Title: 50 years of paediatric neurology in Australasia

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Prior to the eighteenth century, the concept of childhood as we see it today did not exist, and children were only infrequently the subject of scientific or medical study (1). Paediatrics developed as a distinct field of medicine in the late 19th century, with subsequent gradual delineation of the fields of neuropathology, neurology and psychiatry. Bernard Sachs wrote the first textbook of paediatric neurology in 1895, and Frank Ford produced a monumental text on the subject in 1937, a full 25 years before child neurology became a discrete subspecialty (2). The first child neurology journal in English was established by Ronald MacKeith in the UK in the 1960s. The Society of Child Neurology was founded in the USA in 1972 and the International Child Neurology Association in 1973.

In Australasia, child neurology began to be recognised as a legitimate subspecialty of paediatrics in the late 1960s. Many of this generation trained in the US. Dr David B. Clark, who died in 1992, had a profound effect on the development of child neurology in Australia. Initially trained as a veterinarian, he then completed medical studies and a PhD in neuro-anatomy. A master clinician, having studied with Douglas Buchanan in Chicago and Frank Ford in Baltimore, he trained a generation of paediatric neurologists at Johns Hopkins and the University of Kentucky (3). Ian Hopkins was the first Australian to train with Clark; Grahame Wise, Robert Ouvrier, Peter Procopis and Lloyd Shield followed. Hopkins returned to set up a unit at the Royal Children's Hospital in Melbourne, and Wise did the same at the Prince of Wales Hospital in Sydney (Figure 1).

Over the next decade a second wave of child neurologists commenced practice, but their numbers remained small until the early 1980s. In 1984, eleven child neurologists met in Melbourne and decided to meet annually under the name of the Child Neurology Study Group (CNSG). This was the beginning of the long pathway to the organisation now known as the Australian and New Zealand Child Neurology Society (ANZCNS), which was legally incorporated in 2010. At the time of incorporation, ANZCNS had 60 members; this number has risen to its current 105 members from Australia, New Zealand and internationally.

The evolution of child neurology over 50 years

During the 50 years of child neurology in Australia and New Zealand, there have been very significant technical changes which have revolutionised our ability to characterise and treat neurological conditions in children, and which have affected all aspects of neurological investigation and management.

Had there been a specifically trained child neurologist in Australia in 1965, that person would almost certainly have been male. He would have had reference to only one contemporary child neurology textbook, and only one English-language child neurology journal (Developmental Medicine and Child Neurology, in print from 1958). The focus of child neurology diagnosis and treatment at that time would have been very different to the

present time. For instance, in the fifth edition of Frank Ford's Diseases of the Nervous System in Infancy Childhood and Adolescence, published in 1966, there were 24 pages on poliomyelitis, but only 58 - in total - about epilepsy (2). In 1965, a child neurologist had no means of directly visualising the parenchyma of the brain, except by brain biopsy or at autopsy, and no way to record a seizure contemporaneously except by chance observation. Muscle and nerve function could not be assessed except by biopsy and very basic electrophysiological testing. The congenital myopathies were unknown, the leukodystrophies diagnosed only at autopsy, and the major developmental anomalies largely undescribed.

Training in child neurology in the 1960s and 1970s was heavily weighted to clinical history-taking and thorough physical examination, for obvious reasons: the imaging modalities available were extremely limited, both in number and diagnostic capacity. Even the humble domestic torch was used, admittedly with a special adaptor, to diagnose newborn abnormalities including hydranencephaly, subdural collections and large porencephalic cysts (4).

In 1965, a skull or spine X-ray was usually the starting point of investigations, demonstrating abnormalities of the sutures and inner table of the skull, calcification within the brain, erosion of the pituitary fossa and abnormalities of the cranio-cervical junction. Echoencephalography had some value in trauma and in children with rapidly enlarging heads (5). For the nervous system, nuclear medicine revolved around Technetium⁹⁹ scans for tumours, vascular malformations and inflammatory processes such as abscesses. Radioisotope cisternography was undertaken in children with suspected CSF leaks after trauma, injections being made by lumbar puncture or ventricular tap. More invasive and potentially complicated investigations commonly undertaken in this period included carotid and vertebral angiography, myelography, ventriculography and pneumoencephalography. Angiography, by femoral or carotid injection, was the investigation of choice for suspected arteriovenous malformations, aneurysms, tumours and other masses. Deviation of vessels from their natural path, and neovascularization, were the usual markers of an underlying tumour. In the early years, angiography was often performed using catheters and needles designed in house (6). Myelography, by lumbar or cisternal routes using air or contrast media, was often informative, but the patient often paid the price with hospitalisation for several days with fever, back stiffness and pain. Ventriculography via the cranial sutures or fontanelle (at the lateral angle to avoid the sagittal sinus) was used to investigate suspected masses or hydrocephalus.

