's now available over the counter in Britain – it's just extraordinary. That was the biggest issue – if the marketeers had to do anything, it was to support efforts to evaluate safety issues to show people that it was safe, rather than it worked because it really did work, that was obvious.

Weatherall: I'd like to concentrate on one final issue, which is the reception of sumatriptan and the triptans in clinical practice. Jes, could I ask you for your recollections of where this compound first hit the radar and what the uptake was like and how that process happened?

Olesen: We were, of course, part of the drug development programme and the classification was used actually before it was published, it was already used in the Glaxo trials. I just want to mention the first experience with intravenous

¹⁰⁷ See, for example, Brown *et al.* (1991).

sumatriptan; it was just unbelievable. We said all along: ‘If this drug is going to work it’s going to change the whole field because it’s so selective.’ So far we never had something like that. But the odds that it was going to work were not that high. I still remember my PhD student who was treating patients with slow infusion of sumatriptan intravenously. She treated a couple of patients and came back to me and said; ‘This is unbelievable. As we are injecting this compound the patient says, “Now my headache stops throbbing,” and before I finish the injections the patient says, “Now my headache is gone.” It’s like giving glucose to a patient in hypoglycaemia when they wake up during your actual infusion.’ That was, of course, very, very convincing. So I don’t know which country registered first; Denmark registered this drug very early.

Humphrey: I think Holland was earlier.

Olesen: Holland was just a little bit before Denmark but was it 1991 or something like that?

Humphrey: I could tell you in a minute, I’ve got a list (Table 3).

| Date | Country | Date | Country |
|-------------------|----------------|------------------|----------------|
| 1991 June 17 | Holland | 1992 July 7 | Venezuela |
| 1991 August 1 | New Zealand | 1992 August 4 | Mexico |
| 1991 September 30 | UK | 1992 August 25 | Malaysia |
| 1991 November 1 | Sweden | 1992 October 1 | Iceland |
| 1991 November 11 | Luxembourg | 1992 October 5 | Uruguay |
| 1991 November 25 | Portugal | 1992 October 14 | Poland |
| 1992 January 10 | Singapore | 1992 October 14 | Belgium |
| 1992 January 13 | Italy | 1992 November | Paraguay |
| 1992 February 3 | Canada | 1992 November 11 | Austria |
| 1992 February 3 | Denmark | 1992 November 21 | Chile |
| 1992 February 18 | Hong Kong | 1993 February 1 | Germany |
| 1992 March 5 | South Africa | 1993 February | Colombia |
| 1992 March 31 | Greece | 1993 March | Cyprus |
| 1992 April 1 | Israel | 1993 March 8 | Argentina |
| 1992 May 18 | Australia | 1993 March 29 | USA |
| 1992 July 3 | Finland | | |

Table 3: Launch dates of sumatriptan. Information supplied by Dr Patrick Humphrey

Olesen: I think it varied a lot how it was taken up because it had to do with the reimbursement in the different countries. People thought that this was outrageously expensive, to treat this disease, which was at that time really not recognized as anything other than more or less hysterical women who were psychologically out of balance or something – that was the general prevailing view of migraine before the advent of the triptans. It was far too expensive – £5 to treat a migraine attack. It's much better to lie in bed for two days and vomit. So that was the attitude in most countries – they were not willing to give good reimbursement of the drug up front – but in Holland and Denmark and other Scandinavian countries it gradually got the reimbursement. I think that was crucial for the take up of the drug.

Blackburn: It still is today.

Olesen: It spread very rapidly in those countries where it was reimbursed, for example in Denmark. A few years later and almost every patient was offered a triptan.

Peatfield: I was going to make that very point that the price was always a major problem here, because of course there hadn't been a budget for migraine. It's easy in Britain to introduce a technique or a device if you're saving money but in this situation the reverse applied. There was no perceived disease, so there was no clinical problem. Suddenly we were spending vast amounts of money on individual patients, which is why Glaxo had to market it in the aggressive way they did, and the marketing did work. But even now we tend to put this drug fairly far up a spectrum with aspirin and paracetamol and ibuprofen and you name it, albeit on separate attacks as a way of trying to keep costs down and only allow the patients who really are desperate for it to take it, simply because it still costs a lot of money.

Saxena: I do remember sumatriptan was marketed in 1991 in Holland and, as the laws were at that time, there was no reimbursement for the tablets because they were grouped together with ergotamine and then you'll only get little back. Patients then learnt to inject themselves. So everybody was injecting in Holland. By the way, I remember I was sitting next to Pat and I happened to remark: 'Look, this drug is very, very costly; it is more costly than gold, platinum and diamond taken together.' The marketing boys didn't take me very kindly.

Blackburn: I think addressing your point, Jes, with regard to price reimbursement, we're still faced with the same issues and challenges 22 years later. Migraine is not seen as a life-threatening disorder, like anxiety and depression, yet price reimbursement is still a major concern for any new medication being launched today.



Figure 16: Mrs Wendy Thomas

Jones: That's very true. Allergan's most recent migraine drug is Botox.¹⁰⁸ You will understand that the cost of Botox is high but if you think about how much it cost to actually invest in the kind of research that Pat and Alec did, and we did in Wellcome, and at Allergan, how many years it takes and, nowadays, the increased burden of the regulatory numbers of patients that you have to include – and then double that to get enough data for health technology assessment, not to prove safety and efficacy but to convince pricing bodies about its cost-effectiveness – then you can understand why the cost is high. The one thing that Allergan have managed to do with Botox in that context is to show payers the economic gain that they get in terms of 'back to work' or reducing 'carer cost', etc.

Mrs Wendy Thomas: I'm Chief Executive of the Migraine Trust and I was on the NICE guidelines development group on headache, which published guidelines last September.¹⁰⁹ It's interesting about cost because what was discovered in terms of cost-effectiveness, which is why the advice now to GPs in upping treatment, is that when a patient with migraine goes to see a doctor they are offered an NSAID and a triptan. That was actually cheaper than any other particular way

¹⁰⁸ For the use of the botulinum toxin in the treatment of migraine, see, for example, Becker and Amirlak (2012); Rapoport (2012); Frampton (2012); Durham and Cady (2011). See further comments by Professor Trevor Jones on page 57.

¹⁰⁹ NICE (2012).



Figure 17: Dr Jeffrey Aronson and Dr Richard Peatfield

of treatment. The other thing that astonished all the health professionals around the table was that the evidence showed that an antiemetic was as good on its own as with other treatments. So, though cost is obviously terribly important, the business of the NSAID and the triptan turned out to be the cheapest and most effective option, which of course keeps NICE very happy indeed. Also the point being made about Botox and other things is absolutely right. We forget how many people suffer from migraine; there are 25 million days a year of work and education in this country lost through migraine, and that is part of the problem when you do the economic costs. Tim Steiner has done some excellent work on the epidemiology and the economic cost of migraine, which the government has taken on board for figures.¹¹⁰ But that's what we've got to keep pushing at, given that the reason why migraine doesn't get funding, and I'm sure we'll talk about this afterwards, of course, it doesn't actually kill you.

Aronson: Can I give a patient's view?

Weatherall: Please do.

Aronson: I have migraine, at least I have what I call migraine. It sounds sexier than cluster headache or tension headache or any other syndromic abnormality that you might describe. But I'll tell you my story and you'll decide whether I have migraine, and I've had it pretty much all my life. Certainly I remember as a child at the age of seven or so suffering sick headaches, what my mother called bilious

¹¹⁰ See, for example, Steiner (2010); see also Steiner *et al.* (2003).

attacks. Headache, severe; a few hours later vomiting; going to bed; waking up, feeling as if your brain has been scrambled. It's debilitating. I had it until I was in my early or mid-teens and then not again for 20 to 30 years, when it came back. These attacks are very severe. In me, they start with a pain in the neck about an inch behind the mastoid process. They then spread up over the right side of the head into the forehead. Occasionally I get a dull aching on the left side but the usual way of it is as I've just described, on the right. It gets worse over a few hours and I vomit, the intensity of the vomiting being proportional to the intensity of the headache. During this time I have sought a darkened room but photophobia is not a major aspect, nor is hyperacusis or any other local symptoms, tenderness, or whatever; just the headache and the vomiting. After the vomiting, I sleep and I wake up the next morning, as I said, feeling as if my brain has been put in a liquidizer and poured back into my skull and I am mentally pretty much out of it for that day. So this is a 24–36-hour disease as far as I'm concerned, and it is incapacitating. I have tried everything: aspirin, paracetamol, prochlorperazine as an antiemetic sublingually or buccally rather than orally. I haven't tried ergotamine or methysergide, I certainly haven't tried clonidine. Nothing worked.

I was visiting my friend and colleague Robin Ferner in Birmingham one day;¹¹¹ we were writing a paper. It was a sunny day; dehydration brings it on, not in my case chocolate, but wine brings it on. Any alcohol actually, more than one unit, except the day after an attack after a triptan when I'm refractory and can drink, which is another benefit of the triptans. So I got a migraine during that day. It was a beautiful spring bank holiday and Robin said: 'What do you do about it?' I said: 'Nothing works.' I said: 'The only thing that works is exercise, half an hour on the bicycle up the Banbury Road, down the Woodstock Road to St. Giles, back up to Summertown, that relieves the headache. But I'm not in Summertown and I don't have my bicycle. What am I going to do?' He said: 'We'll go to the chemist and get you a triptan.' Now at that time there was this caution about being aged over 45 and a risk of myocardial infarction because of coronary vasoconstriction, and I had avoided triptans because of that. But he said: 'Oh no, don't worry about that, forget it.' I said: 'Fine, let's go and get it.' So we went to the pharmacist's and he only had naratriptan in stock – Naratriptan Melts.¹¹² So I bought a tablet at a vast cost; Robin wrote a private

¹¹¹ Professor Robin Ferner is a Consultant Physician and Clinical Pharmacologist at Birmingham City Hospital and Honorary Professor of Clinical Pharmacology at the University of Birmingham.

¹¹² Naratriptan, marketed as Naramig, was launched by GlaxoSmithKline in 1997. See comments by Dr Patrick Humphrey on pages 63–4.

prescription. We walked back to his house and I put it under my tongue. Now I thought, nitrates under the tongue act very rapidly. So I thought that this melt under the tongue would act very rapidly. So I let the tablet melt under my tongue, and suddenly [snaps fingers] – nothing happened. Well, the saliva accumulated under the tongue until I had to swallow it and I thought: ‘Well, that was a waste of ten quid or whatever.’ I went on writing the paper, because I knew nothing would affect the migraine and I thought I’d better get as much work done as I could before I conked out. One and a half hours almost to the minute after putting that melt into my mouth the headache switched off – just like that. If you’d told me that that would happen I would not have believed you. It was like a switch and the headache disappeared instantaneously. It’s happened once to me before in other circumstances¹¹³ but I would not have believed it. Since then I’ve taken naratriptan regularly. I take it orally, and it works within about an hour and a half to two hours. And the other thing that I’ve noticed, as the last part of this story, is that having been taking it now for about ten years I suppose, and the frequency of my attacks has increased, but the severity is aborted by taking a tablet of naratriptan as soon as I feel the headache coming on. Occasionally I wake with it and then it’s sometimes too late and I have to take two tablets, and even then sometimes that doesn’t help, but that is rare.

Weatherall: Speaking on behalf of the clinicians in the audience, you have migraine, and an effective treatment which is thanks to Pat and to Alec and Pramod and all the others who worked on the triptans.

I’d like to move on to one other aspect really of the 5-HT story and then take that into the scientific impact of the triptans. One thing that I think that Pat may have briefly alluded to and rang some bells with me in terms of what Richard Peatfield, I believe, found himself doing in the early days in Clifford Rose’s group was the platelet story.¹¹⁴ There are bits and pieces of migraine

¹¹³ Dr Jeffrey Aronson wrote: ‘On that occasion I was down to give an after-dinner speech at a dinner hosted by the erstwhile magazine *The Listener*, at the Café Royal, and my migraine came on during the dinner. I went to the toilet to vomit and the chairman for the evening found me there. I said that I didn’t think that I could give the speech and he persuaded me just to give the toast. When the time came he introduced me, and as I got to my feet the headache switched off instantaneously. I gave the whole speech, sat down, and the headache flooded back. Could it have been an effect of endorphins?’ Note on draft transcript, 30 July 2013.

¹¹⁴ See also the discussion in the Witness Seminar on drugs affecting 5-HT systems (Overy and Tansey (eds) (2013)).

research from a historian's point of view that rise and fall and this is something that was quite prominent in the 1960s, 1970s, and 1980s but has fallen out of view. Richard, what can you recall?

Peatfield: I had five minutes' notice of this question and I would need a few days to reread all the material because it has slightly faded from memory. I was appointed by Frank Clifford Rose¹¹⁵ to work at Charing Cross in 1979 on a fellowship supported by the Migraine Trust, so there was a bit of an obligation to do some sort of headache-oriented research. It soon became clear that I needed a source of wise guidance, which was kindly given to me by Merton Sandler who is now sitting in front of me. So Marek Gawel and I trailed off to Merton Sandler's lab at Queen Charlotte's and we worked out what we could do.¹¹⁶ As with most science it's all based partly on the availability of patients and partly where the technology had got to, and this was the era of platelet function and platelet testing for monoamine oxidase. Merton, as you know, is a world authority on monoamine oxidase and had spent a long time chasing monamine oxidase in platelets.¹¹⁷ He had a number of research fellows, PhD students, who were biochemists and pharmacologists who did much of the technical work and I was just responsible for recruiting the patients, taking the blood samples, and making quite sure that someone else centrifuged them rather more skilfully than I was able to.¹¹⁸ That became very clear very early but Merton was very sweet about my utter inability to actually stand in the laboratory all afternoon when I had outpatient letters to dictate. So basically the vogue at the time was that platelets were hyperactive in migraine and really nothing has happened to gainsay that view, it's just that technology has moved on, and particularly pharmacology has moved on. They have bigger and bigger scanning machines and cleverer and cleverer algorithms for working with them and so the cutting edge has moved elsewhere but that doesn't mean that the platelets have forgotten about migraine, though we may have forgotten about platelets. I'm sure that somewhere in the heart of the pathogenesis of migraine, platelets are still there and are still somehow acting as blotting paper between attacks and

¹¹⁵ Dr Frank Clifford Rose (1926–2012) was a Consultant Neurologist at Charing Cross Hospital from 1965 to 1991 and Chairman of the Migraine Trust from 1987 to 1995. See further biographical details on pages 106–7.

¹¹⁶ Dr Marek Gawel is a Neurologist at the Sunnybrook Health Sciences Centre, Toronto, where he runs the Headache Research Unit, and is Associate Professor of the Division of Neurology, University of Toronto.

¹¹⁷ Collins and Sandler (1971). See also Sandler (2004).

¹¹⁸ See, for example, Littlewood *et al.* (1984).



