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Historical Records of Australian Science

James Graham McLeod (1932–2022)

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ABSTRACT

James McLeod was an outstanding clinical neuroscientist who achieved Australian and international renown and leadership in two distinct areas of clinical neurology, disorders of peripheral nerve and multiple sclerosis. He introduced and established clinical neurophysiology in Australia, which facilitated the diagnosis and management of neuromuscular disease and multiple sclerosis prior to the advent of magnetic resonance imaging (MRI). His careful and detailed clinical and neurophysiological studies were essential to the discovery in his laboratory of the gene mutation for the commonest hereditary neuropathy Charcot Marie Tooth disease. He and his team were among the first internationally to define a disabling autoimmune neuropathy and collaborate with appropriate hospital departments (immunology and haematology) to introduce effective therapy for it. With Professor Basten (Immunology) he conducted the first clinical trial of immunotherapy for multiple sclerosis (MS) and participated in the first international studies of immune therapies which greatly improved the outlook for patients with this disease. McLeod also made major contributions to the epidemiology of MS. McLeod worked tirelessly not only to improve disease but to support the patients afflicted by these conditions and his students and colleagues working in this endeavour. He was committed to the practice of medicine, education and the improvement of disease outcomes through research. His life of service was extraordinary. McLeod died on 27 June 2022 and the University of Sydney arranged a memorial service in his honour. Jim McLeod was appointed to the first named chair of neurology in Australia, the Bushell Chair in 1978, and in 2025 the University of Sydney established the James McLeod Chair of Neurology in his honour.

Keywords: autonomic neuropathies, electrophysiological studies in neurology, epidemiology of MS, genetic neuropathies, immunotherapy in MS, immunotherapy in neuropathy, inflammatory neuropathies, leadership, multiple sclerosis (MS), peripheral neuropathy.

Family background

Jim McLeod (Fig. 1) was born in Ashfield NSW in 1932 the youngest by several years of four children. His father Reginal McLeod was a builder who came from a long line of family builders with their own successful building company, McLeod Bros. During World War 1, Jim's father trained as an officer in England and fought in France on the Western Front, while his mother Dorothy Shirley (Craig) McLeod also went to England to support the war effort, training as a nurse.

Education

Secondary

Jim started his education at Trinity Grammar School in Summer Hill and later moved to Sydney Grammar in early high school. He excelled at school; in 1948 he became a prefect, a cadet Lieutenant Officer, Captain of the rifle shooting team and was awarded the Wigram Allen Prize for Natural Science. In that same year he was Dux of the school and awarded the Knox Prize for General Proficiency. In 1949 he was awarded the School's Morehead Scholarship to the University of Sydney. Although as a young boy Jim had a great interest

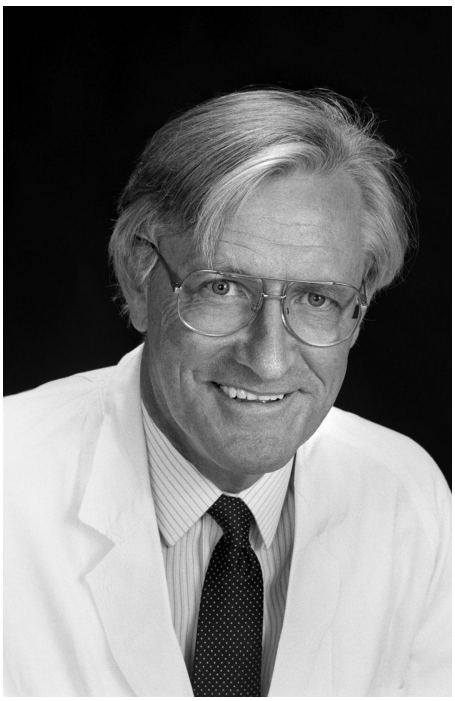

Fig. 1. James McLeod Professor of Neurology, Royal Prince Alfred Hospital 1984 (From Robert McLeod with permission).

in animals and expressed a strong desire to become a veterinary doctor, his father encourage him to take up medicine.