E. Graeme Robertson, one of the founders of neurology in Australia and the honorary neurologist to the Royal Children's Hospital Melbourne in the pre-child neurology era, was also the world authority on pneumoencephalography (PEG). Little wonder, then, that PEGs were performed in Australian tertiary centres up to the mid-1970s. Air was introduced by lumbar puncture, usually under general anaesthesia, and the patient was then positioned to facilitate the flow of air into the ventricular system and subarachnoid spaces. The X-ray images showed bone and air, but not brain parenchyma; what was happening in the brain was a matter for deduction. The mortality rate of PEG, of approximately 0.2% in adults and children (7) was low, considering the risk of anaesthesia, lumbar puncture in patients who

might have raised intracranial pressure, and the frightening performance, in young children at least, of a slow somersault of the anaesthetized infant or child, strapped in a special chair, to manoeuvre air into the temporal horns of the lateral ventricles (see Figure 2).

All of these procedures were time-consuming, technically demanding and carried significant risks, but none actually showed brain or spine parenchyma. All interpretation was by inference, except for the angiographic imaging of vascular lesions and malformations.

It was not until the mid-late 1970's that early computer assisted tomography (CAT, CT) scanners were installed in adult hospitals in Australia; it took several years for stand-alone children's hospitals to have CT scanners installed. Access to these was initially limited, and the risks of transferring a sick child by road to undergo anaesthesia in an adult environment required careful consideration, but the reward for this effort was visualisation - for the first time - of a murky, grainy facsimile of the brain. With later, more powerful scanners the increasing speed of imaging dramatically reduced the need for anaesthesia or even sedation, and the clinical utility of imaging increased, inroads being made into hitherto difficult-to-diagnose conditions such as cerebral dysgenesis, demyelinating and degenerative diseases.

These conditions were even better delineated after the advent of magnetic resonance imaging (MRI) which became generally available in the mid-1990s, although (arguably) the introduction of MRI was not the quantum leap forward presented by CT.

Epilepsy and electroencephalography (EEG)

Had there been a specifically trained child neurologist in Australia in 1965, that person would have had limited access to treatments for epilepsy and technologies for investigating its aetiologies. In 1965, EEG was an important tool in the assessment of epilepsy, along with a plain skull x-ray, lumbar puncture, air encephalography, ventriculography and cerebral angiography. The work of Hans Berger in the 1930s, and the later work of Lennox and Gibbs, truly revolutionised characterisation of the epilepsies based on their electrical correlates on EEG (8). With the advent of CT imaging there were further advances in understanding the causes of epilepsy.

The ability of the EEG to aid localisation of sites of seizure onset expanded the possibilities for neurosurgical procedures for the treatment of epilepsy, which became much more widely available from the 1950's onwards in London, Montreal and Paris. The finding of an enlarged temporal horn on air encephalography was a well-described marker for hippocampal atrophy at this time, identifying possible surgical candidates.

In 1965, the first internationally accepted classification of the epilepsies had not yet been published. This was published by the International League Against Epilepsy (ILAE, founded in 1909 in Budapest) in 1967. This classification depended greatly on the information available from EEG, from x-ray imaging (where abnormalities associated with skull bony abnormality, intracranial calcification or with vascular abnormality could be characterised) and from early intra-operative neurophysiological studies. The classification of seizures as 'partial' and 'generalised' was introduced at this time. There have since been several further revisions of this original classification, as new technologies have shed further light on epilepsy

aetiologies including structural, genetic, metabolic and immune aetiologies, but the dichotomy 'partial' (now 'focal') and 'generalised' remain.

