Epilepsy & Behavior 65 (2016) 56–59

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Reflections on a Career in Epilepsy

A bridge between neurology and psychiatry

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1. Early influences

I was born in 1935 in Caerleon, a village in Monmouthshire, South Wales, but formerly a "city" on the edge of the Roman Empire known as Isca Salurium, where the second Legion of Augustus was based. Perhaps this kindled in me an enduring interest in history. I was the eldest of three siblings of a Welsh father and Irish mother. My father was the village general practitioner and two uncles were also doctors, which clearly influenced my choice of a medical career. My earliest memories included 1) accompanying my father to rural surgeries and patients and 2) an awareness of the Second World War while at a boarding school in Weston-super-mare, Somerset, where I had been sent to be exposed to sea air for my childhood asthma. After the War, I moved on to the Oratory School in Berkshire, where my greatest achievement was playing cricket for the school at the famous Lord's Cricket Ground in London in the days, long gone, when a few privileged schools were allowed to hold an annual match there.

The Welsh National School of Medicine in Cardiff, where my father had trained, was a natural next step. In retrospect and in comparison with modern mega-medical schools, such as the Guy's, King's, and St. Thomas' School, where I spent most of my career, I had an excellent general grounding in medicine in Cardiff with its emphasis on 1) clinical clerking supervised in small groups and 2) the importance always of a family, psychological, and social history. However, although J.D. Spillane was an inspiring clinical demonstrator in neurological examination and diagnosis, I learned nothing about epilepsy. Furthermore, because psychiatric lectures clashed with cricket, I learned almost no psychiatry, entirely my own responsibility.

I qualified in 1959, and after junior hospital posts in Cardiff and its environment, I was inclined towards a career in hospital medicine. I was fortunate to enter the London postgraduate circuit via the Brompton Hospital (cardiothoracic medicine), from where I moved to the National Hospital for Nervous Diseases, as it was then called, as a "house physician". This coincided with my membership of the Royal College of Physicians and set me on the path of a neurological career.

When I began training in neurology at "Queen Square" in 1963, epileptology was at a low ebb there, despite its great historical tradition going back to Jackson and Gowers in the 19th century. The only neurologist with an interest in the disorder was Denis Williams to whom I was first attached. He was unique also in displaying an interest in the emotional and social problems of his neurological patients, highly desirable in an epileptologist but largely alien to other neurologists there at the time. Excellent neurologist and electroencephalographer though he was, Denis Williams had no influence on the academic program at the National Hospital, which was narrowly focused on peripheral nerve and muscle by Professor Roger Gilliatt. As I began to develop an academic interest in epilepsy, I got around the problem by an attachment to the Medical Research Council Neuropsychiatry Research Unit in Epsom, Surrey, under its enlightened director, Derek Richter, while I still kept a foot in the door of the National Hospital, an endless source of patients with epilepsy.

As I was completing my neurological training, a new influence was the anglophile Professor of Neurology at Yale, Gill Glaser, who noted my early research into antiepileptic drug (AED) monitoring and chronic toxicity, including folate metabolism, and invited me to spend the year of 1970 in his department. This opened up new horizons for me in both neurology and epileptology, not least through my contacts that year with J Kiffin Penry at NINDS in Washington, where he was just developing the Epilepsy Branch.

When I returned to the UK in 1971, my interest and course in neurology and epileptology was firmly established. Indeed influenced by Professor David Marsden, I was appointed to the newly created Department of Neurology attached to the Institute of Psychiatry, the Maudsley and King's College Hospitals in South London, in part, to develop clinical and academic epileptology within the context of neurology, alongside that of neurosurgery and psychiatry.