Tertiary

With his Morehead Scholarship Jim enrolled at Sydney University to study medicine. After his fourth year he completed a BSc (Med) degree working with the renowned vision physiologist Professor Peter Bishop, the year after his friend James Lance completed his BSc (Med) and these were Bishop's first two candidates for this degree; both subsequently became professors of neurology, McLeod at Sydney and Lance at the University of New South Wales. McLeod had a distinguished record at the University academically and in the field of sport. Whilst completing his BSc (Med) he met with Professor Frank Cotton who was assessing students for their physical capacity for rowing. Although he had no experience in this sport, results of McLeod's tests suggested he might succeed as an oarsman. Indeed, he won a university blue in rowing (Fig. 2) and in rifle shooting, and he represented his state in the King's Cup. Based on his academic and sporting achievements McLeod was awarded a Rhodes scholarship to Oxford University in 1953, where he worked on the physiology of pain and graduated DPhil(Oxon) in 1956. During his candidature he

Fig. 2. Jim McLeod rowing for Oxford University 1954, 3rd rower from the right (Permission, Robert McLeod with permission).

represented Oxford in the Oxford and Cambridge boat race and in 1954, with three other Australian students in the crew, helped Oxford win the centenary race between these two famous universities. Perhaps it was juggling the demands of intense rowing training and research which led to his life-long work ethic. He was indeed a hard worker and recalled being so immersed in research that he missed watching his friend Roger Bannister break the four-minute mile nearby in 1954.

McLeod returned to Sydney and completed his medical training at Royal Prince Alfred Hospital, where he was appointed Clinical Superintendent in 1963. It was there that he met Robyn Rule, a nurse, and they married in the University of Sydney's St. Paul's College Chapel. He had been sub-warden at the college and the family returned there in 2022 to commemorate his life.

McLeod was awarded two travelling fellowships which enabled him to spend sequential years at the Institute of Neurology Queen Square London in 1964 and at Harvard University in 1965. At the Institute of neurology, he studied clinical neurophysiology with Professor Roger Gilliat and at Harvard (Massachusetts General Hospital) clinical neurology with Professor Derek Denny-Brown.

Academic positions

McLeod was appointed senior lecturer in medicine in 1967 and three years later, associate professor. In 1978 he was appointed Bosch Professor of Medicine at the University of Sydney, a position he held until retirement. In that same demanding year, he was appointed the Bushell Professor of Neurology—the first named chair of Neurology in Australia—and appointed Head of the Department of Neurology at Royal Prince Alfred Hospital and Head of the Department of Medicine at the University. In 1984 he became Head of the Division of Medicine, Royal Prince Alfred Hospital Sydney, and in 1990 Chairman of the Institute of Clinical Neurosciences, Royal Prince Alfred Hospital. He was appointed Director of Clinical Neurosciences, Central Sydney Area Health Service in 1995. In 1997 McLeod was appointed Emeritus Professor at the University of Sydney and Honorary Consultant Neurologist at Royal Prince Alfred Hospital. In 2025 the University of Sydney and Royal Prince Alfred Hospital created a named Chair of Neurology in his honour, the James McLeod Chair.

Major research contributions

At the university and the hospital McLeod worked intensely; there was never an unproductive hour. He did not stop for lunch but sustained himself on an apple combined with a constant flow of instant coffee. He claimed not to have time for lunch, reasoning that the food drained blood from the brain to the stomach and would therefore make the afternoon less productive. He would likewise work long into the evening in his home office—writing, dictating and marking.

Nothwithstanding that a large amount of his time was spent caring for patients, teaching medical students, trainee physicians and researchers in addition to undertaking numerous administrative roles, he published prolifically and became an international authority in two major areas of neurology, diseases of peripheral nerve and multiple sclerosis. He was the author of almost 400 articles including principal publications, invited review articles, contributions to books, shorter articles and published abstracts.

Peripheral neuropathy

The first clinical neurophysiology unit in Australia was established by Dr George Preswick in the early 1960s at Prince Henry Hospital in Sydney. In the late 1960s and early 1970s McLeod established with Dr John Walsh the first dept. of clinical neurophysiology in Australia, at Royal Prince Alfred Hospital. These new techniques that he had learned in London, Oxford and Harvard allowed the definitive diagnosis of common neuropathies such as carpal tunnel syndrome, the differentiation of nerve diseases from those of muscle and definition of the characteristics of treatable neuropathies such as the autoimmune inflammatory neuropathies, for example Guillain Barré Syndrome and chronic varieties of this disorder. When applied to disorders of the brain and spinal cord, before the advent of Magnetic Resonance Imaging (MRI), neurophysiological techniques (Evoked Potentials) also enabled the confirmation of the clinical suspicion of Multiple Sclerosis, again with major therapeutic implications. Neurologists and other physicians from around Australia and New Zealand came to Sydney to learn these valuable techniques.

Genetic neuropathies

As part of his neurophysiological and clinical studies McLeod examined many patients with inherited neuropathies, collecting and constructing careful family histories with detailed clinical and neurophysiological data. Using the valuable data, Garth Nicholson, a protégé of Jim McLeod was able to obtain US MDA funding and later NHMRC funding to establish a DNA research Laboratory, separate from McLeod's peripheral nerve laboratory. There he aimed to search the whole human genome to find the gene mutations causing genetic neuropathies. These neuropathies were classified at the time as hereditary motor and sensory neuropathies (HMSN) types 1 and 2, also known as Charcot Marie Tooth (CMT) neuropathy types 1 and 2, and are the most common human hereditary neuropathies.