Figure 18: Dr Richard Peatfield and Dr Jeffrey Aronson

discharging some kind of noxious small molecule, almost certainly 5-HT or something closely related to it, during the attack. Probably they're filtered out in the lungs, which is probably the reason why patients with persistent patent foramen ovale have rather worse migraine, because they can bypass the lungs. This would explain why patients with hereditary haemorrhagic telangiectasia, the disease with the large arteriovenous malformations within the lungs, also have extremely bad headache.¹¹⁹ So there's probably more to platelets than meets the eye but the technology has moved on and the whole thing has rather shrunk from public viewing. But when somebody in 150 years' time writes a comprehensive textbook of the pathogenesis of migraine (I look forward to reading it if I'm still around), I'm sure that platelets will be somewhere in there as a contributory factor.

Sandler: I just wanted to say that Richard wasn't such an idiot as he makes out; he was really quick on the uptake for a clinician. [Laughter] I'm an ex-clinician myself when I say that. What he's trying to tell you is, I think, that platelets contain only monoamine oxidase B, they don't contain any A at all. But in migraine we found a transitory decrease in monoamine oxidase B during the period of the attack of migraine. Why or how I have no clue, but that's just another chance finding and we put it on record, we wrote a paper to *Nature* on all that.¹²⁰

¹¹⁹ See Nightingale and Ray (2010).

¹²⁰ Sandler, Youdim and Hanington (1974).

Blackburn: Just following on from Richard's comment, like Merton I followed this work with great interest and I was pleased to share a train going up to Manchester with Merton on many occasions. However, I published a paper in 1990 in a book entitled *Cardiovascular Pharmacology of Serotonin* edited by Pramod Saxena and David Wallis, where data was presented on another ICI compound, ICI 170,809, a selective 5-HT_{2A} receptor antagonist, showing an inhibition of human platelet aggregation *in vitro* and *ex vivo*.¹²¹ It was a double blind randomized study which showed that the compound was extremely potent at 0.1mg/kg p.o. (per oral) and at the time I felt this was extremely important in understanding the pathogenesis of migraine and trying to link the platelet with either vascular or the neurogenic events. And, I'd love to hear Pat talk a bit later about some of the discussions he had with John Fozard at the time where the Sandoz group were coming from the neurogenic approach, where modulation of dorsal raphé and other raphé nuclei could well be important in the pathogenesis of migraine. And, there was often some great debate between Pat and John and Brian Richardson. At that time in the 1980s and 1990s we all were trying to piece together the vascular events, with platelet events and the control of these raphé cell bodies, what they were actually doing and the neurogenic consequences of migraine.

Weatherall: I'm going to ask Pat to come to that point in a minute but can I just mention another aspect of the problem that was happening around the same time, that is some of the studies that you Jes, Martin Lauritzen, and your group, were doing on regional cerebral blood flow in aura. I wondered if you might just tell us a little bit about that please?

Olesen: As I mentioned, I did my thesis on the physiology and pharmacology of brain blood flow in humans using the intracarotid injection of radioactive xenon technique developed primarily in Copenhagen by Professor Niels Lassen, who was my mentor. Having finished the thesis I thought, 'Migraine is an interesting disease to study with brain blood flow' because there had been some studies; Michael O'Brien did the first study with not very precise methods but it was really pioneering work.¹²² Then my neurological mentor, Skinhøj, studied a few patients with intracarotid xenon, showing decreased blood flow during the aura.¹²³ So that's why I decided to focus studies on this and we worked

¹²¹ Blackburn *et al.* (1990).

¹²² O'Brien (1967); see page 5.

¹²³ See, for example, Skinhøj and Paulson (1969).

on this for some 10–15 years because it's very, very difficult to get patients in during an attack and study the brain blood flow. The first years of study were done in the days before the CT scanner came around, where patients who had perhaps migraine aura, perhaps transient ischemic attack, were angiogrammed. We actually proved that the injection of saline or the puncture or the injection of contrast medium would elicit a migraine aura at a lag time of about one hour. We worked closely with radiologists so we could take patients after an angiogram to the flow laboratory and when they were in there we had time to take a resting state measurement and then they got the aura. Therefore we could follow the development of the aura with repeated brain blood flow measurement and we could show the slow spread of reduced blood flow, which was very similar to spreading depression. We could also show lack of functional activation in the area affected by the aura. And there was preserved autoregulation and abolished or decreased response to CO₂, many things that were similar to the animal experiment model of cortical spreading depression. But at the same time we saw that in migraine without aura there were no changes in brain blood flow.¹²⁴

I followed up on the City of London Migraine Clinic and created a similar clinic in Copenhagen in order to get access to lots of patients during acute attack and, with Martin Lauritzen, we studied a large number of spontaneous attacks. At that time with single photon computerized tomography and xenon inhalation, which was atraumatic, we could show that blood flow was perfectly normal during migraine attacks without aura but quite abnormal during the migraine aura.¹²⁵ That was actually the basis for a distinction between migraine with and without aura in the first edition of the International Headache Classification in 1988.¹²⁶ We could also demonstrate that the original simple idea of vasoconstriction followed by hyperaemia was not explaining the migraine attack, because people got headache while blood flow was still low and sometimes blood flow stayed high long after their migraine attack had gone. So there was no good association between blood flow and migraine pain. Clearly the Wolff hypothesis of vasoconstriction was not right; it was cortical spreading depression and this has later been substantiated by PET studies and fMRI studies and so on. But the enigma after that was really: (a) why does cortical spreading depression cause headache? And (b) why do patients without aura get a headache? What's the basis of their attacks?

¹²⁴ See, for example, Olesen (1978).

¹²⁵ See, for example, Lauritzen and Olesen (1984).

¹²⁶ See pages 14–15 and note 29.

Weatherall: Thank you. So we have a situation in the late 1980s and early 1990s where we have a very effective new drug developed out of work on 5-HT. We have a breaking down of the biphasic view of migraine pathogenesis that Michael O'Brien mentioned right at the beginning. But Pat Humphrey, can I turn to you and ask: in that context were people discussing and debating how your drug actually worked?

Humphrey: Well, can I just slightly precede that because if we're still in the early 1990s then we were discussing platelets and whether they were relevant and, yes, John [Fozard] and I did have a number of debates on this. I think he was a little bit more positive than I was, but at the end of the day I think we probably got to a similar space because we both wrote reviews and mine was written in the *Journal of Neurology* in 1991 where I sort of debunked the belief in platelets and migraine because it just didn't really seem to hang together.¹²⁷ I think there's some question about how reliably it happens in every patient. Clearly in some patients you can get the metabolite of 5-HT, 5-hydroxyindole acetic acid, in the urine. You get a substantial drop of 5-HT, about 40 per cent, in platelets, so clearly something's happening in many of these patients. In fact, it was quite interesting that Lance thought that maybe when people were sick that there was some sort of physiological mechanism whereby, by being sick, you released 5-HT from enterochromaffin cells in the gut and then this replenished the 5-HT in the platelets. But he actually made all the measurements, thankfully, and disproved his own hypothesis because there's not enough 5-HT coming out of the gut to replenish what was lost from the platelets.¹²⁸ There are a lot of reasons for thinking it's difficult to put anything into a pathophysiological scenario. However, what causes the 5-HT to be released from platelets? It does beg the question: is there some humoral agent circulating that may be intimately involved in the pathophysiology that we still haven't found out about? That's worth a PhD research study without a doubt. I'm not sure whether John and I both agreed on it, but certainly in my review of the platelets I said: 'Well, okay, the platelets may not be important but maybe this release mechanism is happening somewhere else too, i.e. in the brain.' That's when you start to think, is 5-HT involved in control of trigeminal neurons and central pain pathways? But if you're talking about the early 1990s, sumatriptan was only released in

¹²⁷ Humphrey (1991). See also Fozard and Kalkman (1992).

¹²⁸ See, for example, Anthony, Hinterberger and Lance (1969).

1991; yes, there was a lot of interest in mode of action, and there were a lot of people saying, ‘No, it can’t possibly be a vasoconstrictor mechanism, it must be something else.’ It did set off a whole lot of research but I think that went over that whole decade and beyond, and I think a lot of people will want to contribute to that discussion.

Jones: I’m fascinated by the discussion we’ve had many times this afternoon about chasing the mechanism of action of drugs.¹²⁹ Of course, we all want to understand more how drugs work so that we can determine possible side effects or develop improved drugs, but the complexities are huge and I have said on many occasions there are virtually no ‘magic bullets’, they’re all ‘magic shotgun pellets’ and they work on all sorts of receptors. That’s especially true of botulinum toxin (Botox). We really don’t understand all the mechanisms of how Botox is working in this condition. We know how it is effective in patients who’ve had more than 15 days of migraine problems a month and what we are now doing is teasing the molecule apart – it’s a very complex piece of biology – and looking at segments of it, to find those elements that are effective in pain.¹³⁰ We believe that this will open up, I hope, another generation of products which will be more specific in action and reaction.

MacGregor: Going back to the way research was being done in the 1980s, particularly to the comment I made about how much of it may have included aura and not included without aura, is that the potential reason why we’re seeing different things?¹³¹ So, for example, could the platelet hypothesis be more related to migraine with aura rather than migraine without aura – which leads into the wonderful debates during the 1980s: are migraine without aura and migraine with aura two different disorders?¹³² Nowadays we’ve shifted onto ‘Tension type headache is a mild version of migraine’ and this new disease of chronic migraine. We’re beginning to muddy the waters as to what we’re actually researching. But if we’re bringing in these heterogeneous conditions under our label of migraine

¹²⁹ The mechanism of the action of drugs has been discussed in various Witness Seminars; see, for example, the Witness Seminars on clinical pharmacology (Reynolds and Tansey (eds) (2008a and b)).

¹³⁰ See page 48 and note 108.

¹³¹ See pages 10–11.

¹³² See, for example, Ziegler (1985); Dalessio (1985); Hachinski (1985); Wilkinson and Blau (1985); Olesen (1985).

when we have such a clear classification that we could be using, we are going to get things that don't match up – we don't know if people are looking at a condition that isn't as heterogeneous as perhaps we now like to think it is?¹³³

Saxena: I have a question actually to clinicians mostly. I have a conviction: I do not have any proof of it, but my conviction is that migraine is a syndrome rather than a disease. I'd like to know whether this classification which Jes has done can explain whether or not it's a syndrome or what views people have. And if it is a syndrome then, of course, there are going to be different mechanisms and different treatments and that may also say why triptans are not effective in some patients.

Volans: One of the things that may be muddying the waters and which we need to consider in more detail, is the importance of what we call drug-induced headaches. This appears to be a problem for almost every class of drugs that are used in migraine. I was very convinced about drug-induced headaches with ergotamine but beyond that I can't really claim any clinical experience.

Sandler: There was something we haven't talked about at all. In about the 1990s there was a rash of papers indicating that patients with a right to left cardiac shunt tended to get migraine pain and that this was confirmed at a number of different centres at the time.¹³⁴ This was the actual migraine pain, not the spreading depression that we're talking about. This was one of the reasons that I said before that I always think of the Leão's spreading depression as nothing but another trigger of migraine pain.¹³⁵

Olesen: To answer Pramod's question about syndrome: because migraine is a heterogeneous syndrome and it's illustrated very well by the rare variant familial hemiplegic migraine where there are already three different genes involved and the mutations in these genes have different mechanisms¹³⁶ But there is probably a final common pathway in the mechanisms. We have to look at biochemical pathways somehow. It's clear that migraine can have many, many

¹³³ Professor Anne MacGregor clarified this: '... the classification of migraine seems to be expanding to incorporate an increasing number of headaches labelled as migraine. Research into the true nature of the condition becomes difficult as the classification includes more heterogeneous disorders under this label.' Email to Ms Caroline Overy, 19 December 2013.

¹³⁴ For a more recent discussion of cardiac shunts, see, for example, Bussone (2006).

¹³⁵ See page 5.

¹³⁶ See, for example, Ferrari (2008).

different initiating mechanisms but somewhere down the line there is a final common pathway, and sumatriptan and the other triptans have actually helped us understand that, because when they are given as injection they are effective in 80 per cent of the patients. By the way, that's also an external validation of the clinical diagnostic criteria that we made for migraine in the mid-1980s. We were able, from purely clinical symptoms, to identify a disease that has 80 per cent response to a very selective kind of drug. So it works both ways but what people are really looking for now, of course, is to hit the final common pathway because if you go out and try to hit all the individual initiating mechanisms there may be a hundred different mechanisms and we would never be able to have a drug that could work for more than a small percentage of patients. But down the pathway is the hot spot that we all want to identify.

Aronson: I look at this nosographically the other way around. Instead of thinking that 80 per cent of all migraineurs respond to triptans, and I've used triptans for a lot of patients with migraine-like headaches, I think of them as triptan-responsive headaches. I don't think that's necessarily nosographically very useful, but it's very useful clinically that there are headaches that respond to triptans. I don't know whether they're migraine or what the mechanism is, maybe they're heterogeneous with multiple mechanisms, but they respond to triptans and that's my diagnostic category.

Olesen: In classification you cannot use drug response. When we did the first edition of the International Headache Classification that was before the triptans and there were actually several members of the committee who wanted to include response to ergotamine as a diagnostic criterion for migraine and I was able to fight that. There were also other people who wanted to include a positive family history as a diagnostic criterion of migraine. But if you include that in the criteria you can't study genetics and migraine. If you include response to a drug in the criteria you are stuck there, how are you going to test new drugs that may work and so therefore you cannot do it like that. Now that has been said, when you have cases where it is difficult to distinguish between tension-type headache and migraine, you don't really know what precisely is this in your clinical practice, it is obviously perfectly fine to try to give them a triptan. If they respond to a triptan you think this is probably more migraine-like. If they don't respond but have a better response to aspirin you think this is probably more like a tension headache.

Aronson: No, I don't go that far. I agree entirely with what you've said nosographically. That's absolutely right. But clinically I think it's useful to label the headache in that way. I don't then say it's migraine because it responds to a triptan, I just say: 'it's triptan-responsive; aren't you lucky?' [Laughter]

Weatherall: There is an absolutely fundamental issue here of how you define what you're dealing with and how you differentiate different types of headaches. Of course, there is a philosophical point whether one is a lumper or a splitter in terms of trying to define what one's dealing with from the clinician/historian point of view. One of the great successes, I think, of the first edition of the International Headache Society (IHS) criteria is that it allowed a definition of a coherent group for clinical trial purposes. I think those of us who look after patients would recognize that not everybody has read the IHS criteria, and not all their headaches fulfil them, even though we feel quite comfortable as clinicians labelling them as migraine. I'd like to move on really briefly to bring us back to the business of the impact of the triptans on the science of migraine.