2. Research interests

My interest in AED therapy was immediately stimulated at the National Hospital by two patients with epilepsy with megaloblastic anemia. In collaboration with I. Chanarin, a hematologist at the nearby St. Mary's Hospital, we soon found that the majority of our patients with chronic epilepsy had low folate levels related to treatment with phenytoin and barbiturates. During my neurological training I followed 26 of these patients on folic acid therapy over the next 3 years. To my surprise, it gradually became apparent that the vitamin was having a positive effect in most on their mood and mental state but paradoxically seemed to increase seizure frequency in some [1]. These observations were controversial at the time and contrary to the prevailing view that folic acid could not be beneficial to the nervous system as it was well-known that the vitamin was harmful to the nervous system in the presence of vitamin B12 deficiency. Even the convulsant properties of the vitamin were a novelty, but it has since been consistently confirmed experimentally that folate derivatives are epileptogenic and can be utilized in animal models of epilepsy. Wellcome Laboratories (now GSK) took up my "antifolate = antiepileptic" hypothesis, and this led to the development of lamotrigine [2].

This early folate interest led to the introduction of AED monitoring studies with Peter Lascelles at the National Hospital in the mid-1960s,

http://dx.doi.org/10.1016/j.yebeh.2016.08.017

encouraged by the work of F. Buchthal in Copenhagen and H. Kutt in New York. This, in turn, opened up for me a new field of chronic toxicity of AEDs, often associated with rampant polytherapy, which had hitherto been neglected [3]. The subtle impact of short and long-term AED therapy on cognitive function, mood, and behavior was an especially fertile area [4]. The greatest impact of AED monitoring was in revealing unnecessary polytherapy in patients with chronic epilepsy and facilitating effective monotherapy in 70 to 80% of newly diagnosed patients with epilepsy [5].

The question then arose which of the several old or new AEDs was the drug of choice for different epilepsy syndromes in newly diagnosed patients? Supported by the Medical Research Council during the 1980s, I led large-scale multicenter comparative monotherapy trials of phenobarbitone, phenytoin, carbamazepine, and sodium valproate for 2 to 5 years in adults and children. Like the simultaneous VA studies in the USA led by my Yale colleague, Richard Mattson, we found no differences in efficacy but some differences in toxicity, which is therefore the greater influence on choice [6,7].

Despite the multiple new AEDs that have emerged in the last 25 years, there is still no clear answer to the question whether a patient whose seizures do not respond to optimum monotherapy should be treated by adding a second AED or by switching to an alternative monotherapy. Epileptologists, neurologists, and physicians remain bewildered by the number of individual drugs and potential drug combinations available in affluent countries [8]. Furthermore, the marketing of these new drugs has been associated with the unwise abandonment of blood level monitoring so that the decline in polytherapy in the 1970s and 1980s has since been reversed.

Prior to our studies of newly diagnosed patients with epilepsy at King's in the mid-1970s, all previous clinical trials had been in patients with chronic epilepsy. The surprisingly good outcome on monotherapy in our new patients, long since confirmed, raised interesting questions about why seizures in the minority of patients with epilepsy become intractable [9]. Several of the factors having an adverse influence on prognosis were and are well-known, such as brain lesions, psychological disturbances, and social disadvantages. The most important factor in our prospective monotherapy trials was the number of seizures prior to treatment. This raised again the questions of 1) whether seizures beget further seizures? and 2) whether early treatment would improve long-term prognosis? [10]. Do our AEDs merely suppress the electrical and chemical “discharges” of Todd and Jackson, or do they, as implied by Gowers, “arrest” the evolution or propensity to further seizure discharges? These important and longstanding issues in the management of epilepsy syndromes still require clarification today. It seems possible that there are competing processes in the brain in between seizures which facilitate either relapse or remission of epilepsy and about which we have little understanding.