To share the gene search Nicholson set up a collaboration with Duke University to search American families. The Duke laboratory found indications of a possible CMT 1 locus near the neurofibromatosis locus they were studying on chromosome 17. Because of the extent of the clinical resources developed by

McLeod, Nicholson was able to make a definite link to a locus on chromosome 17 (Vance and others 1989). This discovery led to the finding of a large DNA duplication in the region containing a myelin gene, PMP22. Nicholson was able to find mutations in the families collected and studied by McLeod (simultaneously with other world laboratories), proving that this was the gene causing CMTA (Valentijn and others 1992). A subsequent finding by Nicholson and McLeod was that loss of function PMP22 mutations caused hereditary liability to pressure palsies (HNPP) (Nicholson and others 1994). This showed that loss of one copy of the PMP22 gene caused this disease. HNPP is an entirely different disease to CMT, and patients have a liability to develop pressure palsies in nerves commonly subject to pressure such as the ulnar nerve at the elbow, the median nerve at the wrist or the common peroneal nerve at the knee. A genetic diagnosis allows prophylactic measures to be taken in these patients. As a result of this research Nicholson later set up a clinical diagnostic DNA blood testing service for hereditary neuropathies. This was Australia's first molecular neurology diagnostic laboratory, situated at Concord Hospital where McLeod was a visiting Professor; it remains the only comprehensive molecular diagnostic laboratory of its kind for neurological disorders in Australia. Garth Nicholson's father was Professor Alexander John Nicholson DSc, a foundation fellow of the Australian Academy of Science and its first secretary, biological sciences.

With Phillip Low, McLeod performed histological and neurophysiological studies on the trembler mouse showing that this animal was an excellent model for Charcot Marie Tooth neuropathy. Later studies in McLeod's laboratory using nerve transplant, demonstrated that the genetic abnormality expressed in the surrounding Schwann cells was responsible for the morphological and electrophysiological abnormalities in this disorder.

McLeod worked closely with Robert Ouvrier on neuropathies of childhood, when Ouvrier was appointed as paediatric neurologist to the Royal Alexandra hospital for children in Camperdown, and later at the Children's Hospital Westmead. Ouvrier spent many hours in McLeod's neuropathy laboratory at the University of Sydney studying nerve biopsies from children with neuropathy. With McLeod and Pollard, he authored the first textbook of Paediatric Neuropathy (Ouvrier and others 1990, 1999). Ouvrier developed an international reputation in Paediatric Neuropathy. He played a key role in establishing and leading the Institute for Neuromuscular Research at the Children's Hospital Westmead Sydney. On the international scene he became President of the International Childhood Neurology Association. In 2013 he was appointed to the inaugural Petre Foundation Professor of Paediatric Neuropathy at the University of Sydney and in 2016 was awarded Companion of the Order of Australia (AC) for services to medicine, particularly the discipline of paediatric neuropathy. Ouvrier was appointed Emeritus Professor of Paediatric Neurology in 2013.

Inflammatory neuropathies

McLeod was among the first researchers internationally to define a group of severely disabling neuropathies which were shown to have an autoimmune basis (Chronic Inflammatory Demyelinating Polyneuropathy-CIDP). Prineas and McLeod, in 1976 (Prineas and McLeod 1976) described a series of 27 patients with a subacute and relapsing neuropathy and electrophysiological and histological features of demyelination (loss of the compact myelin layer normally surrounding medium and large nerve fibres, and responsible for saltatory conduction). These patients were similar except for their clinical course to well-recognised patients with an acute neuropathy known as the Guillain–Barré Syndrome later termed acute inflammatory demyelinating polyradiculoneuropathy (AIDP). The chronic disorder was subsequently termed chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) a term which considers the underlying pathology, which is multifocal, demyelinating and predominantly affects spinal nerve roots, major plexuses and proximal nerve trunks.

With Professors John Prineas, Pamela McCombe and John Pollard he studied the pathology, detailed clinical, neurophysiological and immunological features of these patients (Pollard and others 1986; McCombe and others 1987*a*, 1987*b*). These studies defined major immunopathological features in the inflammatory neuropathies suggesting responsiveness to immunotherapy. McLeod encouraged research into new therapies for these neuropathies and his team collaborating with the departments of Haematology and Immunology at RPAH, introduced plasmapheresis and intravenous immunoglobulin for the first time in Australia for inflammatory neuropathy (CIDP and AIDP) having previously shown the efficacy of the former in an animal model of CIDP (Antony and others 1981; Pollard and others 1983). Plasmapheresis was also shown to have efficacy in another autoimmune antibody mediated disorder Myasthenia Gravis, and these therapies together with immunotherapy introduced a new therapeutic era for patients with immune mediated neuromuscular disease some of whom were previously wheelchair bound.