Humphrey: Perhaps I could start off with something interesting from the history point of view, that for me one of the major excitements of sumatriptan, other than the major one, which was obviously to find a drug to treat patients, was the stimulus that it gave to trying to understand the aetiology of migraine better. It was kicked off beautifully by a meeting that Merton Sandler organized at Leeds Castle in 1988. I've got the book here and it's called, a brilliant title, I don't know whether you came up with it, Merton, *A Spectrum of Ideas*.¹³⁷ There are a lot of people who I wish were here, like John Fozard and other people that were talking. John was talking about evidence from 5-HT receptor antagonists for a neural aetiology. He was trying to push something very different to what I was trying to push in terms of an idea, it was 5-HT₃ antagonists for migraine. As it turned out they didn't work but it nevertheless stimulated a huge amount of debate and a lot of experimentation, which led to other ideas. Even Richard Peatfield was there talking about the role of platelets in migraine with a personal perspective. This was all before sumatriptan was actually marketed but the story was out, and everybody wanted to know how it worked. That was a tremendous meeting. It was also a tremendous meeting because we had the privilege of having dinner with Princess Margaret, who was then the patron of the Migraine Trust, and we had a jolly good evening and I think she did as well. But what was

¹³⁷ This volume, *Migraine. A spectrum of ideas*, contains the papers presented by the 25 participants at the Migraine Workshop in 1988 (Sandler and Collins (eds) (1990)).

interesting was that we had a very interesting menu and one of the things on this multi-course menu was lettuce soup and I was really looking forward to lettuce soup because I'd never had it before and I thought: 'That will be interesting to taste.' Anyway, there was so much wine flowing, I don't think anybody noticed the lettuce soup didn't come except me and I was muttering. It turned out that Princess Margaret didn't want lettuce soup so it was all poured down the sink. And the maddest person of all in the whole castle was the chef who had to put five gallons of his best lettuce soup down the sink. [Laughter]

Sandler: This is absolutely true.

Humphrey: I think that really did set the scene and I'll pass over to other people, but my own reflection of that next decade was wanting to know: is sumatriptan acting as a vasoconstrictor or is it acting neuronally? There was a huge amount of experimentation focused on this. Just suffice to say, another exciting point was that I was put in a debate with Peter Goadsby, again another person who really should be here, who contributed a massive amount to understanding the mechanism of action of the triptans.¹³⁸ I was put in a debate with him in Whistler in Canada so it was very appropriate, apart from the fact that it was my 25th wedding anniversary and that was a bit of a difficult one to pull off. 'Go and give a lecture in Whistler', I was told, so I took my wife. Anyway, it was like a prize fight, I was in the ring with Peter Goadsby and it was very exciting. I thought I won on the vasoconstrictor story while still alluding to the fact that sumatriptan will inhibit neurons and maybe there's partially an involvement via that. Peter Goadsby, of course, thought he won and he refused to talk about the vasoconstrictor side of things even though he knows very well that it's quite important. At the end of the day they had a vote and the whole audience were neurologists and migrainologists and I think they were all very diplomatic and they agreed it was a draw (Figure 19). [Laughter] Again, there was a very interesting article associated with the debate that still stands. I read it for the first time nearly 20 years or something later, and it still is quite a good read.¹³⁹ But things have moved on since then.

¹³⁸ Peter Goadsby is Professor of Neurology in the Department of Neurology, University of California, San Francisco, and Director of the UCSF Headache Center. He became Director of the Wellcome Trust Clinical Research Facility at King's College London in 2013. For his research on the mechanism of actions of the triptans, see, for example, Ferrari *et al.* (2002); Goadsby, Lipton and Ferrari (2002); Goadsby (2007).

¹³⁹ The debate was held at the second International Sumatriptan Symposium, a satellite symposium to the World Congress of Neurology, on 11 September 1993. See Humphrey and Goadsby (1994).



Figure 19: Dr Goadsby and Professor Humphrey after their debate at the 2nd International Sumatriptan Symposium, in September 1993 at Whistler, BC, Canada

Weatherall: Yes, it's a shame that Peter couldn't be with us today because I would have liked to really ask him about the work that he did with Lars Edvinsson using sumatriptan essentially as a tool to try to unpick which of the neuropeptides, calcitonin gene related peptide (CGRP), Substance P, and so on, are actually relevant in migraine pathogenesis.¹⁴⁰ Jes, do you want just to say a little bit about that side of things?

Olesen: We must not forget Michael Moskowitz's important work.¹⁴¹ One of the ways in which it stimulated research was that his neurogenic inflammation model for some time looked like an important model that could predict the efficacy of anti-migraine drugs, but then was proven to be unspecific because many drugs worked in this model but did not work in migraine.¹⁴² On the other hand it may still be a sensitive model because all effective drugs inhibit neurogenic inflammation. So maybe all drugs that work in migraine have to

¹⁴⁰ See Edvinsson and Goadsby (1994).

¹⁴¹ Dr Michael Moskowitz is Professor of Neurology at the Neuroscience Center at Massachusetts General Hospital. His laboratory's research has focused on cerebral blood vessel function and translational studies of stroke, migraine, and traumatic brain injury.

¹⁴² See, for example, Moskowitz (1993); Buzzi and Moskowitz (2005).

also work in this model, we don't know yet. Mike and others too showed that triptans bind to the peripheral sensory nerve endings and hyperpolarize them. So stabilizing peripheral nerve endings was one mechanism. Later on, also in Boston, Rami Burstein has done wonderful work showing that the triptans also work pre-synaptically in the brain stem to inhibit the transmission of impulse in the first synapse of the trigeminal system.¹⁴³ So there are at least two neurogenic mechanisms that may or may not be important – we still don't quite know – together with vasoconstriction. I favour that the triptans are effective because they work at three different sites at the same time, not one mechanism.

Humphrey: Can I just add to what Jes has said. I think the Moskowitz data was really interesting and we knew before that triptans would inhibit neuronal transmission so that wasn't unique, but there are two things against the Moskowitz concept. One of them is some drugs didn't work in migraine even though they worked in his model, that's a killer for a start. I pointed out right from the start that 5-HT doesn't work in his model, yet we know 5-HT can relieve the symptoms of a migraine attack, so there's that issue. The final point for me is that we designed sumatriptan not to get into the brain, hence the poor bioavailability that Trevor has referred to,¹⁴⁴ and I believe it does barely get in the brain. In fact, even Peter Goadsby's got data to show that it doesn't get in the brain in animal models and yet the newer triptans are all very lipophilic, they get into the brain, so does naratriptan by the way, and they're no better clinically.

Jones: Just briefly, about the lipophilicity of zolmitriptan. We knew that the onset of activity of sumatriptan was about an hour or more. The marketing team said to us, 'If you can get something which is faster acting then that will be an advantage over sumatriptan.' So that was why we tried to increase absorption.

Humphrey: But, as I was saying to Jeff, we already had a much more lipophilic compound than any of them and that was naratriptan. And, funnily enough, what happened was they got one or two triptan-like side effects in a very early study and so they went to a much lower dose. So that negated any side effects (indiscernible from placebo) and in fact naratriptan is a very interesting triptan because you can't get any triptan-like side effects with that drug at all. And yet, because it's a lower dose, it may not be as effective for some people, but Jeff says

¹⁴³ For a general review, see for example, Burstein, Jakubowski and Rauch (2011).

¹⁴⁴ See page 39.

he still uses it and it's very good for prophylaxis around menstrual migraine and so on, so it's got a place. But if you're talking about who's got the best lipophilic compound, naratriptan beats the lot.¹⁴⁵

Saxena: To add to what Jes and Pat have said, is that you've got to ask two other questions, namely there are 5-HT_{1D} receptor agonists, there are 5-HT_{1F} receptor agonists and they were being promoted as anti-migraine agents. Well, this is fine; the notion was that they will be effective in migraine because they work on the neurons and not on blood vessels. It turned out that these types of compound are completely inactive. Some people still say that they are active. I don't believe in it because the drug companies are not stupid, they are very clever. If there was any chance of developing a 5-HT_{1F} or 5-HT_{1D} compound they would have done it by now. So, that's a response to Peter Goadsby.

Weatherall: For once he's not here to defend himself. [Laughter]

Blackburn: Just talking on the 5-HT_{1F} I went across to join my first biotech company in the States in 1999, Synaptic Pharmaceuticals, and Dr Terry Branchek was working alongside Eli Lilly at that time. I think I arrived on the Monday and the project died on the Thursday. That was a sad day with regard to the 5-HT_{1F} receptor theory and migraine.

Saxena: So they don't want to look further.

Weatherall: I'd like to take the discussion in a slightly different direction. One of the things that's really struck me, listening to what's been said about the way that research was done in the 1960s, 1970s, and 1980s, is the importance of being able to recruit patients relatively easily and straightforwardly from walk-in clinics. We've obviously got the City of London Migraine Clinic; Jes, you've mentioned purposely copying that pattern, presumably to treat patients as well as to recruit people for research. I just wondered about the issue of studying patients with an episodic condition and the limitations that would put and how people would try to counter those limitations.

Olesen: Yes, we had a problem when we wanted to study brain blood flow during migraine attacks. It's very difficult to recruit patients to actually come in during a spontaneous migraine attack. They are nauseated, they may vomit in a taxi. Even if you pay for a taxi for them they want to stay in bed at home and so on. So our experience has been that you need to recruit at least 10 times more

¹⁴⁵ For a review of naratriptan, see Mathew (1999). See also comments by Dr Jeffrey Aronson on pages 50–1.

patients than you end up studying, maybe 20 times more patients than you end up studying. There are some really formidable problems there and today we see the same problem in magnetic resonance (MR) studies, for example. We have managed to study 19 patients during spontaneous attacks, which we just published in the *Lancet Neurology*.¹⁴⁶ But others have only managed to study one patient. We could do it because we have a huge flow of patients and we have an inpatient unit also, it's very difficult.

Weatherall: Do you still run a clinic where people can just walk in?

Olesen: No, we did away with that years ago because it's quite resource-demanding. You have to have doctors on duty and if you have the normal Neurology Resident responsible for a walk-in clinic, they really have other problems they consider to be more important, so the patient can lie there and wait for the Junior Registrar to come and treat them. It's very difficult to make it work.

MacGregor: I was going to say that sumatriptan, with its brilliance, killed off research on acute patients. When I first started working at the City of London Migraine Clinic towards the end of the 1980s, we were still getting one or two people in a month for acute treatment of migraine. I think when Glyn Volans had been working there, there was no problem getting patients coming in because they weren't being treated effectively by their GPs. As soon as sumatriptan came on the market there was something that people could take that enabled them to carry about their usual daily business. So why on earth would they want to not take their triptan, to come along, and be involved in clinical trials when they would then be throwing up in a taxi on the way there? However much you pay them, however much you organize it for them, you can now not get acute patients to come along to a clinic for treatment.

Volans: I tried to provoke migraine and failed miserably in a small number of volunteers who were fed whatever they said caused their migraine attacks and it never worked. Has anybody any better experience than me?

O'Brien: In my original series I had seven patients measured in the prodrome and all seven worked at Guys. The equipment was all set up to run and these people were asked to come straight to the lab as soon as they'd had the first inkling of a migraine attack. But from outside the hospital it would have been impossible.

¹⁴⁶ Amin *et al.* (2013).

Peatfield: I think we ought to pay tribute to Mike Cutrer at this point; he was one of the authors in many of Mike Moskowitz's papers and is actually the brain you see on the published scan because he could quite literally elbow people out the way and get himself scanned within minutes of his own migraine starting.¹⁴⁷ There are a lot of his own scans in print. There aren't many people like him.

Olesen: To add a couple of things here also, almost by definition it's impossible to study spontaneous migraine attacks at the time when you most want to study them – that is at the very initiating moment of the attack. It's not possible because patients have to go to the clinic, there has to be something done either to draw blood or to put them in a scanner and so on. So it's almost by definition impossible to study attacks until after one to two hours into the attack and so you cannot measure the initiating mechanisms. That was one reason why I switched over, around 1990, to study provoked migraine attacks because there you can provoke the attack with nitroglycerin and CGRP and many other substances that we have studied and you can study the patients before and just as they are developing attacks and so on. The problem is, of course, are these induced attacks identical to spontaneous attacks?

Weatherall: The City of London Migraine Clinic, to my understanding, was set up initially as a treatment exercise and was pretty much the first migraine clinic of its type. I think that Macdonald Critchley ran a clinic from somewhat earlier. And obviously the Danish had a centre that dates back 30 years or so at this stage. I wonder whether I could ask about the importance of specialist headache clinics in terms of not only the research but also actually building and promoting knowledge about headaches more generally. Richard, you've been actively working in the clinic that bears Princess Margaret's name for over 30 years.

Peatfield: One point I think I should make. I started working for Frank Clifford Rose in 1979 and I was effectively second down from Princess Margaret. The patients weren't sent to Princess Margaret, they weren't sent to Frank Rose, they were sent to me. And I have to say my therapeutic effect was far greater when I was Princess Margaret down two notches than when I went to Leeds as a Senior Registrar. There I had actually much more status and was paid more but I was clearly a trainee whereas before, I was God minus two. [Laughter] A lot

¹⁴⁷ See Cutrer *et al.* (1988). Fred Michael Cutrer is Associate Professor of Neurology at the Mayo Clinic, Rochester, MN.

of migraine clinic work is actually giving the impression you know what you're doing, actually getting the real problem out of a patient, not wasting time doing unnecessary investigations, and not starting them on a treatment they've already tried, especially ones that they themselves had bought at the chemist, but trying something different, something that only I had some expertise about. As well, of course, as using them as material to collect blood samples for this, that, and the other research project. So specialist clinics did have a major role and I think they still have a major role. I think now that neurology is breaking up into more and more special interest clinics, it's vitally important that every major centre should have a clinic specifically for migraine patients.

Olesen: And other headaches please.

Peatfield: Oh yes.

Weatherall: Anne MacGregor, much of your working life is based in and around the City of London Clinic. What role do you think that that clinic has played in the life of migraine in this city, in this country?

MacGregor: It started off as the City Migraine Clinic originally, with a little ambulance that was supposed to pick people up from their place of work. Marcia then opened the City of London Migraine Clinic in 1980, when the Princess Margaret Migraine Clinic was moved to Charing Cross Hospital.¹⁴⁸ It was interesting to see the difference between NHS-based and charity-based clinics. In the charity setting, you could meet the needs of the patient rather than necessarily meet the needs of a manager, which can sometimes make the organization a little bit more complicated. But I think the main thing we gave patients was time. Patients wanted somebody who understood what they were talking about, who would let them speak, and who would help them to understand what they were experiencing. This was very different from what they were experiencing in general practice, which was: 'You've got a condition, you've got migraine.' Some of it was: 'well, just go off and deal with it because

¹⁴⁸ The City Migraine Clinic was opened by Princess Margaret in 1970 in Little Britain near St Bartholomew's Hospital, it then moved in 1973 to Charterhouse Square and larger premises on a six-year lease. The Migraine Trust ceased funding the clinic in 1979 to focus spending on research rather than patient care, and in 1980 the City of London Migraine Clinic (now the National Migraine Centre) was founded as a registered charity by Dr Nat Blau and Dr Marcia Wilkinson. The name of the Princess Margaret Migraine Clinic transferred to a new clinic at the Charing Cross Hospital. For a history of the Migraine Trust, including the migraine clinics, see Rose (2006).