Outside the field of epilepsy, my interest in folate and AEDs, which was my academic point of entry into epileptology, also took me into much wider fields of neurology and psychiatry. Throughout my career, I have had an abiding interest in the neuropsychiatry of folate and vitamin B12 deficiency, their overlapping clinical syndromes, and their intimate metabolic relationships. With many collaborators at the MRC Neuropsychiatry Unit, Yale, Northwick Park Hospital and King's, this journey has proceeded through homocysteine, S-adenosylmethionine, methylation, and monoamines to peripheral neuropathy and subacute combined degeneration and especially mood/depression, motivation, cognitive function, and dementia/Alzheimer's disease [11,12].

3. Local, regional, national, and international initiatives

As my clinical and academic career evolved in the 1970s, I became increasingly aware of the scale of the problems of epilepsy locally, nationally, and internationally. This included the psychological and social dimension; the hidden, neglected, and stigmatized nature of the disorder; the lack of resources for services, research, and teaching; the low public visibility of both the disorder and the epilepsy movement; and the consequent lack of political action.

In the mid-1980s, I set up the first National Health Service regional neurological Epilepsy Clinic in the country, based at King's College Hospital and serving the south east region from south London to the coast. In collaboration with several colleagues at the Maudsley and King's College Hospitals with an interest in epilepsy from different clinical backgrounds, I led the first multidisciplinary clinical Centre for Epilepsy providing a comprehensive service to children and adults of all ages based at King's since 1994. With the same colleagues and with local and national political support, we also launched in 1994 the world's first university-based academic Institute of Epileptology for research and teaching under the umbrella of King's College, University of London [13], which I directed until 2000. With the help of wonderful volunteers, especially Jane Sykes, our Trust Fund Secretary in Halifax, Yorkshire, we set up a new charity, the Fund for Epilepsy, which I chaired for a decade, to support the Institute and to promote greater public awareness of epilepsy and also greater collaboration within the epilepsy movement in the UK. By the time the Fund for Epilepsy merged with the Epilepsy Research Foundation, a UK-wide research charity, to form Epilepsy Research UK in 2005, it had raised 5 million pounds for the Institute.

As President of the British Chapter of the International League against Epilepsy (ILAE) in the mid-1990s, I led a consortium of all the UK epilepsy charities, supported by the All Party Parliamentary Group on Epilepsy, in a bid to the Millennium Commission to establish a National Centre for Epilepsy. The application did not succeed, but it did lead to unprecedented collaboration between the various epilepsy charities.

By 1993, I had been elected President of ILAE after 4 years of international experience as a Vice-President, which had sensitized me to global aspects of epileptology (Fig. 1). The ILAE and the International Bureau for Epilepsy (IBE) are among many global NGOs affiliated to WHO. Influenced by my political and advocacy experience with the King's Centre, Institute and Charity in the UK, especially the political support I had received from the then Minister of Health, John Bowis, who later became a member of the European Parliament, it occurred to me that a partnership between the ILAE (professional), the IBE (patients/public), and the WHO (political) could be a very powerful one for addressing the needs of the millions of people with this universal but misunderstood and neglected disorder, especially in developing countries where the treatment gap varied between 60 and 98%. I was naturally delighted that the leadership of IBE and WHO endorsed this concept. Following a conference on “Epilepsy in developing countries” in Geneva in June 1996 [14], the ILAE/IBE/WHO Global Campaign against Epilepsy “Out of the Shadows” was launched in Geneva and at the Dublin International Congress in the summer of 1997. With a program of global, regional, and national initiatives, the strategic aims of the Campaign were 1) to raise public and political awareness and understanding of epilepsy (phase 1) and 2) demonstration projects in developing countries, notably China, to encourage departments of health to promote the needs, treatment, services, and care of people with epilepsy nationally [15]. By the time of the launch of the second phase of the Campaign in Geneva in February 2001, the WHO had raised the status of the Campaign to its highest level [16]. A speech by the then Director General of WHO, Dr. Gro Harlem Brundtland, was a milestone in the social history of epilepsy. The Campaign has since been gathering momentum around the world, and in May 2015, the General Assembly of the WHO unanimously approved Resolution EB136/SR/14 which urges all member states to develop national healthcare plans for epilepsy management, particularly in low and middle income countries, thus boosting the final objective of the Global Campaign [17].