John Prineas worked with McLeod in Sydney from 1969 until 1975, initially as a Wellcome Fellow and then Senior lecturer in the department of Medicine. In 1975 he accepted an appointment as Professor of Neurology in New Jersey Medical School and the Albert Einstein College of Medicine where he remained until 1998. He then returned to Sydney and continued to work as an honorary Professor of Medicine pursuing his research into MS and supervising postgraduate students. His work on MS was outstanding and in 2009 he was awarded the Charcot prize for his contribution to the understanding of MS pathology and immunopathology and a lifetime of outstanding research into MS. He was the first and only Australian (to date) to be so honoured.

Pamela McCombe became Professor of Medicine at the University of Queensland and is world renowned for her

work in Neuroimmunology focussing on MS and Immune mediated neuropathies.

McLeod's Neuromuscular laboratory was funded essentially continuously by NHMRC from 1983 until 2012

Autonomic neuropathies

McLeod pioneered involvement of the Autonomic Nervous System in neuropathy. With Philip Low and John Walsh, he demonstrated autonomic neuropathy in patients with Diabetic and Alcoholic neuropathies (Low and others 1975*a*, 1975*b*) and with Dr Roger Tuck described autonomic neuropathy in the Guillain Barré Syndrome (Acute Inflammatory Demyelinating Polyneuropathy (AIDP)) and in the experimental model of that disease, Experimental Autoimmune Neuropathy (EAN). They reviewed disorders of the autonomic nervous system in two invited review articles in the leading neurology journal *Annals of Neurology* in 1987 (McLeod and Tuck 1987*a*, 1987*b*). Phillip Low, one of McLeod's earliest research fellows, has for many years been a world authority in disorders of the autonomic nervous system working from his base in the Mayo Clinic Rochester Minnesota. Low, originally a general physician working in Fiji, trained with McLeod in his neuropathy laboratory in Sydney and gained his MD for histological and electrophysiological studies on the Trembler mouse, which proved to be an excellent animal model for Charcot Marie Tooth neuropathy. Low later moved to the Mayo Clinic in Rochester Minnesota and was appointed the Robert D and Patricia Kern Professor of Neurology. His laboratory has been continuously supported by NIH for over thirty years. Low's interest in disorders of the autonomic nervous system, (treatment of autonomic neuropathies and the development of novel autonomic tests and instruments to measure these) began with his early work with McLeod in Sydney in the early 1970s. McLeod encouraged Dr. Judith Spies to follow post-doctoral training at the Mayo Clinic with Professor Low and the renowned neuropathy group there and on return to Australia develop an autonomic laboratory which is the leading Australian laboratory for the management and diagnosis of autonomic neuropathy. Spies has an international reputation in the field of neuropathy and is the leading Australian expert in the field.

Multiple sclerosis

Clinical aspects: diagnosis and therapy

With his expertise in clinical neurology and neurophysiology, McLeod initially focused his interest in Multiple Sclerosis (MS) on Evoked Potential studies, particularly visual evoked responses (VERs) in optic neuritis (ON). In collaboration with John Walsh, Raymond Garrick, Mariese Hely, Philip McManus and Jane Frith over a thirteen-year period, McLeod observed prospectively, clinical and VER changes of acute ON to better define the natural history and to ascertain the risks of subsequently developing MS after ON. They found that the yield of VER abnormalities was increased using central field in addition to wide field stimulation, VER abnormalities could return to normal and VER was more sensitive than ophthalmological examination in identifying past ON in asymptomatic eyes (Hely and others 1986). After thirteen years follow-up half the patients had developed MS. The importance of VERs for diagnosis of MS has recently been reemphasised in the 2025 McDonald criteria.