Figure 20: Dr Mark Weatherall, Professor Brian Hurwitz and Dr Michael O'Brien

that's what you should expect.' Otherwise it was just get the prescription pad out and write a prescription for something that wasn't necessarily effective – be it a preventative treatment or a symptomatic treatment. But the patient never knew how it was going to end. So with a lifelong condition, they would get a drug but still be left wondering how else to cope with their lives. Or they were given a brain scan and told: 'It's okay, your brain is quite normal; it's just migraine. Go away and live with it.' There was an awful lot of 'just deal with it, it's migraine.' I think migraine clinics gave the condition credibility. Then going back to sumatriptan, a drug which was specifically for a condition gave the condition credibility. I totally agree with the need to open more migraine clinics but perhaps more multidisciplinary clinics, with ophthalmologists, gynaecologists, and psychiatrists – not just neurology.

Professor Brian Hurwitz: I was a GP for 30 years on the border of Islington, Hackney, and the City of London. I would just like to say that, in my experience as a GP, the City of London Clinic was a much better option to send patients to for the very reasons that we've just heard. Holistic care was on offer there with continuity of follow up from which people benefited. If you contrast that with the headache clinic at, for example, Queen Square, the thing that really struck me – and I eventually gave up referring patients to that clinic – was they were staffed with numerous clinical research fellows on short tours of duty in the headache clinic with very little continuity of care. Patients had a pretty

poor outpatients' experience, the fellows were constantly saying the same things to quite different people, and, as I generally only ever referred complex-to-manage patients, in my experience they frequently gained little from the clinic. So while some specialist NHS clinics might be helpful in terms of gaining research subjects, in my experience over a 30-year period, they're not very good therapeutically.

Weatherall: Jes, do you have a comment specifically on that?

Olesen: Well, it's wonderful we have this meeting about migraine, we're talking about migraine clinics, but it's really important to say headache clinics because we now know that, even if migraine is the most important headache disorder, what about cluster headache? What about trigeminal neuralgia? What about chronic tension-type headache? What about medication overuse headache, which is now a huge problem?¹⁴⁹ What about all the many other primary headaches that we have identified and defined in the headache classification?¹⁵⁰ So really we should move away from the idea of migraine clinics. That is one thing. The other thing is that there are different kinds of clinics and people don't always understand that. The original concept in the City of London Migraine Clinic and my own clinic originally in Copenhagen and a few other places was to let people come in with an acute attack, get treatment, and send them home. Of course, at the time this was good because patients got no other service but today it's a useless exercise. In Denmark, we have identified three tiers of service: the first level, which takes care of the great majority of patients, are the GPs. The next level in Denmark is a practising neurologist or a non-specialized department of neurology. The third tier is the highly specialized, multidisciplinary headache centre that we now have in Copenhagen, which covers the whole country, which is only five million people, but we only get patients who have seen a neurologist before they come to us. That brings up an important thing: the knowledge about headache has escalated enormously – just look at our big textbook called *The Headaches*, 1100 pages.¹⁵¹ There is so much knowledge about this that a general practitioner has no chance of knowing it all. Even a non-specialized neurologist has no chance of knowing it all. If you really want to utilize all the available knowledge about headache today there must be

¹⁴⁹ For discussions of chronic medication overuse headache and migraine, see, for example, Negro and Martelletti (2011); Sun-Edelstein, Bigal and Rapoport (2009).

¹⁵⁰ For a summary of the primary headache classification, see Appendix 2.

¹⁵¹ Olesen *et al.* (eds) (2006).



Figure 21: Professor Tilli Tansey and Mrs Mary Ayres

specialized centres, and the conclusion is that, even if patients have been seen by a neurologist, we can still help the majority of them. That's simply because there is so much knowledge available that can only be handled appropriately by persons who have specialized in headache.

Weatherall: Mary Ayres, could you talk about the role of patient groups in this process?

Mrs Mary Ayres: First of all I'm going to say the specialist clinic has played a large part in the lives of many of the members of the British Migraine Association (now Migraine Action). Whenever volunteers were needed for a piece of research at the City of London Migraine Clinic they came in their hundreds, and it was a lifeline for many people. Anne was talking about having time to talk. My first visit to the clinic was with my small daughter to see Dr Blau¹⁵² and he said to me: 'Mum, sit there, be quiet. I'm talking to daughter,' which he did, and she was able to tell him how unwell she was. I have seen the success of the Specialist Nurse service linked to Migraine Action. This has been a great help to a lot of our members and to non-members of the Association. I'm sure a lot of people come self-diagnosed and need reassuring or because their doctor doesn't understand and only has ten minutes. So you do need time. I think clinics are vital.

¹⁵² Dr Joseph Norman (Nat) Blau (1928–2010) was a Consultant Neurologist and Clinical Director at the City of London Migraine Clinic from its opening in 1980 until his retirement shortly before his death. He was Honorary Medical Adviser to the British Migraine Association (Migraine Action) from 1980 to 2007.

Thomas: I totally agree with Mary and also with Anne, it is about time. I think there are some good models that we're aware of at the Migraine Trust for patients going to headache centres, and I totally agree with Jes, yes, they should be headache centres. What we know is that there are around eight million people with migraine in the UK, an awful lot of people. It's a pity they don't all put a pound in every year then we might have £8 million to do some decent research. [Laughter] That's another story, which hopefully we'll get on to near the end but we know that about 50 per cent of people don't actually go to their GP – we need more GP education, more GP training. Again Jes is right, obviously they're not going to know everything, but there's a lack of interest and there's a lack of interest within neurology as well. I know a lot of people who get sent on to a neurologist because their GP is fed up with them coming back, they send them to a neurologist who isn't interested in headache (obviously a good GP over there [i.e. Brian Hurwitz] who sent them to the right person), and then they go and they're even more frustrated. Most of the time they don't go because perhaps their parents have had migraine and they've said: 'Oh, you know, nothing can be done, go and lie down.' There are some very good models where you have a neurologist and a headache nurse who carries on doing the follow ups.

Weatherall: Vicky, do you want to talk a little bit about the role of the headache nurse and what potentially you have to offer?

Mrs Vicky Quarshie: I'm the Headache Specialist Nurse working in Hull with Dr Fayyaz Ahmed.¹⁵³ I've been in post for seven years now, and even in the short space of time that I've been working in headache as a specialty, there have been significant advances in the understanding and treatment of migraine, considering how long it is since triptans were first introduced to the market.

My background is neurology and initially I worked on the neurology ward. The first time the concept of medication overuse was brought to our attention on the ward it was like a revelation and it does make you reflect upon your own practice.¹⁵⁴

¹⁵³ Dr Fayyaz Ahmed is a Consultant Neurologist at the Headache Service Hull and East Yorkshire Hospitals NHS Trust. For an account of the role of the Headache Specialist Nurse, see Appendix 3.

¹⁵⁴ Mrs Vicky Quarshie wrote: 'The realization that possibly many patients who have been treated for headache in the neurology ward often admitted for another neurological condition, have possibly had a co-existing medication overuse headache complicating the underlying headache phenotype, often migraine.' Note on draft transcript, 23 October 2013.



Figure 22: Mrs Vicky Quarshie

Patients would inform nursing staff and say: ‘Oh, I’ve got a headache.’ The nurses would ask: ‘What do you usually take when you have headache?’ The patient would respond with: ‘I take paracetamol or co-codamol.’¹⁵⁵ The nurse would look at the drug card and inform the patient they were not written up for it and the doctor would need to prescribe it or if the patient was written up for it the nurse would administer it to the patient and possibly unwittingly contribute by compounding the medication overuse headache cycle.¹⁵⁶

My personal goal is to inform every nurse and medic within our trust about medication overuse headache and encourage them to stop and think before they add paracetamol or opiate derivatives to the drug card ‘When Required’ or to simply ask the patient about their headaches – whether they have a formal diagnosis, the frequency of the headaches, and acute analgesic use.

¹⁵⁵ Mrs Vicky Quarshie added: ‘Generally this would be something that the patient would have bought over the counter or with their weekly groceries and therefore it would not be prescribed on the hospital drug card or reflected on the repeat GP prescription readout.’ Note on draft transcript, 23 October 2013.

¹⁵⁶ Mrs Vicky Quarshie wrote: With the knowledge of medication overuse headache, the actions of nurses and medical staff would be different. Rather than prescribing the medication, questions would be asked: why does this patient have headaches? Have they been given a formal diagnosis for the headaches they experience and what treatment have they tried previously? Most importantly, the question should be how often do they have headaches and how often do they take medication particularly analgesics and triptans which can quite easily elicit the possibility of medication overuse contributing to the overall headache profile. It is difficult to believe in these enlightened times with the knowledge about medication overuse that this scenario would happen. However, medication overuse is still a significant problem for many patients attending neurology clinics, GP surgeries and many people within the community who do not even consult their GP or a healthcare professional.’ Note on draft transcript, 23 October 2013.

If this scenario was implemented within every healthcare setting, by how many people would it be possible to reduce the incidence of medication overuse and then address the underlying headache phenotype with a more effective strategy with benefits to patients and the overall healthcare budget?

Within our clinic in Hull we have probably around 28 to 30 new referrals a week into the headache clinic and they're seen by Dr Ahmed and the registrars. A large majority of patients are given a management plan and are discharged back to the GP. However, all patients are given my contact details where they can be given rapid access back within the service if required.¹⁵⁷

Sometimes when patients come to me they've had quite a bad experience through the healthcare system via the GP or unfortunately through secondary care providers, and they can be quite negative and angry when they come to clinic.¹⁵⁸

I do agree that generally what I have is more time to sit down with patients to listen to what they actually want. When you listen to patients, it's not a prescription that they want, they want somebody to know and somebody who understands exactly what is going on for them. Quite often patients are surprised when I say: 'Well, how about we start taking away some of those treatments and then see what exactly is going on before we start giving you another medication to try; let's take something away.' Often patients are quite receptive to that because they've come in quite angry about: 'Oh, you just want to give me another tablet', and I've said, 'No, let's just stop and think about this and take everything away if it isn't working; let's strip it back.'

I do provide education sessions for patients, public, and other healthcare professionals, often in association with Migraine Trust, Migraine Action, British Association for the Study of Headache (BASH), within the hospital trust where I work, community healthcare setting, and the pharmaceutical industry, which I do see as an essential part of my role.

One of my interests is migraine in children. Although we don't see young children in clinic, we do see adolescents and that's something that I think is an area that really needs to be addressed because children and teenagers with migraine grow

¹⁵⁷ Mrs Vicky Quarshie added: 'following a telephone call which can be initiated by the patient in addition to their GP or other healthcare professional.' Note on draft transcript, 23 October 2013.

¹⁵⁸ Mrs Vicky Quarshie wrote: 'Often this is because the patient does not feel that they have been listened to or that the healthcare professionals previously involved within their care have failed to understand what it is that they as an individual experience as a result of their condition or during their headache episodes.' Note on draft transcript, 23 October 2013.

up into adults with, what we have all agreed, is a lifelong condition. Children from a young age can experience primary headache disorders, therefore we have to think about the way that we educate about the treatments and effective safe medication use.

The whole issue of medication can start off with Calpol being given to a child as a baby. Then they get a bit older and they can have half a paracetamol and then they get a bit older and are given a full tablet, then eventually allowed two paracetamol tablets and eventually they become teenagers who will reach for the paracetamol just in case they get a headache because they're going out and don't want headache to spoil their time with friends.

We've got to start thinking about educating and addressing this scenario a lot earlier, which is why I go into schools to do awareness sessions. I can't do it on my own; it feels like I am sometimes and I am looking at trying to get other healthcare professionals involved within school nursing. I think the support groups do an absolutely fantastic job because they really do take a lot of heat off me, particularly with the written information they provide, because trying to get good evidence-based papers written through clinical governance in a timely fashion would take a lot more time away that I can spend with patients.

Jones: I wonder, could I just indulge you with a little story about Calpol which you mentioned? The Wellcome Foundation bought a company in the North of England called Calmic. They had a formulation of paracetamol and called it Calpol. This proved to be very much more palatable than the British Pharmacopoeia solution of paracetamol, which was very, very bitter. What Calmic did was to use a very traditional mucilage of tragacanth and acacia (which has been used for centuries in pharmacy) to suspend the paracetamol rather than it being dissolved. Well, I was sitting in my office one day and a man knocked at the door. He said, 'Boss, can you phone the chairman and tell him we can't make any more Calpol.' And I said, 'Why is that?' He said, 'Because the Bedouin have moved south.' 'Excuse me? The Bedouin have moved south?' 'Yes.' Now, you see, tragacanth is a natural gum abstracted from some plants in North Africa by the Bedouin as they tend their goats. That year the weather in the region where the tragacanth grows was bad so they decided to up camp and move south, so no tragacanth. [Laughter] So that's why the man said to me, 'Well, could you phone the chairman, mate, and tell him that we can't make any more Calpol.' I said, 'What's this picture behind me on the wall?' He said, 'Oh, it's a picture of the earth taken from the moon.' I said, 'Well, the man who took that picture got back!' He said, 'What?' and I replied: 'So it's not the end of the

world because the Bedouin have moved south.’ Firstly we chose a chemically modified starch as the replacement to tragacanth, and then used an amount that would make the density of the suspension equivalent to that of paracetamol so it wouldn’t settle and the bitter taste of paracetamol doesn’t get to the tongue. Also, we adjusted the rheology of the formulation so that it doesn’t slip off the spoon so easily – so you can chase the kids around the room when you are trying to give them a dose! I thought you might like to know a bit of Calpol history. [Laughter] I can’t remember the exact date, but it was probably about 20 years ago.

Weatherall: There’s a whole Witness Seminar in agriculture and pharmacology with the ergots and everything else, isn’t there? I want to come back to this question because I asked it right at the very beginning when we were talking about the migraine field in the 1960s and 1970s, and I asked whether neurologists were really interested in migraine and I think Michael O’Brien said that they were. But everything we hear is that actually nobody is very interested in it. GPs aren’t interested in it, neurologists aren’t interested in it. Why not?

Blackburn: It’s not life threatening.

Weatherall: But there are a lot of things that aren’t life threatening that people are interested in.

Blackburn: Yes, I worked in anxiety and depression for a long time with a number of companies, in particular SmithKline Beecham, and I worked on Seroxat/Paxil for ten years. We ‘downstreamed’ the drug into the anxiety-type disorders/stress and migraine, as you know migraine is linked with stress/anxiety. But anxiety and depression weren’t seen as life threatening and it was one of the biggest hurdles to try and get over with regard to the clinical, regulatory, and marketing prejudices. However, the drug still became a multibillion dollar product at the end of it all! It’s the same in migraine, it’s very difficult to get that message across, you can do all of the stats concerning quality of life and lost productivity with regard to the economic consequences of migraine, but government reimbursement policies today will dictate you to prescribe a ‘generic’ non-steroidal, an ergotamine-like compound or over-the-counter sumatriptan. So the future treatment of migraine, I think, is going to be very difficult for young start-up companies or big pharmaceutical companies to bring new products forward because it’s already well treated according to government price control agencies.¹⁵⁹

¹⁵⁹ Dr Tom Blackburn wrote: ‘Unless there is significant differentiation on safety and efficacy and it is an “innovative” therapy.’ Note on draft transcript, 14 July 2013.