4. Historical perspectives

Although trained at the Institute of Neurology in London at a time when neurologists had little interest in psychiatry, I was privileged to

work in a neurological department linked both to the Institute of Psychiatry and a medical school. This stimulated a continuing interest in the relationship between neurology and psychiatry and their historical evolution, especially in the 19th century when they diverged and the latter half of the 20th century when they began to converge again [18,19]. I was a founding council member of the British Neuropsychiatry Association in 1987 and more recently initiated a UK Forum for the History of Neurology and Psychiatry [20]. When I worked with the WHO on behalf of ILAE and the Global Campaign, some of my neurological colleagues were irritated that epilepsy and several other, but not all, neurological diseases were administered within the division of Mental Health [21]. This did not unduly trouble me as epilepsy can be viewed as a bridge between neurology and psychiatry, certainly requiring expertise from both disciplines or from a growing breed of neuropsychiatrists.

I have developed a special interest in Robert Bentley Todd (1809–1860), whose statue stands outside King's College Hospital. Apart from founding the hospital and "Todd's Paralysis", I and my colleagues knew very little about him. I have since learned that this Irish-trained physician and professor of physiology and morbid anatomy at King's College was a pioneer in neurology and epilepsy of which "Todd's Paralysis" was a minor part. In particular, he was the first to develop electrical theories of brain function and "discharges" in epilepsy, influenced by the new electromagnetic concepts of his contemporary in London, Michael Faraday. This he did a generation ahead of Hughlings Jackson, whose own more famous "discharges" were actually chemical in nature as this philosopher physician knew no physics [22].

In 1987, I met James Kinnier Wilson, an assyriologist at Cambridge University, at a symposium at King's to honor his father, S.A. Kinnier Wilson, the distinguished Queen Square and King's neurologist whose name is associated with Wilson's disease (Fig. 2). James drew my attention to a Babylonian medical text in cuneiform script in the British Museum, which is the oldest account of epilepsy, originating in the first half of the second millennium BC. In the last 25 years since our publication of the epilepsy tablet in 1990 [23], I have collaborated with James in studying Babylonian texts on stroke, facial palsy, obsessive compulsive disorder, psychopathic behavior, depression, and anxiety [24]. Although the Babylonians had no knowledge of brain or psychological function, their remarkably accurate and detailed observations are the first clinical foundations of our modern fields of so-called neurology and psychiatry, words and concepts that would have been unknown to them.

It seems that epilepsy is as old as any medical condition known to mankind [25]. The Babylonian view of a supernatural disorder associated with evil spirits, demons, or gods has prevailed for most of the last 4000 years. Although, a millennium later, the Greek Hippocratic school first suggested that epilepsy is a brain disorder associated with an imbalance of humors, it was not until the 17th century AD that such biological ideas began to take root in Europe. As the disciplines of neurology and psychiatry evolved and diverged in the 19th and early 20th centuries, the place of epilepsy within the two disciplines remained controversial, notwithstanding the electrochemical observations of Todd, Jackson, and Berger. It is sobering to recall that not until the 1960s did international classifications of disease finally include epilepsy as a neurological disorder [26].

Fig. 1. With my wife, Angela, at commencement of my presidency of ILAE, Oslo, July 1993.

Fig. 2. With James Kinnier Wilson, assyriologist, Cambridge University, UK, August 2015.

5. Reflections on the future

Any reflections on the long history of epilepsy and one's own relatively brief career, albeit 50 years, inevitably lead to reflections on the future. Anyone confronting at least 4000 years of epilepsy is bound to be struck by the slow pace of progress. The supernatural views of the Babylonian and later civilizations are still echoed today in some parts of the world. Stigmatization and discrimination are still widespread. There is no doubt that the pace of progress is accelerating but not so fast as many imagine with their claims of breakthroughs now or just around the corner. The greatest barrier to biological progress is the incredible complexity of the brain of which we have increasing but still limited knowledge. Some have great faith in genetics and molecular biology, but genetics and epigenetics, as applied to brain development and disease, including epilepsy, sometimes seem as complex as the brain itself. I have not seen much clinical progress except in some rare syndromes influenced by a single or relatively few genes.