In the mid-1970s an important collaboration formed between McLeod and Anthony (Tony) Basten (Professor of Immunology, University of Sydney). With their doctoral student, Graeme Stewart, they published a work looking at aetiology of MS from the immunological, viral and genetic perspectives. Stewart went on to be actively involved in the International Multiple Sclerosis Genetics Consortium (IMSGC) as well as founding and leading the Department of Clinical Immunology and Allergy at Westmead Hospital. Basten continued developing and refining techniques for the manufacture of Transfer Factor (TF). TF is a cell-free, leucocyte extract which had been shown to transfer delayed type hypersensitivity (DTH) from a skin-test positive donor to a skin test negative recipient. The first report of TF therapy being used for MS appeared in 1973 by a Danish group. McLeod and Basten went on to design a two-year, prospective, double-blind, controlled pilot study of TF from close household contacts (many of whom were hyperimmune to herpes viruses) to assess the efficacy of TF as an immunopotentiating medication for MS. Three years later McLeod published the result of this landmark clinical trial (Basten and others 1980), showing TF significantly slowed MS disease progression. MS might be a treatable disease. There followed a Phase 3 study of TF and interferon alpha, designed and lead by McLeod for the Australian trial of transfer factor and Interferon as treatment for multiple sclerosis (AUSTIMS) Research Group. It was a multicentre Australian study with neurologists from other states joining the collaboration. Unfortunately, neither treatment significantly slowed disease progression over a three-year period (AUSTIMS Research Group 1989). Four years later it was a group from the US and Canada with the Betaseron (Betaferon) study of interferon-beta that showed significant reduction in MRI activity sufficient to become the first treatment for multiple sclerosis. With advocacy by McLeod, the neurological community, and MS patient advocates, Betaferon was made available to Australian patients on the Pharmaceutical Benefits Scheme in 1996.

With the advent of a treatment for MS, there was an explosion of interest in finding new and better therapies. McLeod kept Australia at the forefront of this research by being involved in the PRISMS[1]/SPECTRIMS Study Groups and forging international collaborations with many

[1]McLeod was one of approximately 100 members of PRISMS, the Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis group contributed to a report that was communicated by George C. Ebers as lead author (Ebers 1998).

including Don Paty in Vancouver, Ian McDonald at Queens Square, London and George Ebers, Oxford University. When McLeod submitted his work for the Doctor of Science degree one international collaborator commented that, in his reviewing life, he had not come across a body of work led by one person which had covered such a huge area of endeavour.

Coupled with McLeod's interest in peripheral neuropathy as well as central demyelination, for decades the Mc Leod Neuroimmunology laboratory had explored the animal models of demyelinating disease in both the peripheral nervous system, experimental autoimmune neuritis (EAN) and in the central nervous system, experimental autoimmune encephalomyelitis (EAE). Both models in early studies had been shown to be transferable by T cells activated to myelin antigens or by inoculation with these antigens but in these models very little demyelination (the hallmark of MS) was evident. However widespread demyelination was seen in models in which both activated T cells and antimyelin antibody participated. Westland and McLeod (Westland and others 1999) showed that activated T cells could open the blood brain barrier allowing a circulating demyelinating antibody (anti MOG antibody) access to the CNS causing widespread demyelination typical of MS. These studies, along with the results of a collaborative monoclonal antibody trial against CD4 positive T cells, contributed to the body of evidence that helped change the focus of MS research to look more closely at the role of B cells in MS pathogenesis, with the subsequent development of anti-CD 20 monoclonal antibodies (directed against B cells) as highly efficacious therapy.

Patient management

In 1994, recognising the need for early diagnosis and management of people with MS, McLeod, with the MS society of NSW, was instrumental in establishing the first MS clinic in Australia at Royal Prince Alfred Hospital, Sydney. Patients from throughout NSW had the opportunity of specialist consultation at no cost. Neurologists with special interest in MS provided diagnosis, management and up to date information. Later immunotherapy nurses joined the clinic with a longer-term view of having a multidisciplinary team. Patients at the clinic had the opportunity of being involved in international multicentre treatment trials. Under McLeod's stewardship with his international collaborators a clinical trial programme developed which subsequently became the MS Clinical Trials Unit. Involvement in clinical trial networks led to early release of new medications to our patients through Patient Familiarisation Programs and it provided expert training for neurologists with an interest in demyelinating disease.

Another area McLeod recognised was of particular importance for people with MS was research into the risks of pregnancy. In the past some women with MS had been advised not to become pregnant as earlier studies had noted an increased relapse rate especially in the post-partum period. In 1988 Frith and McLeod (1988) in a retrospective study found a relative protective effect of pregnancy followed by an increased risk of relapse in the postpartum. This has subsequently been investigated extensively and advice about motherhood continues to be an important topic of discussion and management at the MS Clinic.

Epidemiology

The change in prevalence between 1961 and 1996 and the latitude relationship studies. It was recognised in the 1960s that Australia was perfectly placed for epidemiological studies of MS, covering 33 degrees of Southern latitude and having a universal health care system. Following earlier work by John Sutherland, John Tyrer and Mervyn Eadie, McLeod designed and facilitated a magnum opus of epidemiological research with thirteen papers published in collaboration with Simon Hammond about Prevalence Day 30/6/81 (Hammond and others 1988*a*) and subsequently Michael Barnett regarding Prevalence Day 30/6/1996 (Barnett and others 2003). Barnett, with mentorship from McLeod and other leaders in the field, is now the inaugural recipient of the McLeod Chair of Neurology, University of Sydney.