Thomas: Just very briefly, I think part of it is that migraine is very much a hidden condition and it has been treated as a hidden condition. People have been stigmatized, they don't like to say they've got it when they get a job because they're afraid they will be seen as unreliable, and you try and get anybody to stand up and say: 'I've got migraine', be it Ryan Giggs, who has migraine, and a few other celebrities who just don't want to back it up. But as well as that, and though I'm sure you're undoubtedly right, and I know what governments are like on this, what is changing today is social media. We've now got a lot of younger people who are on Facebook and Twitter and all those things saying: 'Yes, I've got migraine. I'm not putting up with this; what are you doing about it?' And it's very easy. We have our e-bulletins and we do get patients for research. But actually there are people standing up saying, 'I've got it and I'm proud,' as it were.

MacGregor: The lack of funding is because migraine is not taken seriously. With three charities, Migraine Trust, Migraine Action, and, when I was at the City of London Migraine Clinic, you could never get funding to run the clinic, to get support, or to do research. There's just no money there. People would donate while they had a problem but they very rarely leave anything in their wills. It will go to the donkeys, the horses, the cancer societies, whatever it is, that is much more important to them at that time when they are writing their wills. Unless we can get more money into migraine, we're all going to be beating ourselves with sticks.

Quarshie: In the UK there are only 12 specialist headache nurses.¹⁶⁰ When you consider the incidence of migraine compared to asthma and diabetes alone, the number of specialist nurses that you have to deal with and address those conditions, and, of course, there is also the financial incentive to address such conditions as the primary care physicians are paid for effective outcomes.¹⁶¹ There's a tariff for treating diabetes, for treating heart disease. I think once the NICE quality outcomes are implemented and a tariff attached to them then you'd see an improvement in how migraine is managed and other primary headache disorders.

¹⁶⁰ Mrs Vicky Quarshie wrote: 'Since the Witness Seminar in May 2013, the number of Headache Specialist Nurse posts within the UK have now increased from 12 to 17 which is almost a 33.3% increase and additional posts are in the planning stages which is very welcome news.' Email to Ms Caroline Overy, 3 March 2014.

¹⁶¹ There are 8 million sufferers of migraine in the UK (www.migrainetrust.org/key-statistics (visited 21 January 2014)); 5.4 million sufferers of Asthma in the UK (www.asthma.org.uk/asthma-facts-and-statistics (visited 21 January 2014)); 2.9 million sufferers of diabetes (www.diabetes.co.uk/diabetes-prevalence.html (visited 21 January 2014)).

Humphrey: You asked specifically why clinicians aren't interested; well, it's a transient condition and if you wait long enough it goes away, and people aren't going to die of it. I was going to make a more particular point, which is that it's a female condition and you know probably a lot more doctors are men possibly, or is it 50/50 now, but it's still weighted in the wrong direction. And I think unless you've had migraine or you've got migraine, you're not sympathetic. So you find a doctor who's got migraine himself, he's much, much better at dealing with his patients. So that's an important point as well. But again, sorry about going on about anecdotes, but my wife has for years and years never believed she has migraine but did have a headache at menses. So I used to say: 'Well, take a paracetamol, dear' and that was the end of it. Well, anyway, a friend of mine came, a very famous person who many of you will know, Steve Peroutka, who is a neurologist and pharmacologist,¹⁶² and he said: 'Pat, Mary's got menstrual migraine.' I said: 'No, no such thing.' Anyway, at the time sumatriptan was not freely available, it was just in the very early 1990s so Steve sent sumatriptan from America, saying: 'This is like sending coals to Newcastle.' [Laughter] My wife took one sumatriptan, boom! Headache's gone. She said to me: 'You're supposed to know all about migraine.' And I said: 'But you never told me the headache didn't go away when you took the paracetamol!' So you've got to know about it, you've got to understand it.

Dr Katherine Foxhall: I'm a historian and I've been looking at the history of migraine from the seventeenth, eighteenth, and nineteenth centuries and one of the questions that's most interested me is why, in the twentieth century, does migraine come to be assumed to be a female disorder by many people? When you look at the end of the nineteenth century, the point at which migraine was historically taken most seriously by the medical profession, you get a number of men of science discussing what had previously been seen as a kind of bilious disorder associated with the stomach and with the humours. In the 1870s migraine becomes associated with aura through the philosophical discussions of men like John Herschel and David Brewster; these were very prominent men of science interested in the stars and in vision. And it's in the 1870s you get people like Living and Latham publishing their monographs and articles on what Living called 'nerve storms' and that kind of thing.¹⁶³ Then suddenly, in

¹⁶² Dr Stephen Peroutka is now an independent consultant to pharmaceutical and biotechnology companies in the USA; he has been Chief Medical Officer of Semnur Pharmaceuticals Inc. since October 2013.

¹⁶³ Living (1873).



Figure 23: Professor Anne MacGregor, Dr Katherine Foxhall and Mrs Mary Ayres

the 1880s and 1890s, you get all of these physicians writing to the American medical journals and the *Lancet* saying: ‘Oh, I have this aura too.’ So it’s at that point that migraine becomes taken very, very seriously. What’s very interesting is how then, in the twentieth century, that declines and you get a lot more different kinds of theory. In the early twentieth century, migraine theories break up. You have theories about allergy, you have ideas about hormones, so migraine becomes associated much more with women and I wonder whether that is really part of the problem. Lots of the comments of this afternoon have also been that many people assume that migraine is just a women’s disorder and that it’s about neurotic women or things like that. So I think that’s part of the problem but it’s a very interesting historical shift that is actually quite recent.

Aronson: Pat’s comment about menstrual migraine makes me want to go back to our first session and ask about oestrogens in the mechanism, because I don’t think we discussed them. Can anyone say anything about the roles of oral contraceptives, changes during pregnancy, menstruation?

Weatherall: Anne, I’m sure you’d love to comment?

MacGregor: Richard examined me on my MD thesis so perhaps he should comment?¹⁶⁴ My comment is just that Barnes Wallis might have wished that

¹⁶⁴ Professor Anne MacGregor’s MD thesis explored the role of oestrogen in migraine (MacGregor (2008)).

he had sumatriptan available because he apparently knew every ditch between London and Oxford because of his migraines.¹⁶⁵

Hurwitz: I just wanted to say something about the idea that a condition that's not life threatening is inherently uninteresting: that strikes me as a highly questionable proposition. If true it would make a great deal of neurology decidedly uninteresting, would it not? It also implies 90 per cent of medicine is uninteresting. And it doesn't explain why conditions go through such clear phases, of fading interest and then growing interest. You take a condition like diabetes, which in the 1940s and 1950s was not seen as an 'interesting condition'. It didn't have much clinical work going on, there was very little research happening. Clinics were often not consultant-led but run by non-clinical biochemists and nurses. But it's now an enormous industry, a discipline in its own right that's highly prestigious. Mortality has fallen because of treatment, and, as mortality has fallen, interest and prestige have risen.

Humphrey: I was just going to ask from some of those who know around the table for some clarification on the female disease or not? As far as I am concerned the literature is full of data that says that three times more women than men have migraine and five times more men than women have cluster headache. Is that true or not true?¹⁶⁶

Peatfield: Yes.

Humphrey: That's what I thought.

Weatherall: Although modern epidemiology shows that to be the case, there is a difference between information that you get from epidemiological studies and the perception of a disease, which is what Katherine was talking about. So, for example, if you go back to the end of the nineteenth century you find that migraine is perceived as a disease of educated, nervous undergraduate types, who are stressed out about their exams; it is not perceived as a disease predominantly of the working classes. Whereas if you look at modern epidemiology, everybody gets migraine; it's not class-specific. So there are very interesting questions about the way that diseases are perceived and the impact that that has on funding decisions and so on.

¹⁶⁵ i.e. stopping to be sick. Sir Barnes Wallis (1887–1979) was an aeronautical designer and engineer who is best known for his 'bouncing bomb' and the air raid on the dams of the Ruhr in Germany during World War II.

¹⁶⁶ See, for example, Russell *et al.* (1995); Evans and Bahra (2004).

Humphrey: Well, I was certainly told by an eminent professor of neurology in Japan that ‘we don’t have migraine here’; this was about 15 years ago or more. And another professor, a younger one who had actually trained in America, took me aside later and said: ‘That’s not true, it’s just that the women aren’t allowed to complain.’ [Laughter]

O’Brien: You asked the question as to why there wasn’t the interest but in fact most headache and most migraine was dealt with by GPs and they simply don’t have the time to sit for half an hour or 40 minutes, which is what many of these patients need. The more complicated ones are then referred to hospital. There was a time, going back a generation, when neurology was largely an inpatient speciality and the consultant went round and performed in front of a whole lot of people, at Queen Square for example. The junior consultants and registrars fed the system from outpatients. So there wasn’t anybody at senior level who was necessarily particularly interested in it. I think there are many doctors who like to roll up their sleeves and sink their arms into gore, you know, to the elbows and others who don’t. You have to be interested in the people and be interested in taking detailed histories, and if you aren’t interested in that then migraine has less to offer. Also, I think, because there were not the opportunities for MDs and PhDs in migraine as there were in many other subjects, there weren’t the departments that could support that sort of activity and so the thing just rolls on like that. You get fewer people involved. I think now that neurology is mostly an outpatient speciality and not an inpatient speciality is one of the reasons why the interest in migraine has flourished.

Thomas: Can I just go back to funding briefly, insofar as it is trying to get younger researchers and clinicians interested in headache and seeing that they might have some sort of career and some sort of funding to go on for training. We’ve just managed to get a Migraine Trust fellowship awarded at the Migraine Trust meeting (which is now called the European Headache and Migraine Trust International Congress), which was held last September.¹⁶⁷ It’s the first time we’ve been able to do that for a while and it is about funding. But there’s the All-Party Parliamentary Group on Primary Headache Disorders, which

¹⁶⁷ The 3rd joint biennial congress of the Migraine Trust and the European Headache Federation was held in London, 20–23 September 2012. The 2012 Migraine Trust Fellowship was awarded to Dr Anna Andreou to investigate ‘hypothalamic–thalamic interactions in migraine pathophysiology’ at Imperial College London for three years.

is funded by Headache UK, of which Migraine Trust is the major funder in fact.¹⁶⁸ We did have a session on research about three years ago, and various important institutions were asked to come and say what they were funding, what headache research they were funding. Neither the Medical Research Council nor the National Institute for Health Research (NIHR) nor the Wellcome Trust came. They all just would not come.¹⁶⁹ Stephen O'Brien,¹⁷⁰ who was then the Chair of the All-Party Parliamentary Group, wrote to them privately and asked them if they would come and have a private discussion with me, because I was chair of Headache UK, and him. We did have two people come from the Wellcome Trust. The Medical Research Council and the NIHR just didn't bother to reply.

Olesen: It's very true that the area is grossly underfunded. We did a large European-wide study called Resource Allocation to Brain Research focusing on all brain disorders, including both psychiatric and neurological disorders.¹⁷¹ We've also done another study about the cost of brain disorders and, when we looked at the research funding compared to the societal cost of the disorders, headache research came as the absolute lowest funded of all the brain diseases.¹⁷²

¹⁶⁸ The All-Party Parliamentary Group on Primary Headache Disorders was relaunched in 2008, comprising a cross-party group of MPs and members of the House of Lords, the aim of which is to 'highlight and raise awareness amongst parliamentarians of the key issues affecting sufferers of primary headache disorders, their families, carers and health professionals working in the field. By discussing these issues in parliament the group aims to influence policy and legislation to improve the lives of those affected by primary headache disorders.' See the Headache UK website at <http://headacheuk.org/appgphd/appgphd.html> (visited 26 November 2013). Headache UK is the umbrella group for migraine and headache organizations, which includes the Migraine Trust, Ouch (UK), BASH (British Association for the Study of Headache), Trigeminal Neuralgia Association UK, and Migraine Action.

¹⁶⁹ The first report of the Group 'Headache Disorders – not respected, not resourced' (2010) is available online at www.migrainetrust.org/assets/x/50147 (visited 26 November 2013); see the chapter on company research (Hargreaves (2010)) and the conclusion (Goadsby (2010)).

¹⁷⁰ Stephen O'Brien has been Conservative MP for Eddisbury since 1999. He was Shadow Minister for Health and Social Care from 2005 to 2010.

¹⁷¹ Sobocki *et al.* (2006).

¹⁷² A study commissioned by the European Brain Council: Gustavsson *et al.* (2011). See also Olesen *et al.* (2007). For the economic cost of migraine in Britain, see Steiner (2010) and Steiner *et al.* (2003).

In America they have done some studies of NIH funding and, again, headache and migraine research comes at the very bottom. Compared, for example, to epilepsy, headache disorders have about three times higher cost but epilepsy research has about ten times to fifteen times more funding than headache research.¹⁷³ So the underfunding is not just there, it's outrageous, it's terrible. When the study in America, for example, asked the NIH: 'why don't you fund headache research more when it's such a prevalent disease?' the answer was: 'Because the applications aren't good enough'. So it's a catch 22 situation. When the field is underdeveloped and remains underdeveloped, how can you pull it up? You need funding to do good enough applications. So it's a really difficult situation but I have good hopes because we are now looking at signalling molecules, receptors, and the specific drugs like triptans, not only that but calcitonin gene related peptide (CGRP) receptor antagonists and so on. This will bring headache much more into the neurobiology realm and I think that will support both the esteem of the condition and the funding.

Jones: I just wonder whether we could have some comments from the patient organizations and the medical groups, nursing and so on, about whether, shall we say, you 'have your act together.' I know Jes is part of the European Brain Council and that brings together a cluster of people involved in brain conditions. When I was Director General of the Association of the British Pharmaceutical Industry, I found that when we were in discussions with patient organizations, like in cancer, that there might be three or four competing groups, and they just fought each other, instead of saying, 'Look, we all have a common agenda here.' So, is one of the problems that you are not getting the 'share a voice' because your messages are just too dispersed? And the second question relates to how successful you are in persuading the pharmaceutical industry to put up the money for practice nurses, like Mary Baker did so successfully for Parkinson's disease nurses,¹⁷⁴ because it's in their mutual interest.

¹⁷³ In 2007 the NIH funding of migraine per person was estimated at \$0.36, while for epilepsy the figure was \$35. See Schwedt and Shapiro (2009), page 166.

¹⁷⁴ Mary Baker MBE is President of the European Brain Council. She worked for 18 years for Parkinson's Disease UK of which she was Chief Executive until 2001; she was President of the European Parkinson's Disease Association (EPDA) from its formation in 1992 until 2006; and President of the European Federation of the Neurological Associations (EFNA).

