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Reflections on a Career in Epilepsy

A career in epilepsy

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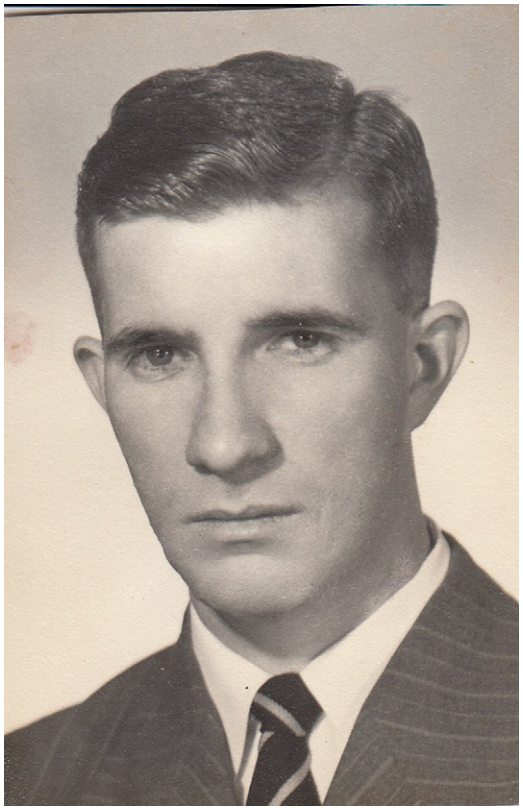
Looking back, I suspect my career, both in regards to epilepsy and overall, has consisted mainly of semi-unthinking responses to the professional circumstances in which I have found myself. Possibly something similar would apply to many a medical career.

Nearly all my life has been spent in the sub-tropical city of Brisbane, situated close to the coast about halfway down Australia's eastern seaboard. Brisbane began in 1824 as a convict settlement and its early development lagged behind that of places in Australia where there was free settlement from the outset. Its first university, the University of Queensland, was established in 1909 and its medical course had existed for only 18 years when I graduated at the end of 1955. Almost all of the medical teaching then depended on experienced practising clinicians, many holding part-time University appointments. Little research went on, except at the Queensland Institute of Medical Research where a major emphasis on investigating tropical medicine problems continued after tropical disease had largely been eradicated from the southern Queensland region around Brisbane.



In 1954 the University of Queensland imported John Tyrer from Sydney as its first full-time Professor of Medicine. He recognised that a heightened research attitude was needed in the academically relatively immature Queensland medical course that was preoccupied with producing clinically omni-competent graduates to thus establish its standing in the eyes of its more senior southern counterparts. Tyrer recruited physicians from outside Queensland with records of research achievement. In 1956 a neurologist, John Sutherland, arrived. He held a research MD from the University of Glasgow, based on laboratory studies into multiple sclerosis, and had carried out a subsequent major investigation into the epidemiology of that disease in northern Scotland and the adjacent islands. I was then working as a first-year resident medical officer at the University's main teaching hospital, the Royal Brisbane Hospital, and was allocated to look after Sutherland's inpatients. He needed a source of local community general knowledge, and an interpreter for his Scottish accent and semi-illegible calligraphy, while I had a grandfather who came from Ayrshire. This combination resulted in John Sutherland taking me under his wing. He later coached me for the examination for Membership of the Royal Australasian College of Physicians, which in those days qualified one for registration in Queensland as a specialist physician. I gained the Membership in 1959, with 18 months remaining before my time on the full-time Royal Brisbane Hospital staff would expire. As the Hospital's second full-time staff physician, I was released from much of the out-of-hours clinical care of patients, and had time for research. Patients with Parkinson's disease were drawn to Royal Brisbane Hospital because the neurosurgeon Kenneth Jamieson was doing some of the earliest chemopallidectomies in Australia. I had read of changes in the dorsal vagal nucleus in the brains of Parkinsonian patients and wondered if there might be disturbed alimentary tract function in the disease. I investigated that possibility, mainly in relation to gastric acid secretory capacity, studied the histopathology of the dorsal vagal nucleus and the adjacent nucleus ambiguus and hypoglossal nucleus, and tried to assess the possible roles of encephalitis lethargica and Australian X disease (Murray Valley encephalitis), both of which had occurred in Australia in the 1917–1920 period, in the later local appearance of Parkinsonism.