The epidemiological studies identified a significant increase in MS incidence, prevalence and mortality with increasing south latitude in Australia (Hammond and others 1987). Although genetic susceptibility to MS was clearly an important determinant in the risk of acquisition of MS in Australia, that factor showed no variation with latitude. Moreover, the distribution of the countries of origin of the populace in Australia in 1981 showed that those people with a potentially higher risk of MS acquisition, especially those of Scottish origin, were more numerous in the lower risk more northerly parts of Australia. Accordingly, the latitude gradient was felt to be attributable to unidentified environmental factors including hours of exposure to sunlight, vitamin D levels or possible virus or other infections (Hammond and others 1988*a*).

No full-blooded indigenous Australians with MS were detected in either the 1961 or 1981 surveys although the potential genetic risk of acquiring MS, as determined by the incidence of HLA-DR2 in their population, was essentially the same as in the non-indigenous population.

Over the thirty-five-year period between 1961 and 1996 there was a significant increase in the incidence and prevalence of MS, an increase in the age at onset of the disease and increased female preponderance (Barnett and others 2003). The principal reasons for the observed change in disease frequency between the 1961 and 1981 surveys were declining mortality rates between the 1950–9 and the 1971–80 decades, recognition of less disabled patients in the 1981 surveys, and an increased representation of incidence cases in the overseas born population in 1981.

Clinical aspects. The clinical features of the disease were similar in all the surveyed areas of Australia with the exception of Queensland where there was a greater tendency for males to develop a progressive disease course and to have greater disability (Hammond and others 1988*b*), which was felt to be due possibly to acceleration of the disease process by exposure to the hotter Queensland climate and perhaps the migration of MS patients to Queensland from the cooler southern regions of the continent.

The frequency of MS was greater in people of higher educational level and socioeconomic status. There was a greater level of divorce and separation in the MS population, and a lower rate of participation in the workforce. There was a worse prognosis for the development of disability in association with: older age at onset; progressive disease; onset symptoms that were multiple or primarily affected the pyramidal or cerebellar pathways; and a short interval between disease onset and the first relapse (Hammond and others 2000*a*).

In the era before the advent of effective disease modifying therapies, the median survival from disease onset was forty two years which represented a 10% reduction in life span for MS patients compared to the general Australian population at the time. The expected disease duration to reach a disability score of 6 on the Kurtzke scale (requiring walking aids) was twenty seven years.

This epidemiological data provided extremely important prognostic information for people with MS, and allowed government and non-government organisations, particularly MS Australia to tailor provision of future health care services for these people.

Migration studies. The initial study of MS in migrants from the United Kingdom and Ireland (UKI) in all the studied areas of the 1981 surveys showed considerably lower prevalence rates across mainland Australia than in concurrent studies in the UKI whilst the prevalence rate in southern Tasmania approached that seen in those concurrent studies. Although there was a significant latitude gradient in the UKI-born MS population as in the Australian-born MS population, that finding was very largely due to the high MS rate of the UKI-born MS population in Tasmania. Analyses of the MS rates in the UKI-born MS population according to their age at immigration (AAI), and in particular in relation to migration before or after the age of 15, found no significant influence of the AAI on the risk of developing MS, thus suggesting that it likely spanned a much wider age range than childhood or early adult life (Hammond and others 2000*b*). These results were significant in the lack of concordance with previous studies by John Kurtzke which influenced the proposed aetiology of MS.

Three subsequent reassessment studies of MS in UKI migrants to Australia were undertaken in collaboration with John Kurtzke to evaluate further the question of the influence of AAI in subsets of the UKI migrant population. The first and third analyses did provide some evidence that migration before the age of fifteen provided a further relative reduction in the risk of acquiring MS in addition to the overall reduction of risk in comparison to their non-migrating counterparts in that era. However, this finding did not negate the overall conclusion of the initial analysis. The second analysis compared MS rates in the UKI-born population in all the 1981 survey areas migrating before (group 1) or after 1947 (group 2), and it concluded that the group 1 patients with onset after 1947 most likely acquired their disease in Australia.