Ayres: We're all in this together. I was just looking at my little list here: we've got the Migraine Trust, Migraine Action, Spectrum Alliance, Pain UK, Ouch, and the Irish Migraine Association.¹⁷⁵

Jones: Do you speak with one voice?

Thomas: I would say we have a different way of doing things but essentially we're still putting the person with migraine at the centre of it; it's perhaps just doing it slightly differently. I think you're right, one shouldn't be fighting each other and I don't think we are, but I think that today's patient goes onto the internet and expects to see more than one organization. In fact, we have scientific trustees, including Mark, on our trustee board and Peter Goadsby and others. We have a slightly different way of doing evidence-based stuff but the fact is it's important to, we're a bit of a hybrid, but we are there. I'm sure that a lot of the people who look at our website and who are supporters, are the same people who look at Migraine Action and it's a pick and mix. You've got to give people some choices.¹⁷⁶

Jones: I'm thinking about funding.

Thomas: Actually, if you look at any of the evidence on organizations getting together, there's very rarely any money saved. There's very clear evidence on that from mainly the charity governance groups.¹⁷⁷ Funding is a problem.

¹⁷⁵ The Migraine Trust, founded in 1965, is the health and medical research charity for migraine; see <http://www.migrainetrust.org/> (visited 27 November 2013). Migraine Action (formerly the British Migraine Association) is a national charity founded in 1958, for people affected by migraine; see www.migraine.org.uk (visited 26 November 2013). Spectrum Alliance UK was founded in 2007, representing various charities and support groups for people who suffer adverse health effects from modern low energy lighting; see www.spectrumalliance.co.uk/ (visited 27 November 2013). Pain UK was founded in 2011 as an organization to help people in pain and support charities dealing with pain; see www.painuk.org/ (visited 27 November 2013). Ouch (UK) is an organization established in 2001 for the understanding and raising awareness of cluster headache; see, <http://ouchuk.org/> (visited 27 November 2013). The Migraine Association of Ireland is a charity set up in 1994 to support and provide information to people with migraine and other headache disorders; see <http://www.migraine.ie/> (visited 27 November 2013).

¹⁷⁶ Mrs Wendy Thomas wrote: 'The Migraine Trust is a research charity that responded to patients wanting evidence based information and the other patient groups tended to use forums etc.' Email to Ms Caroline Overy, 18 November 2013.

¹⁷⁷ See La Piana and Harrington (2010). Mrs Wendy Thomas wrote: '[This publication] showed that charities which merged didn't actually have cheaper costs. Mergers rarely happen but takeovers do.' Email to Ms Caroline Overy, 18 November 2013.

Jones: Would it attract more funding for research and nurses and so on if you had just one organization?

Thomas: Nobody's interested in funding.

Quarshie: When I first came into post seven years ago my post was funded through sponsorship from a drug company and our Headache Research Fund. After two years there was a real uncertainty around whether the NHS Trust I am employed by would actually continue funding the post, or whether I would become redundant and return to the neurology ward and the service would discontinue. Due to the current economic climate there is a real problem within healthcare trusts in that, if you can get funding and demonstrate that there is a need for that service, then there should be a commitment from the NHS trust to take over and continue funding at the end of the initial two-year period.

Sandler: I think the answer to funding is 'bring on the stars'. I was just about to say that there can't be many of us left who remember the board of the Migraine Trust in round about the early 1960s. And there we had total glamour. There was C P Snow and his bad tempered wife.¹⁷⁸

Ayres: Sorry to disagree, but C P Snow was one of my predecessors as President. Indeed, that was very glamorous.¹⁷⁹

Sandler: Well, the British Migraine Association had more than C P Snow. They had, as they say, his bad tempered wife, Pamela Hansford Johnson. She was terrible. [Laughter] There was also Cyril Kleinwort.¹⁸⁰ They all gathered in a little cabal beforehand in a meeting room and then all streamed in; when I say 'all' there were other big names in this collection. And in the meeting room Princess Margaret suddenly came in, if there was a lecture by somebody or other, some eminent American visitor and then everybody sat down. She came

¹⁷⁸ The writer and scientific administrator, Charles Percy Snow (1905–1980), Baron Snow of the city of Leicester from 1964; his wife was the writer and playwright, Pamela Helen Hansford Johnson (1912–1981).

¹⁷⁹ Mrs Mary Ayres clarified this: '1962–1974, Lady Snow (Pamela Hansford Johnson) was President of the British Migraine Association; 1964–1975, Lord Snow was one of several Vice Presidents of the Association. He retired when he was elevated to the Peerage.' Email to Ms Caroline Overy, 26 March 2014. For a history of the British Migraine Association see *A Brief History of Migraine Action* available online at www.migraine.org.uk/js/plugins/filemanager/files/downloads/History_of_Migraine_Action.pdf (visited 31 March 2014)

¹⁸⁰ Sir Cyril Kleinwort (1905–1980), a partner in the private bank Kleinwort Benson, suffered from migraine and was Honorary Treasurer of the Migraine Trust, donating £10 000 a year until his death.

in late, took her gloves off, sat down gently, put her head down, slept during the whole lecture, and then sort of streamed out again. The Migraine Trust never seemed to be short of money at that time.

Thomas: It wasn't because of Princess Margaret though.

Ayres: Princess Margaret was not associated with the British Migraine Association except insofar as they were the cause of the Migraine Trust becoming the Migraine Trust and they were very proud of that. So I think our founder just went for as many people with double-barrelled names as he could for his first set of members of the committee. [Laughter] And there were about 17 for many years.

Weatherall: I'm just going to say a few things to close. Firstly I'm going to thank you all very much indeed for your attendance and your contributions to the Witness Seminar. It's always difficult to know how these things will go because I could sit down and grill any one of you one-to-one and get a huge amount of interesting and exciting stuff out of you; but one of the things that we look for is an emergent collective voice on this, and I think we've been reasonably successful in getting that today. So many thanks for all your contributions.

I'd like just to say a couple of things with my historian's hat on that arise out of what Katherine was saying about the situation 100–120 years ago. When migraine first does become an area of interest, there were people like the rather strange, and otherwise completely obscure, Cambridge pair of Edward Liveing, who published his work on nerve storms, which is the sort of archetypal neural theory, and Peter Latham, who published his lectures where he outlines an embryonic version of the biphasic theory, which Michael O'Brien mentioned at the beginning of the seminar, that is vasoconstriction followed by vasodilation.¹⁸¹ My view on this, which may or may not be historically correct, is that actually they were blown apart by no less a luminary than William Gowers, who, of course, was the leading British exponent of neurology.¹⁸² And Gowers, as he was wont to do, picked apart both Liveing's and Latham's theories on the basis that they did not explain the phenomena that he saw in his patients. Unfortunately, that left a bit of a gap in terms of theories of migraine pathogenesis; that was

¹⁸¹ Liveing (1873); Latham (1873). See also Weatherall (2012a).

¹⁸² Sir William Gowers (1845–1915) was Consulting Physician and Professor of Clinical Medicine at University College Hospital. His *Manual of Diseases of the Nervous System* was internationally recognized (Gowers (1886–8)).

the gap into which not only Harold Wolff walked in the 1930s (looking at pain both as a function of pain-sensitive structures within the scalp, particularly the dura and the blood vessels, and also as a function of changes in the blood vessels using ergotamine as the very powerful research tool), but also the gap into which psychoanalytic and psychological theories of migraine pathogenesis fitted. One of the things that we didn't get a chance to explore fully today is how powerful those psychological concepts of migraine have been, and of the fact that it's incredibly pervasive that headache is not an important problem, leading to the strange situation that headache is either incredibly dangerous because it means you've got a brain tumour, or it's not at all dangerous, and in fact your complaining of headache means you are either morally deficient or you're swinging the lead, trying to get out of what you're supposed to be doing. These polarities are very entrenched from a cultural point of view. All the work that we've talked about today still has yet to shift those very deeply entrenched views of what headache is about. The great thing about all the work that we talked about, especially the triptan story, is that of course it has materially led to improvement in the lives of people with headaches, which is what all of us who are clinically and scientifically interested in the subject want to promote. And, of course, the discussions that we've had at the end show that we are really still struggling to take that forward in the future, to continue to translate the scientific interest into benefits for patients, which is still very much there in the work that Jes and his group, and Mike Moskowitz and Rami Burstein and all the scientists that we've talked about have done. So thank you very much indeed for coming today. I hope you enjoyed it as much as I did; I hope you found it interesting and valuable.

Tansey: May I also add my thanks to Mark and to all of you for coming and contributing so much. It's been a very thought-provoking afternoon. I'm particularly impressed by Trevor Jones' knowledge of the birthplace of British pop stars. [Laughter] You have hidden talents, Trevor, you really do. I would also like to add my particular thanks to Mark Weatherall, an ideal chairman. There are not many neurologists with a PhD in the history of medicine even if you did have a very generous external examiner, Mark. [Laughter] No, he very well deserved his PhD. He's a great loss to the subject so I'm very pleased that he's coming back into history of medicine because it's very important that practitioners, scientists, and clinicians do engage with contemporary history of medicine. So, thank you very much indeed, Mark.

Appendix 1

Theories of migraine 1900–1960: a brief background to the Wellcome Witness Seminar

Mark Weatherall

Migraine is found in the medical and lay literature throughout recorded history. By 1900 scientific theories of migraine fell into two broad camps: neural theories, as epitomized by the theory of ‘nerve-storms’ expounded in the monograph *On Megrin*, published in 1873 by the English physician Edward Liveing; and vascular theories such as those put forward by du Bois Reymond, Mollendorf, and Peter Wallwork Latham. Liveing’s work was regarded by the great English neurologist William Gowers as the best work on the subject, and in recent decades, through the advocacy of Oliver Sacks and John Pearce, it has become regarded as a masterpiece of the genre. It did not, however, lead to changes in the understanding or treatment of migraine at the time, and it is the vascular theories that provide the main background for the understanding of migraine between 1900 and 1960, not least because of the gradual introduction of an effective medication with clear vascular effects: ergotamine.

During the 1920s and 1930s several reports attested to the effectiveness of ergotamine in treating migraine. At the same time advances in neurosurgical technique allowed increasingly sophisticated attempts to localize brain function, including pain. These two strands were brought together in the 1930s by the American neurologist Harold Wolff in classic papers published in 1938 and 1940.¹⁸³ In the first of these he investigated the effect of ergotamine upon the extracranial arteries during attacks of migraine, showing that it reduced pulse amplitude as it diminished the intensity of the headache; in the second he demonstrated that pain could be evoked by stimulation of dural blood vessels and sinuses, and of the large intracerebral arteries, the painful sensations being localized to the ophthalmic branch of the trigeminal nerve, where migraine typically manifests. These observations were central to Wolff’s landmark 1948 monograph *Headache and Other Head Pain*, which immediately became the standard work on the subject.¹⁸⁴

¹⁸³ Graham and Wolff (1938); Ray and Wolff (1940).

¹⁸⁴ Wolff (1948).

Wolff himself was cautious about extrapolating his findings in the extracranial arteries to those of the intracranial arteries, but nonetheless a simple vascular theory – that aura was due to constriction of cerebral vessels, and headache to vasodilation – was distilled from his monograph into countless student lectures and textbooks. The problem with this simple theory was – as Gowers and others after him pointed out – that it did not explain the phenomena, particularly those of visual aura, the gold standard clinical description of which was published by the visual physiologist Karl Lashley in 1941.¹⁸⁵ Lashley studied his own visual auras meticulously, noting that they always started at or near the centre of fixation, spreading laterally and never impinging upon the midline. Some of his auras had scintillating zig-zag edges; others were exclusively negative. He mapped these phenomena onto the known anatomy of the occipital cortex, postulating that a wave of inhibition (sometimes preceded by intense excitation) must propagate away from the occipital pole at a speed of approximately 3 mm/min.

This concept was initially difficult to reconcile with the prevailing orthodoxy, but in 1958 the Canadian neurologist PM Milner pointed out that a potential alternative physiological mechanism might be cortical spreading depression, first demonstrated in 1944 by the Brazilian physiologist Aristedes Leão.¹⁸⁶ When Leão tried to induce experimental seizures by electrical stimulation of the cortex of rabbits, he found instead an orderly and progressive flattening of cortical electrical activity, spreading away from the point of stimulation, followed some time afterwards by recovery of function in the same pattern; the speed at which this wave crossed the cortex was – tantalizingly – 3 mm/min.

Wolff himself believed that migraine pathogenesis involved not only vasodilation, but also the release of perivascular nociceptive factors that damaged local tissues, and increased sensitivity to pain in migraine attacks, thought possibly to have an allergic basis. Various candidate substances were studied during the 1940s and 1950s, including histamine, acetylcholine, bradykinin, and 5-HT. The most powerful known 5-HT antagonist, lysergic acid (LSD), was not clinically useful because of its hallucinogenic effects. In 1959, however, the Italian neurologist Federigo Sicuteri published a study demonstrating that 1-methyl-D-lysergic acid butanolamide (methysergide), a more powerful 5-HT antagonist than LSD but not a vasodilator, was a safe and effective prophylactic

¹⁸⁵ Lashley (1941).

¹⁸⁶ Milner (1958); Leão (1944).

treatment for headache.¹⁸⁷ A spate of further studies followed, including the first well-conducted randomized controlled trial in headache, published by Southwell *et al.* in the *Lancet* in 1964.¹⁸⁸ Sicuteri showed that increased levels of 5-HIAA (the main metabolite of 5-HT) could be found in the urine during migraine attacks, and a series of papers from Jim Lance's group in Sydney began to delineate the role of platelet dysfunction in migraine (platelets being the main repository of 5-HT in the body). A second 5-HT antagonist, pizotifen, was developed as a migraine prophylactic by Sandoz in the 1960s, appearing at around the time that reports of methysergide-induced retroperitoneal, cardiac, and pulmonary fibrosis began to appear.

Harold Wolff's final service to migraine was to sit on an Ad Hoc Committee of the US National Institutes of Health on the Classification of Headache.¹⁸⁹ In 1962, the year that Wolff died from a stroke at the age of 63, the Committee produced a diagnostic classification that was influential throughout the 1960s and 1970s. The basis of this classification was clinical, heavily influenced by extensive patient case series such as that published by Selby and Lance in 1960.¹⁹⁰ At the period at which this Witness Seminar commences, therefore, there was a relatively recently proposed classification system for headaches (including migraine), various prevailing theories (predominantly with a vascular basis) regarding migraine pathogenesis, and a series of established and novel treatments for migraine, including ergotamine and methysergide.¹⁹¹

¹⁸⁷ Sicuteri (1959).

¹⁸⁸ Southwell, Williams and Mackenzie (1964).

¹⁸⁹ Ad Hoc Committee on Classification of Headache (1962).

¹⁹⁰ Selby and Lance (1960).