A research MD resulted in early 1962, and I was appointed Junior Neurologist to the Hospital, where I remain a member of the staff of the Department of Neurology, now as Honorary Consultant. My original senior was John Sutherland, who had left the University and who took me into private consulting neurological practice with him in the city. I also had a part time Research Fellowship in University of Queensland's Department of Medicine. There then were only three neurologists practising in Brisbane, and any subspecialisation within

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neurology was impracticable. In southern eyes, Queensland then was something of a medical backwater.

In that pre-levodopa era, there seemed little prospect of taking the anatomical pathology work on Parkinson's disease further and I began studying the quantitative microscopic cytochemistry of oxidative enzymes in neurons of the vestibular nuclear complex in the brainstem. This work ultimately yielded a Ph.D. but also led to my quite unplanned involvement in matters concerning epilepsy.

My chemist colleague, Wayne Hooper, and I had used a spectrophotometer to study tetrazolium salt reduction for the oxidative enzyme cytochemistry. The Australian medical director of the pharmaceutical firm Parke Davis, while talking with John Sutherland, asked me what I had been doing. Mention of 'spectrophotometer' produced sudden interest, and I was asked if we could measure blood phenytoin concentrations. I knew Wayne Hooper would greatly prefer that to looking down a microscope. Just as the assay was ready for use an Australasian outbreak of clinically recognisable phenytoin intoxication occurred [1], symptoms nearly always appearing within days of patients taking phenytoin capsules from a new container of the drug. The assay confirmed the diagnosis, blood phenytoin levels consistently exceeding 20 mg/L, the upper limit of drug concentration that most patients tolerated. It took about three years to reasonably fully understand what had happened. During World War II the excipient in the market leader's phenytoin capsules in Australia had been changed from lactose to calcium sulphate, because of supply problems. Both were approved British Pharmacopoeia excipients. In 1967 the excipient was changed back to lactose. When the capsules with this excipient reached pharmacies the intoxication outbreak began. Studies in individual patients showed that about 25% of the phenytoin in the calcium sulphate-containing capsules would not absorb during passage through the alimentary tract. A 25% difference in absorbed drug dose seemed insufficient to explain the size of the blood phenytoin concentration increase when the lactose-containing preparation was substituted [2], until we showed that phenytoin clearance in humans followed Michaelis–Menten rather than linear elimination kinetics [3] and that the average adult's capacity to eliminate the drug was already half saturated at sub-therapeutic blood phenytoin concentrations.

To achieve an understanding of circulating drug concentrations I had to acquire some knowledge of pharmacokinetics. I am sure that topic was never covered, or even mentioned, in my undergraduate medical course. All I can remember about my pharmacology education is that the girl who has tolerated my existence for almost 2/3rd of a century had spent several Saturday afternoons testing my capacity to memorise a long series of drug doses.

Having more or less sorted out one peculiar situation concerning an antiepileptic drug, I suspect my involvement with epilepsy may have ended had it not been that, following the epidemic of phenytoin overdosage, unaffected patients began to appear, professing delight that, after many years of uncontrolled seizures despite faithfully taking phenytoin, they had become seizure free without any change in their nominal drug dosage. Obviously for years they had been inadequately dosed when taking the conventional number of dosage units of the old calcium sulphate containing preparation, as measurement of circulating phenytoin concentrations showed. Thus therapy with at least one antiepileptic drug could be made appreciably more effective if its dosage was guided by circulating drug concentration measurement. Would this also be the case for other antiepileptic drugs? This was a matter of immediate practical importance, whose answer might yield important clinical dividends. It also was much more congenial to Wayne Hooper's organic chemistry interests than the rather tedious enzyme cytochemistry measurements were. Our endeavours shifted progressively into antiepileptic drug clinical pharmacology.