The legacy of this epidemiological portfolio of MS in Australia spanning thirty five years from 1961 to 1996 provides a detailed natural history of MS prevalence, prognosis and patient impact prior to the advent of disease specific treatment. It is also a detailed exposition of migration data as it relates to proposed MS aetiology. Over this period there have been numerous neurologists around Australia involved in data collection including Ian Maxwell, Mike McCall, Carolyn de Wytt, Ted Stewart-Wynne, Terry Holland, Pam Macaskill and David Williams. McLeod's vision has ensured that Australia wide there are neurologists who share a special interest in MS and this has led to the formation of a network through ANZAN of a subspecialty society for MS. This collaboration has strengthened advocacy for patients and made Australia attractive for international therapeutic trials for MS as well as strengthened the bond between neurologists around Australia who continue to collaborate in further MS research.

McLeod advanced our understanding of multiple sclerosis (MS) and improved the lives of people with MS by building on his sound cognisance of the literature, establishing fruitful collaborations and basing his research on meticulous study design and execution. A complete bibliography of his published work is included in the Supplementary Material to this memoir.

Character and behaviour as a researcher and project leader

McLeod was an outstanding mentor and inspiration for a generation of neurologists and scientists. As a supervisor his approach was one of rigour matched with tolerance. He provided a strongly supportive environment in which young researchers could learn and flourish. In his early years following appointment at the University of Sydney McLeod spent many hours in the practise and study of clinical neurophysiology and nerve pathology at the light and electron microscope level. He personally taught these skills to his early students Walsh, Low, Pollard and others. As his responsibilities at the hospital and University grew McLeod nevertheless made time for discussion and guidance with his students and fellows and over many years held a weekly research forum to discuss their progress and provide an opportunity to present their work. He encouraged them to pursue learning in newer disciplines such as genetics and

immunology which facilitated further understanding and ultimately effective therapy in certain neuropathies and multiple sclerosis. Likewise with the advent of newer technologies such as computerised axial tomography (CAT scanning) and magnetic resonance imaging (MRI), both of which revolutionised the practise of neurology, he ensured these technologies were available at the hospital together with expert neuroradiologists and that his students and fellows applied the new insights they offered to research. Indeed, prior to MRI (1980) the lesions of MS could not be seen by any imaging technique, but MRI imaging is now an essential part of diagnosis and management and therapeutic clinical trials in MS. Michael Barnett a former student of McLeod and recently appointed to the McLeod chair of Neurology is a national and international authority in the application of MRI to MS research and MS management and his MS group contribute strongly to the international clinical trials.

McLeod was characterised by integrity in his life and work. His extraordinary number of positions of leadership reflect his ability in this role. He had so sharp a mind he could define the essential issues in complex problems and situations and was not afraid to take the actions he believed would make a difference. In his research he generated new ideas and strongly supported his students in their endeavours. McLeod never spoke of his many achievements; they did not motivate him but nevertheless came in abundance, more a by-product of his excellence in academia, his incisive mind, commitment and integrity: in short, his strength of character. He spent countless hours assisting his colleagues for promotion and other honours. He was committed to the practise of medicine, education and improvement of disease through research.

Disciplinary activities

McLeod's engagement with and service to his discipline was extraordinary as detailed in the Supplementary Material. When he was appointed as Head of the Department of Neurology at RPAH, it was an excellent clinical and teaching service, but he saw the need to introduce specialised units within neurology, and he established units in Stroke, Molecular Neurology, Hearing and Balance, Neuromuscular, Multiple Sclerosis, Neuropsychology and others. This was a bold plan, and he achieved it with distinction, and several of these units are now internationally renowned including Hearing and Balance led by Professor Michael Halmagyi, Multiple Sclerosis and Neuroimmunology (Professor Michael Barnett) and Neuromuscular (Dr Judith Spies).

In addition to his demanding work at the coalface of research McLeod laboured to develop the necessary infrastructure to support research and the patients affected by the disease. He was actively involved with the Multiple Sclerosis Association of Australia for over twenty years as a member of the Research Advisory Board, including Chairman and Vice-Chairman. He was a member of the International Advisory Board of the International Federation of MS Societies. With colleagues he established the Nerve Research Foundation at the University of Sydney to support research into MS and other neurological diseases. With Richard Guy, John Hargraves and John Pollard he explored a technique for nerve transplantation as treatment for severe sensory loss in Leprosy and made visits to the East Arm Leprosy Hospital in Darwin to treat indigenous patients. Later with Guy (Professor of Neurosurgery) and Stan Lamond (neuroradiologist) he introduced a consultant neurosurgery/neurology service in Fiji. Richard Guy had also been a student of Peter Bishop and in later years became head of neurosurgery in Oxford and then Dean of Medicine at the University of Sydney.