The proliferation of new drugs for epilepsy in the last 25 years does not seem to me to be a great advance as I have yet to see a significant improvement in prognosis, except in some individual patients. I was surprised how effective our older drugs were when we studied newly diagnosed patients. It has been hard to show that the newer drugs are overall any more effective, although some seem to be less toxic, which is modest progress. On the other hand, monitoring of individual drugs has been abandoned, and as a result, reductions in polytherapy with its attendant toxicity have been reversed.

Furthermore, we still do not know how the drugs, old or new, work. They have originated from serendipity, screening, or a "me-too" approach. They probably interfere with multiple neurochemical pathways, but which ones are important? The nearest successful rational approach to AED development is vigabatrin, a derivative of GABA and, so we are told, a specific irreversible suicide inhibitor of GABA-aminotransferase, which therefore enhances GABA-mediated inhibition. Despite its proven efficacy, the demise of vigabatrin due to unforeseen toxicity illustrates the complexity of the challenges ahead, including genetic predisposition either to a more efficacious outcome or to undesirable toxicity for any individual AED.

Nor do we know whether the drugs merely suppress seizure discharges or perhaps in some cases "arrest" (Gowers) a relapsing tendency

towards a more chronic and therefore drug-resistant disorder. Are there multiple epilepsies with multiple physical and metabolic causes, or is there a common biological thread predisposing to synchronized electromagnetic discharges in complex and dynamic nervous systems? [27,28]. We need to focus more on what is going on in the brain between seizures, including the biological impact and consequences of the seizures themselves. One key to progress would be an understanding of the build up of "tension" culminating, sometimes under provocation, in discharge, before a fresh accumulation of energy results in another periodic discharge. Magneto and electroencephalography, functional imaging, molecular genetics, neurochemistry, and other disciplines will all have a role to play, but the ultimate key might even be detected outside the nervous system in the study of synchronization in nature. Epilepsy is unique in that all mammalian brains are vulnerable to seizures, although within each species, some are more vulnerable than others, perhaps for genetic or other reasons. The clinical and experimental study of epilepsy is rewarding not only because it opens a window on brain function (Penfield) but also because it is a bridge between neurology and psychiatry, illuminating other neuropsychiatric disorders [18].

Epilepsy is almost universally distributed around the world with no age, racial, geographical, or social boundaries. One of the greatest advances during my career is that current knowledge of diagnosis, treatment and care in all its aspects, including neurosurgery, psychology, and sociology, is being applied more effectively to vastly increased numbers of previously neglected patients of all ages as a result of improved services, education, and public and political awareness. This is certainly true in economically advanced countries, such as my own. Hopefully, progress is beginning to be made in developing countries, but as the recent 2015 WHO Resolution EB136/SR/14 makes clear, there is still a long way to go.

Acknowledgments

I have been privileged to collaborate with numerous excellent colleagues, too many to acknowledge here. A few deserve special mention. In the field of epilepsy, I am grateful to Professors David Chadwick, Simon Shorvon, and Michael Trimble, my earliest research assistants and long-term collaborators. Malcolm Laundy, Louis Vydelingum, and Teodoro Bottiglieri provided invaluable technical and neurochemical assistance over two decades. For psychiatric collaboration, I am indebted to Brian Toone and Michael Carney (RIP). I thank the Trustees of the Fund for Epilepsy and many international colleagues within the ILAE, IBE, and WHO, especially Executive Board members of ILAE and IBE. Finally, I am grateful to numerous patients with epilepsy from whom I learned the most.

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