¹⁹¹ For secondary sources, see Tfelt-Hansen (2010); Tfelt-Hansen and Koehler (2011); Weatherall (2012b).

Appendix 2

Summary of the classification of primary headaches¹⁹²

1. Migraine

- 1.1 Migraine without aura
- 1.2 Migraine with aura
- 1.3 Chronic migraine
- 1.4 Complications of migraine
- 1.5 Probable migraine
- 1.6 Episodic syndromes that may be associated with migraine

2. Tension-type headache (TTH)

- 2.1 Infrequent episodic tension-type headache
- 2.2 Frequent episodic tension-type headache
- 2.3 Chronic tension-type headache
- 2.4 Probable tension-type headache

3. Trigeminal autonomic cephalalgias (TACs)

- 3.1 Cluster headache
- 3.2 Paroxysmal hemicrania
- 3.3 Short-lasting unilateral neuralgiform headache attacks
- 3.4 Hemicrania continua
- 3.5 Probable trigeminal autonomic cephalalgia

4. Other primary headache disorders

- 4.1 Primary cough headache
- 4.2 Primary exercise headache
- 4.3 Primary headache associated with sexual activity
- 4.4 Primary thunderclap headache
- 4.5 Cold-stimulus headache
- 4.6 External-pressure headache
- 4.7 Primary stabbing headache
- 4.8 Nummular headache
- 4.9 Hypnic headache
- 4.10 New daily persistent headache (NDPH)

¹⁹² Adapted from the Headache Classification Committee of the International Headache Society (IHS) (2013), 636–37.

Appendix 3

The Role of the UK Specialist Nurse in Headache

Ria Bhola and Victoria Quarshie, Headache Nurse Specialists

The role of the specialist nurse has developed rapidly across specialties over recent years. This has been facilitated by several factors in the UK: reforms in nurse education and guidelines created for role expansion, government targets for health outcomes, reduction in junior doctors' hours, patient demands for greater choice and accessibility, and the development of headache services.

Currently in the UK there are just 12–14 headache nurses and many are members of the British Association for the Study of Headache (BASH).¹⁹³ The numbers may increase as new services develop and the impact of the role is recognized as a crucial, cost-effective component of these services.

Within the UK group there is an awareness of the diversity in each other's practice and the variation in skills, knowledge, and experience. This diversity in practice is often discussed at the annual nurse meetings where knowledge and experience is shared within the group.

Role components

While it is accepted that there is diversity in the way that individual nurses practise there are some elements of the role that are generic and remain the core of practice:

- **Professional**

Maintaining professional registration by reviewing and maintaining own professional education, knowledge, and practice, and complying with the Nursing and Midwifery Council (NMC) Code of Professional Conduct at all times is essential, as is participation in professional interest groups and bodies by sharing experiences as this aids in the process of identifying and promoting best practice.

- **Clinical expert**

By understanding and delivering care to individuals with a diagnosis of primary headache disorder from diagnosis and throughout their

¹⁹³ See note 160 on page 76.

periods of need, the nurse will be involved with the ongoing assessment, planning, reviewing, and evaluation of an individual's care and ensuring all documentation complies with the NMC Guidelines. In possessing the ability to acknowledge their own boundaries in expertise, experience, and knowledge and that of professional colleagues in doing so, the nurse is able to ensure that the most appropriate member of the multidisciplinary team is consulted for specific management issues.

The majority of the nurses operate a telephone clinic or an advice-line where patients, their carers, and others involved within their care can contact the nurse between hospital appointments for advice, support, information, and review. The contact with the specialist nurse is not intended to replace the general practitioner's (GP) role. It rather assists and compliments their practice, highlighting the specialist needs of the patient.

Many headache specialist nurses will be involved in the development of care pathways for patients presenting with primary headache disorders, and many nurses develop and run their own nurse-led clinics, working as autonomous practitioners within their own scope of competence.

- **Consultation and leadership**

Other healthcare professionals can also utilize the specialist nurse as a resource to inform their own practice. Essential parts of the role are to liaise with primary care groups/Trusts and foster these relationships by offering advice, education, and support, while being aware of the boundaries of one's own role and knowledge. For the care of headache patients to develop and improve it is essential that the nurses share their specialist knowledge, experience, and research with their colleagues, providing leadership and support to nursing colleagues and peer groups in the management of patients with primary headache disorders.

- **Educator**

The specialist nurse operates as educator to patients and colleagues. Some are actively involved in the development of educational programmes for other healthcare professionals and patient groups, within both the primary and acute Trusts locally. Often nurses are invited to participate in educational programmes for other professional bodies, national support groups, private organizations, and members of the public. As an educator, it is essential that the nurse is able to promote the needs of this patient group and enable

greater understanding of primary headache disorders and the optimistic outlook for patients. Enabling patients to manage their condition better is crucial in long-term disorders.

Patient education is at the core of the headache specialist nurse role. Providing patients with the information they require to understand their condition and make informed choices about their headache management makes them better equipped to become active managers and responsible for their own healthcare and well-being.

Also, when management strategies do not deliver the desired outcome, the specialist nurse is often the first point of contact when problems are encountered and it is at this stage the nurse is required to re-evaluate the symptoms and planned care, offer support and alternative treatment options, and address inappropriate or unrealistic expectations of treatment. The nursing philosophy and patient education strategies employed by the headache specialist nurses are generally based on health promotion models, with the focus being on adding quality to life when living with a lifelong condition.

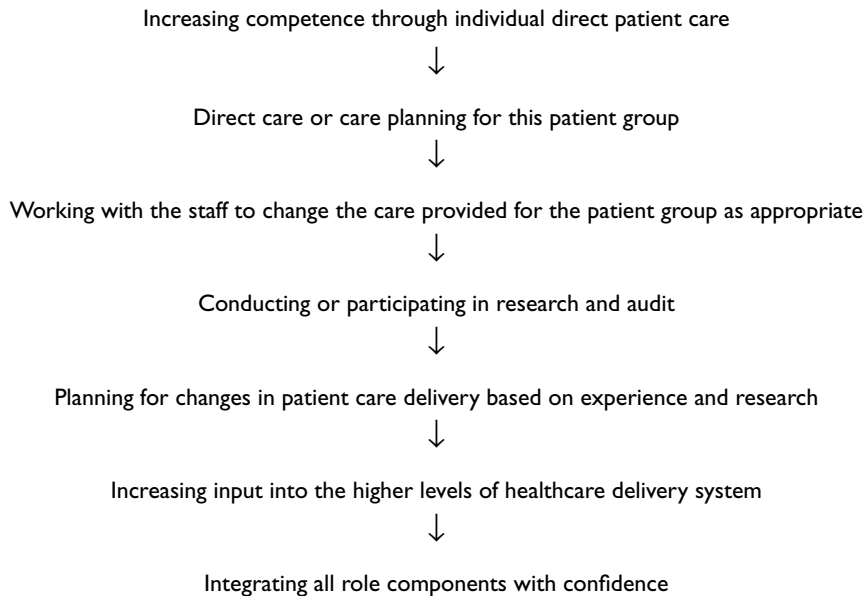
- **Research**

The nurse's role in research requires that they are able to develop their own critical appraisal skills and are thereby able to identify and utilize good quality, research-based evidence to underpin and inform their nursing practice. Frequently the specialist nurse will be involved in the audit of services delivered; this is essential for monitoring the quality and identifying areas that require improvement. Audit is also essential for providing evidence that the specialist nurse role is a viable option for delivering high-quality, cost-effective care to service users.

Often the research role will require the specialist nurse to be involved in clinical trials, and it is imperative that the nurse remains objective, adhering strictly to study protocols and ensuring that meticulous detail is given to the documentation of data to ensure that the trial does not become compromised; this is particularly important as research findings shape and inform future patient management and care.

Developing and refining the role

It is acknowledged that specialist nurses go through a role development process to acquire skill and competence to function with maximum effectiveness. Stages of the role development process have been identified which facilitate the process:



Common activities for headache nurses

Individual headache services will vary in the degree to which the nursing role covers these components, but the main activities undertaken will include:

- **Telephone consultations**

To monitor patient progress at intervals such as follow up from a clinic consultation or inpatient episode, to monitor drug efficacy and tolerability, and to support patients with treatment changes or to address patient queries.

- **Outpatient clinic role**

To take a headache history, assess level of disability, provide and assess headache diaries, and to provide support and advice (on lifestyle issues, use of medication, change of medication, analgesia withdrawal, and deliver treatment procedures, e.g. nerve blocks).

- **Inpatient care (where applicable)**

To assess patient needs and ensure they understand the plan of care in hospital, to monitor progress of treatment, and optimize care and ensure effective discharge planning.

- **Organizational activities**

Working with relevant areas of the organization to negotiate and improve service delivery and developments.

- **Research and education**

Monitor future developments and stay apprised of new and emerging therapies. Input into research and audit to improve patient and service outcomes.

Conclusion

The specialist nurse is a non-traditional nurse with expanded boundaries. These roles have a valuable contribution to make in the global effort to reduce the burden of headache and meeting the vision of the World Health Organization to the benefit of headache sufferers.

Biographical notes*

Dr Jeffrey Aronson

MA DPhil FRCP FBPharmacolS
FFPM(Hon) (b. 1947) trained in the University of Glasgow (1964–1973) and the Medical Research Council Unit and University Department of Clinical Pharmacology, Oxford, under the late Professor David Grahame-Smith. He is currently Reader in Clinical Pharmacology at the University of Oxford and Honorary Consultant Physician in the Oxford University Hospitals Trust. He was President of the British Pharmacological Society (2008/9) and is now Emeritus President. He was Vice-Chairman of the Medicines Commission (2002–2005) and Editor-in-Chief of the *British Journal of Clinical Pharmacology* (2003–2007). 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. For further details see www.phc.ox.ac.uk/jeffrey-aronson.

Mrs Mary Ayres

(b. 1935) studied in France in the early 1950s, trained as a bilingual secretary, and worked at the WHO's Mental Health Section in Geneva and the Royal College of Psychiatrists. Daughter of a migraine sufferer, married to a migraine sufferer, she is no stranger to the disabling qualities of the affliction and the effect on family and working life. She has always had a personal interest in Migraine Action's Young Migraineurs' Project. A recent task was to prepare a short history of the British Migraine Association, now Migraine Action, founded in 1958 by the late Peter Wilson MBE, marking 55 years of supporting migraine sufferers and their families. For well over 30 years she has been an active volunteer for the Association and has been Chair of Trustees, Association Chairman and is now Honorary President. She often represents Migraine Action at regular meetings of the All-Party

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

Parliamentary Group on Primary Care and Public Health and the Self Care Forum.

Dr Tom Blackburn

MPhil PhD DSc FBPharmacolS (b. 1949) received his degrees from Nottingham University and Manchester University. He has held C-level executive and senior management positions at ICI Pharmaceuticals PLC, Beecham Pharmaceuticals PLC, and SmithKline Beecham in the UK, and with two biotech companies in the USA, 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, Galanin R3, and the SSRI antidepressant, Seroxat/Paxil. His passion, based on an extensive knowledge of pre-clinical and clinical drug development and marketing, is helping to define strategies and positioning of pharmaceutical products for biotech startup companies. He 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 British Pharmacological Society and a member of the American College of Neuropsychopharmacology. He is also a non-Executive Director for Motac Neuroscience Ltd., a neuroscience biotechnology company specializing in Parkinson’s disease, cognition, and neurodegenerative disorders.

Dr Macdonald Critchley

CBE MD FRCP (1900–1997) qualified in Bristol in 1922. After appointments in Bristol, Great Ormond Street, and the Maida Vale Hospital, he trained as a neurologist at the National Hospital, Queen Square, gaining his MD in 1924. In 1928 he was appointed Consulting Neurologist at King’s College Hospital and Consulting Physician at the National Hospital, Queen Square. He was President of the Association of British Neurologists (1962–1964), President of the World Federation of Neurology (1965–1973), and Founder President of the Migraine Trust. His book on the parietal lobes, published in 1953, was central to the growth of cognitive neurology (Critchley M. (1953)). See McDonald (2000).

Dr Giles Elrington

MBBS MD FRCP (b. 1956) qualified from Barts in 1980, and in 1982 became Senior House

Officer in Neurology where he met his wife, the mother of three now adult children. Further neurological training was at the Wessex Neuro Centre, National Hospital Queen Square, and the Radcliffe Infirmary, Oxford. His MD thesis was on the cross-reactive neuro-immunology between small-cell lung cancer, and the neuromuscular junction, in relation to the Lambert–Eaton myasthenic syndrome. On becoming a Consultant in 1993, a more practical special interest was needed so he established a headache clinic at the London Hospital, Whitechapel, which he ran until 2011 when he moved to the National Migraine Centre (formerly the City of London Migraine Clinic) where he is Consultant Neurologist and Medical Director. He remains involved with clinical trials in the therapeutics of multiple sclerosis at the London Hospital, has contributed also to clinical trials in headache, including Allergan's PREEMPT Botox study. He is a former Treasurer of the British Association for the Study of Headache and former President of the Anglo Dutch Migraine Association.

Dr John Fozard

PhD, studied pharmacy at the University of London and received his PhD in Pharmacology from the University of Bradford in 1968.

After a lectureship and senior lectureship at the University of Manchester and a year at the University of Mainz, he was appointed Head of Pharmacology at the Merrell-Dow Research Institute in Strasbourg in 1977, where he remained for ten years. He was subsequently Head of Hypertension Research and then Head of Asthma Research at Sandoz in Basle. In 1996 he became Head of Respiratory Disease Research at Novartis and after three years a Novartis Distinguished Scientist in the Respiratory Disease Research section of the Novartis Institutes for BioMedical Research. He retired in 2005. See the biographical information submitted by Professor Daniel Hoyer to the Serotonin Club Newsletter, Autumn 2005 to mark Fozard's retirement, at www.serotoninclub.org/newsletters/Nwsltr66.pdf (visited 26 March 2014).

Dr Katherine Foxhall

PhD (b.1981) is a medical historian specializing in the history of illnesses and patient experiences. She gained her PhD from the University of Warwick in 2008, and then worked at the Centre for the History of Science, Technology and Medicine at the University of Manchester, before receiving a Wellcome Postdoctoral Research Fellowship to research the social,

cultural, and medical history of migraine at King's College London from 2011 to 2013. She joined the School of History at Leicester in September 2013 as Lecturer in Modern Extra-European History.

Dr Patrick Humphrey

OBE, DSc, PhD,
FBPharmacolS (Hon) (b. 1946)
was born in South Africa and graduated from the School of Pharmacy, University of London, in 1968, with a strong interest in drug receptor theory. After obtaining a PhD in pharmacology at St Mary's Hospital Medical School and briefly working as a Lecturer in the Department of Physiology, he joined Allen & Hanburys at Ware to initiate a project on migraine. His work on cerebrovascular pharmacology led directly to the development of sumatriptan, the prototype of a new drug class (the triptans) for the treatment of migraine. During this time, he became the overall Director of the Glaxo Division of Pharmacology that was not only instrumental in the discovery of sumatriptan, but also naratriptan, alosetron, ondansetron, vapiprost, and salmeterol, covering a broad spectrum of therapeutic areas. He has received many important academic honours, including an honorary Professorship from the University of Cambridge, as well

as the Royal Society's Mullard medal. In 1999, he was awarded the OBE for 'services to migraine research'. He maintains a passion for research aimed at drug discovery and was latterly the successful Head of Research and Executive Vice President at Theravance in 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.