McLeod was President of the Australian Association of Neurologists (1981–4). Internationally, within the World Federation of Neurology he was a member of the Neuromuscular, Multiple Sclerosis and Autonomic Nervous System groups, and a member of the Nominating Committee. He served on the Editorial Advisory Boards of eight major Neurology journals including *Brain*, *Annals of Neurology* and *Neurology Neurosurgery and Psychiatry* and multiple Research Advisory Committees including the NHMRC Research Council, the Motor Neuron Research Institute Inc and the Muscular Dystrophy Association of NSW. He was also a member of the Australian Science and Technology Council (1987–93) working on important issues such as the Profile of Australian Science(convenor), Core Capacity of Australian Science, and setting directions for Australian Research.

Within the Faculty of Medicine at the University of Sydney McLeod acted at various times between 1972 and 1994 as Sub-Dean, Pro-Dean and Acting Dean.

Major honours and awards

Jim McLeod was elected to Fellowship of the Australian Academy of Science in 1981 and was a member of Council (1985–8; 1993–7), Vice-President (1987–8), Vice-President's Committee 1987 (Chairman 1988–9), and Treasurer (1993–7). He was elected to Fellowship of the Australian Academy of Technological Sciences and Engineering in 1987. In 1986 he was made an Officer in the Order of Australia (AO) for services to Medicine particularly in the field of Neurology and in 2001 was awarded the Centenary Medal for services to Australian Society and Science in Clinical Neuroscience. He received a Lifetime Achievement Award from the World Federation of Neurology (Neuromuscular Group) in 2002. McLeod was appointed Sir Arthur Sims Travelling Professor in 1983 and gave lectures in Canada, South Africa and Zimbabwe and in 1989 was awarded a Commonwealth Medical Senior Fellowship to study and report on medical teaching in the United Kingdom. In 1992 he received an Honorary Doctorate of the University of Aix-Marseille. The Australian Association of Neurologists

Fig. 3. Jim McLeod and Robyn relaxing in retirement (From Robert McLeod with permission).

created the James McLeod Young Investigator award to be presented at the Association's Annual Scientific Meeting, in recognition of his contribution to Neurology in Australia.

Retirement

McLeod retired in 1997 aged 65 but was appointed Professor Emeritus at the University and Consultant status at Royal Prince Alfred Hospital where he continued to contribute to the weekly Neurology clinical and academic meetings. He continued to collaborate with former students and colleagues in publications concerning his major interests in MS and Neuropathy resulting in a further twenty seven, most in major journals, particularly involving epidemiological studies and results of international clinical trials in MS.

Family life

Jim McLeod met his wife Robyn Edith Rule, at Royal Prince Alfred Hospital, where she worked as a nurse. They were married in 1962 and remained happily married and devoted to each other for sixty years (Fig. 3).

The family resided in Northwood, a suburb on Sydney's lower north shore where Jim and Robyn had four children (Anne, Robert, Philip and Rebecca) and established numerous lifelong friendships. Robyn played a pivotal role in Jim's success providing unwavering support and balance in the family; she was actively involved in the local art community, and the family frequently participated in arts-related activities. A charming morning ritual involved the family dog. Each morning Jim would prepare tea and toast to take upstairs to their bedroom where he and Robyn would sit in bed, reading the paper and enjoying the view over the bay. The family dog played a key role in this routine, as most mornings, Jim could be seen in the front garden retrieving the newspaper from the dog's mouth. This playful interaction became a cherished part of their daily routine.

Jim's dedication to his family was evident in his interaction with his four children with whom he took a close and active interest in all aspects of their lives. The family enjoyed modest holidays, often camping during Christmas and participating in trips with the local art community.

After Jim's retirement the family experienced a very special twenty years together, with their holiday home at Hyam's Beach in Jervis Bay playing a significant role. This was a place where family and friends gathered for various celebrations, including birthdays, honeymoons and Christmases. It was also a place where Jim and Robyn could spend quality time with their eleven grandchildren (Fig. 4).

Fig. 4. The McLeod family enjoying the winter sun at Hyams beach (From Robert McLeod with permission).

Jim's deep devotion to Robyn and their mutual love for each other created a wonderful home life. Robyn was incredibly proud of Jim and was an integral part of his success.

Concluding remarks

James McLeod was a visionary clinical neuroscientist with an incisive mind and a gift for leadership. He achieved leading roles in his hospital, university, Academies national and international. McLeod worked diligently lifelong and was known for his integrity, commitment to education, the practise of medicine and the improvement of disease management through scientific research.

Over his working life he witnessed remarkable improvements in disease management within his own areas of expertise—multiple sclerosis and neuropathy, to which advances his own work contributed strongly. McLeod is remembered fondly by his students, patients and colleagues. It is most fitting that his university, The University of Sydney, has recently established the James McLeod Chair of Neurology in his honour.

Supplementary material

Supplementary material can be accessed from the article page online.

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