In 1965, treatment options for epilepsy were limited. Anticonvulsant medication choices were limited to bromide (1857), phenobarbital (1912), phenytoin (1938) and primidone (1954). Ethosuximide was first licenced for use in 1958, while carbamazepine and sodium valproate were first licenced in Europe in 1965 and 1967 respectively (9). Benzodiazepines - initially diazepam - were still in development. Anticonvulsant drug development exploded from the late 1980's onwards, with a large number of drugs licenced thereafter, many with improved tolerability when compared to their older counterparts.

Epilepsy surgery was, in the 1960s, a known treatment for certain forms of focal epilepsy aetiologies, having been first described by Viktor Horsley in 1886 (10). This publication was followed by a wave of subsequent publications in the 1890s, but there was a decline in interest after the introduction of phenobarbitone in 1912. The second wave of interest in this surgery occurred in the 1940's, with the work of Penfield and colleagues in Montreal, but it remained a potential treatment for epilepsy only in a few centres with the necessary expertise. The ketogenic diet was a known therapy for epilepsy in 1965, having been described in the medical literature as early as 1911 (11). By the 1920s techniques for induction and maintenance of the diet were well established in US centres, but it remained available only in specialized centres. Vagal nerve stimulator (VNS) therapy for epilepsy would not be developed until the late 1980's. In 1965, therapies such as epilepsy surgery, the ketogenic diet and VNS therapy would not have been available for Australasian children with epilepsy. These treatments are now offered in many tertiary centres in Australasia.

Neuromuscular conditions

In 1965 there were no defined genetic myopathies, the inherited neuropathies were unclassified, there were very few recognised muscular dystrophies and the genes for Duchenne muscular dystrophy, spinal muscular atrophy, all forms of Charcot-Marie-Tooth disease and myotonic dystrophy were unknown. Neurophysiologic testing was in its infancy in the USA, and the treatment of neuromuscular disorders was purely symptomatic.

Within 50 years, the genes for more than 250 paediatric neuromuscular disorders have been defined, and our understanding of the pathophysiologic basis and course has been much advanced. In the last five years the 'new genetics' – linkage studies, next generation sequencing and now whole exome and genome sequencing- have resulted in a massive increase in our understanding of the causation of many of the conditions we have recognised for decades. Australians have made a very strong contribution to paediatric neuromuscular disorders, not only with gene discovery but also with well-designed clinical research defining novel entities and, more recently, evaluating possible new therapies. Australian centres are now involved in trials of potential new therapies for Duchenne muscular dystrophy, spinal muscular atrophy, Charcot-Marie-Tooth disease, Friedreich ataxia, ataxia telangiectasia and a number of inborn errors of metabolism causing neuromuscular disorders.

Challenges for Australasian child neurology

Until the mid-1990's, the lack of child neurology training positions was a major barrier to the development of the discipline in Australasia. Curriculum requirements for training of child neurologists, along with the issue of supervision of child neurology training, have remained an issue for the subspecialty. A number of training positions have been created in the major centres in the last ten years, but most are funded by private donations or external funding, with most children's hospitals providing minimal or no institutional support for training the next generation of paediatric neurologists. The establishment of the ANZCNS has reflected paediatric neurology's move away from being a minor branch of adult neurology, or a subspecialty within paediatrics, to its current role as a discrete medical speciality.

Ongoing challenges include ever-increasing referral numbers in the face of a small workforce and the demands of balancing low-complexity general paediatric neurology with the increasingly high complexity of very sub-specialised areas such as epilepsy surgery, neuroimmunology, stroke and neurogenetics.

Fifty years ago percussion hammers (plessors) were valuable possessions, bamboo-handled and typically bent into an arc by the cumulative effect of thousands of applications over years of use. Today, they're typically made from metal or plastic, often left in clinics or on the wards, non-descript and essentially disposable. Like percussion hammers, many things have changed in Australasian paediatric neurology in the last 50 years, but the lynchpins of neurological diagnosis and management have not changed, and probably never will: a thorough clinical history, an age-specific neurological examination and an empathic approach to the child and family. Child neurology has become an established, respected and increasingly complex Australasian paediatric subspecialty with close and important relationships with genetics, metabolic and pathology.

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Figure 1: The Kentucky contingent (left to right): Robert Ouvrier, Peter Procopis, Grahame Wise, Lloyd Shield and Ian Hopkins

Figure 2: An anaesthetised 2 year old child in a pneumoencephalography chair. (From Hagberg et al⁷ with permission).

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