I might simply have continued studying correlations between seizure control, adverse effects, and circulating drug concentrations, and perhaps gone into the effects of physiological changes and disease on these correlations had I not by then become associated with a second PhD qualified organic chemist (Ron Dickinson). Increasingly, I found myself involved in questions concerning drug metabolism and mechanisms of drug–drug interactions, and coming to envy the organic chemist's ability to predict reliably the outcome of his chemical manipulations, in contrast to the sometimes unintended outcomes of my therapeutic efforts. In moments of self-delusionary hubris I occasionally thought of working through the clinical pharmacology of all drugs commonly used in neurological therapeutics, beginning with antiepileptic agents and then moving into agents employed for common disorders such as migraine and Parkinsonism. A little work was done on ergotamine and aspirin absorption in migraine, but with the available facilities, staffing and research funding, and the limits of human finitude, the envisaged grand endeavour never got beyond the more common antiepileptic drugs available in the 1990s before I became to an extent diverted by spending some nine years chairing the Australian Drug Evaluation Committee, the local equivalent to the British Committee for the Safety of Medicines and the oversighting body for the United States FDA. By the end of that diversion I was close to emeritus status, when laboratory facilities would no longer be available. By then, the various studies on the antiepileptic drugs had over the years provided a basis for a monograph *Anticonvulsants Therapy-Pharmacological Basis and Practice*, authored by John Tyrer and myself, which appeared in three editions (1974, 1980, 1989) [4].

Without mentioning all the various studies carried out on each individual antiepileptic drug, two or three lines of investigation that were initiated in response to clinical issues may hold a little interest.

The so-called 'therapeutic' or 'target' ranges of plasma antiepileptic drug concentrations appear to have been determined mainly on the basis of clinical impression rather than through any rigorous statistical approach. It therefore seemed worth attempting to correlate plasma concentration of the more commonly used antiepileptic drugs with reliable information on seizure control in various types of seizure disorder in personally managed patients. Unfortunately, the attempt provided little reason for departing from the accepted values for the ranges, except for showing that the rate of seizure control from carbamazepine increased sharply once the plasma drug concentration exceeded 5 mg/L. Correlating control with the sum of the simultaneous plasma concentrations of the drug and its biologically active metabolite carbamazepine-10,11-epoxide, or with the concentration of the metabolite alone, offered no advantage over using concentrations of carbamazepine itself. However the attempt led to the insight that, once a therapeutic range of concentrations of a new antiepileptic drug is first proposed, for both practical and ethical reasons prescribers try to achieve drug concentrations within that range in their patients. Consequently, the opportunity for the unrestrained seeking of threshold beneficial and toxic concentrations of the drug in larger populations soon disappears, and the initially proposed values for the range become enshrined.

In the earlier years after valproate came into frequent use, there were reports of serious and sometimes fatal liver failure associated with intake of the drug, with some 10 instances in Brisbane. We obtained blood and urine on a number of occasions during the toxicity from four of these. At that time the valproate metabolite 4-en-valproate was thought responsible for the liver damage, because a structurally analogous metabolite of hypoglycin A produced histologically similar liver damage after children in the West Indies ate unripened ackee fruit. However, during the toxicity in the local cases, the circulating 4-en-valproate to valproate concentration ratios were not higher than in those without liver toxicity. Instead, there was impairment of various stages of valproate branched chain fatty acid β-oxidation. We therefore studied quantitative aspects of valproate's β-oxidation pathway in healthy patients to obtain norming values, aiming to identify those at danger of hepatotoxicity by measuring