Professor Brian Hurwitz

MA MSc MD MBBS FRCP
FRCGP (b. 1951) is a clinical academic who worked as an NHS GP in inner London for 30 years. Since 2002 he has been Professor of Medicine and the Arts at King's College London, where he directs the Centre for the Humanities and Health, which is funded by the Wellcome Trust (see: www.kcl.ac.uk/innovation/groups/chh/index.aspx) and hosts MSc, PhD, and postdoctoral programmes. Based in the Department of English at King's, his research interests include narrative studies in relation to medical practice, ethics, law, and

the literary shape of eighteenth- to twentieth-century clinical case reports. He has co-authored and edited 120 peer-reviewed papers, 40 book chapters, and several books. He holds honorary professorships in the Centre for Value, Ethics, Law and Medicine at the Faculty of Medicine, University of Sydney, the Schools of Humanities and Medicine at Hong Kong University, and at the Institute of Neurology, Queen Square, University College London. Prior to his current position he was Professor of Primary Health and General Practice at Imperial College London.

Sir David Jack

Kt CBE PhD FRS FRSE (1924–2011) studied pharmacy and pharmacology at Glasgow University where he became Assistant Lecturer before National Service. After working in the pharmacy research department at Glaxo (Greenford) and at the pharmaceutical company Menley and James (later part of Smith Kline and French), completing a part-time PhD at London University, he was appointed Head of Research at Glaxo (Allen & Hanburys) at Ware in 1961, becoming Research and Development Director from 1978 to 1987 when he retired. He pioneered major developments in the treatment

of asthma (salbutamol), gastric ulcers (ranitidine), migraine (sumatriptan), and cancer therapy-induced emesis (ondansetron). He was awarded the CBE in 1982 and knighted in 1993. For further details, see Watts (2012); Barnes and Breckenridge (2012).

Professor Trevor Jones

CBE PhD HonDSc FRSC
FRSM FKC HonFRCP FFPM
FBPharmacolS FCPP (b. 1942)
graduated in pharmacy and chemistry. After teaching at Nottingham University he joined the Boots Company where he was Head of Pharmaceutical Development and then moved to the Wellcome Foundation, firstly as Head of Technical Development, then succeeded Professor Sir John Vane as Group R&D Director. For ten years he was Director General of ABPI and is now a member of the Boards of Directors of a number of pharmaceutical companies in the USA and EU, including Allergan Inc. (California). He is a founder member of the Geneva-based, public-private partnership, Medicines for Malaria Venture (MMV) and in 2004 was appointed to the World Health Organization (WHO) Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH). He was for 12 years a member of the UK Government

regulatory agency – the Medicines Commission – and Chair of the UK Government Advisory Group on Genetics research. He is currently on the Research Board of the EU Commission Innovative Medicines Commission (IMI) and the Board of the UK Stem Cell Foundation (UKSCF). He is a visiting professor at King's College, London and holds honorary degrees and Gold Medals from six universities.

Professor Anne MacGregor
MD FFSRH MICR DIPM
(b. 1960) is a specialist in Headache and Women's Health. She works at Barts Sexual Health Centre, St Bartholomew's Hospital, London and is Honorary Professor, Centre for Neuroscience and Trauma, Blizard Institute of Cell and Molecular Science at Barts and the London School of Medicine and Dentistry. She is Vice Chair and CRQ Convenor of the Examination Committee of the Faculty of Sexual and Reproductive Healthcare and is joint Faculty Deanery Advisor for NE Thames. She has published over 180 research papers and book chapters, five single author books, five co-authored books, and has co-edited three books. She was an expert advisor for the NICE headache guidelines and is co-author of the BASH guidelines for the diagnosis and management of

migraine, tension-type, cluster, and medication overused headache, now in their third edition. Her research crosses the fields of neurology and reproductive healthcare, with her MD thesis exploring the role of oestrogen in migraine.

Dr Michael O'Brien
MD FRCP (b. 1938) qualified from Guy's Hospital Medical School in 1962 and trained in neurology at Guy's Hospital, the National Hospital for Neurology and Neurosurgery, and at the Regional Neurological Centre in Newcastle. His MD thesis (1973) was on 'Cerebral Cortex Perfusion Rates in Migraine'. He has held three MRC research posts: at Guy's Hospital 1965–1966, in Newcastle 1969–1970, and at the University of Minnesota in Minneapolis 1971–1972. He was Consultant Neurologist at Guy's Hospital from 1978 until his retirement in 2003. His special interests include cerebrovascular haemodynamics and pathophysiology, mononeuropathies, and women with epilepsy. He has held Civil Aeronautics Authority (CAA) and Federal Aviation Administration (FAA) private pilot's licences since 1982 and became Consultant Advisor in Neurology to the UK CAA in 2001. He is a past President of the Harveian Society, the Clinical

Neurosciences Section of the Royal Society of Medicine and the South of England Neurosciences Association. He lectures for the National Association of Decorative & Fine Arts Societies (NADFAS) and at the School for Oriental and African Studies on Khmer Art and Architecture and on Hindu Temple Art, Architecture and Mythology.

Professor Jes Olesen

MD DMSc DHonC (b. 1941) received his MD in 1967 and his doctorate degree in Medical Science in 1974 from the University of Copenhagen. Since 1985 he has been Professor of Neurology at the University of Copenhagen (Assistant Professor 1975–1985), and is Founder and co-Chair of the Danish Headache Center, Department of Neurology, Glostrup Hospital in Copenhagen. He has published 33 books and over 600 scientific articles and book chapters. He is one of the founders of the European Federation of Neurological Societies and of the European Brain Council. He has received several Danish and International awards, including the Niels A Lassen award, the Mogens Fog award, the Mångberg prize, the Great Nordic Research prize of the Lundbeck Foundation, and he is honorary member of many societies, including the Association of British Neurologists, the German

Neurological Association and the French Neurological Association. He is an honorary doctor of La Sapienza University of Rome. He has given many invited/named lectures throughout the world. His research interests are focused on migraine and other headaches, and span from clinical studies and classification over human pathophysiological studies involving particularly brain blood flow and MR all the way to basic research into neural and vascular signalling mechanisms.

Dr Alec Oxford

MA DPhil (b.1940) read chemistry at St Catherine's College, Oxford. He joined Allen & Hanburys in 1967 as a senior research chemist, subsequently progressing to senior research leader in 1977. Then for 14 years, from 1979, he directed teams of synthetic organic chemists identifying agents that interact with 5-HT receptors leading to the discovery of the anti-migraine drug sumatriptan and the antiemetic agent ondansetron. From 1996 to 2007 he was an independent consultant on medicinal chemistry.

Dr Richard Peatfield

MA MD FRCP (b.1949) qualified from Queens College Cambridge and the Middlesex Hospital in 1973. After general medical training he was appointed Migraine

Trust Research Fellow at Charing Cross Hospital in 1979, completing a Cambridge MD thesis in 1982 (examined by Marcia Wilkinson and Merton Sandler). He then moved to be Senior Registrar in Neurology in Leeds, returning to Charing Cross as a Consultant Neurologist in 1989. Until he was joined by Dr Mark Weatherall in 2007, he was the only neurologist with an interest in headache at Charing Cross. He was Chairman of the British Association for the Study of Headache from 2007 to 2010. He maintains a research interest in possible triggers for migraine.

Mrs Vicky Quarshie

Dip HE Adult Nursing (b.1972) is a Headache Specialist Nurse and works within the Headache Service based at Hull and East Yorkshire Hospitals NHS Trust. She has held this post for the past eight years, prior to this she worked as a staff nurse in the general neurology ward since completing her Diploma in Adult Nursing in 2000. She is a council member of the British Association for the Study of Headaches (BASH) and also a member of both the British and European Headache Specialist Nursing Forums. She has given presentations on headache management and treatments to patient groups,

healthcare professionals, and the pharmaceutical industry at local, national, and European level, and is committed to increasing awareness of headache disorders and providing quality, effective, evidenced-based care for headache sufferers. She has also recently written a chapter for the second edition of the textbook *Childhood Headache*, ‘Drawing as an expression of migraine symptoms in Children; can a picture really paint a thousand words?’ (Quarshie (2013)), and contributed to clinical research regarding the use of Botox in the treatment of chronic migraine.

Dr Frank Clifford Rose

MBBS MRCS FRCP (1926–2012) qualified in medicine at King’s College, London and the Westminster Hospital in 1949. Following posts at the National Hospital, Queen Square and St George’s Hospital, in 1965 he was appointed Consultant Neurologist at Charing Cross Hospital where he established his specialist migraine clinic in 1974, which became the Princess Margaret Migraine Clinic in 1980. He was active in the World Federation of Neurology and was Chairman of the Research group on Migraine and Headache from 1980 to 1995; he was a founding member of the European and International Headache

Societies and was Chairman of the Migraine Trust from 1987 to 1995. See Goadsby, Evers and Peatfield (2012).

Professor Merton Sandler

MD FRCP FRCPATH FRCPsych (b. 1926) graduated in medicine at Manchester University, and held various house and registrar jobs leading to a lectureship in Chemical Pathology at the Royal Free Hospital Medical School. He was Professor of Chemical Pathology, University of London from 1973 to 1991. He was President of the British Association for Psychopharmacology (1980–1982). He has received various international honours and awards, including the CINP Lifetime Award for contribution to monoamine studies in human health and disease. For an interview with Merton Sandler, see Healy D. (1996), pages 381–400.

Professor Pramod Saxena

MBBS MD (b. 1939) studied medicine and went on to receive his MD in pharmacology from King George's Medical College, Lucknow, India in 1965. After working in pharmacology and as a family physician he joined the Pharmacology Department of Organon, the Netherlands, where his research focused on the development of muscle relaxant and

antidepressant drugs. In 1970 he became Professor of Pharmacology in the new Medical Faculty at Rotterdam; he was Chairman from 1990 to 2004. There he continued his research into migraine and 5-HT. In 1998 he set up Erasmus Pharma and was Managing Director until 2005. He has a large number of scientific publications, which have been extensively cited; he has organized many national and international meetings and has been on the editorial board of several scientific journals. He was awarded the Harold G. Wolff Prize (1973) and John Graham Senior Clinician Award (1996) by the American Headache Association, and the Dutch Headache Society instituted a 'Prof. Dr. P. R. Saxena prize' awarded annually to the author of the best scientific paper in the headache field, published in an international journal.

Professor Tilli Tansey

OBE PhD PhD DSc HonFRCP FMedSci (b. 1953) graduated in zoology from the University of Sheffield in 1974, and obtained her PhD in *Octopus* neurochemistry in 1978. She worked as a neuroscientist in the Stazione Zoologica Naples, the Marine Laboratory in Plymouth, the MRC Brain Metabolism Unit, Edinburgh, and was a Multiple Sclerosis Society Research Fellow at St Thomas'

Hospital, London (1983–1986). After a short sabbatical break at the Wellcome Institute for the History of Medicine (WIHM), she took a second PhD in medical history on the career of Sir Henry Dale, and became a member of the academic staff of the WIHM, later the Wellcome Trust Centre for the History of Medicine at UCL. She became Professor of the History of Modern Medical Sciences at UCL in 2007 and moved to Queen Mary, University of London (QMUL), with the same title, in 2010. With the late Sir Christopher Booth she created the History of Twentieth Century Medicine Group in the early 1990s, now the History of Modern Biomedicine Research Group at QMUL.

Mrs Wendy Thomas

BSc (b. 1949) has spent over 30 years in the voluntary sector, mainly in sexual health, in the UK and in the developing world. She has spent the past 25 years in the Chief Executive role, and been Chief Executive of The Migraine Trust since 2006.

Dr Glyn Volans

BSc MD FRCP (b. 1943) read medicine and gained an intercalated BSc in physiology and biochemistry at the University of Newcastle upon Tyne. After gaining his MRCP he moved to

St Bartholomew's Hospital in London and the Princess Margaret Migraine Clinic where he was funded by the Migraine Trust (1972). He undertook the research for his MD on drug absorption during migraine. In 1975 he was appointed Consultant Clinical Pharmacologist at the Guy's Hospital Poisons Unit and became Director of the Unit in 1980. Since that time he has not been directly associated with migraine research but has maintained an interest in the safety of analgesic drugs, including over-the-counter preparations. He retired from clinical practice in 2009 but remains an Emeritus Consultant in the Department of Clinical Pharmacology, Kings College London (STH).

Dr Mark Weatherall

MB BC FRCPEdin PhD (b. 1968) is a Consultant Neurologist at Charing Cross and Ealing Hospitals, council member of the British Association for the Study of Headache, a Trustee of the Migraine Trust, and a Fellow of the Royal College of Physicians of Edinburgh. Before studying clinical medicine at Cambridge, he was a historian of medicine with interests in the development of the medical sciences and medical education between 1800 and 1950. He lectures on the

emergence of modern medicine at Imperial College, London, and is currently researching the meanings of headache in the journals of Dorothy Wordsworth and the novels of Wilkie Collins.

Dr Marcia Wilkinson

MA FRCP DM (1919–2013) qualified in medicine at Oxford in 1943 and trained in neurology at the Royal London Hospital. In 1953 she was appointed Consultant Neurologist at the Elizabeth Garrett Anderson Hospital where she remained until 1984. There in 1963 she started a migraine clinic for the treatment of patients and research into migraine. She was appointed Medical Director of the City Migraine Clinic when it opened in 1970 and, together with Dr Nat Blau, established the City of London Migraine Clinic as an independent charity in 1980. She was a founding member of the International Headache Society and was President from 1985 to 1987. See MacGregor (2013).

Professor Harold Wolff

(1898–1962) received his MD at Harvard in 1923. Following training in neurology and psychiatry with posts at Cornell and Johns Hopkins, and periods in Russia and Austria, he was appointed Chief of the Neurology Division at Cornell's new Medical Center at New York Hospital in 1932. In addition to this post, he was Professor of Neurology and Director of the Neurological Division at Bellevue Hospital, New York. He became the first Anne Parrish Titzel Professor of Medicine at Cornell in 1958. His research focused on cerebral circulation and made major contributions to the understanding of the mechanisms of migraine and other vascular headaches. He was the author of over 500 papers and 14 textbooks, including *Headache and other Head Pain* (1948, 2nd edn 1963). See Blau (2004) and Wolf (1962).

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* Please note that references with four or more authors are cited using the first three names followed by 'et al.'. References with 'et al.' are organized in chronological order, not by second author, so as to be easily identifiable from the footnotes.

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