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James Waldo Lance 1926–2019

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James W. Lance was a clinical neurologist who created the first university-based department of neurology in Australia. He championed academic enquiry and the scientific basis of clinical practice, and his research had two major themes, motor control and headache. After his doctoral studies on the pyramidal tract of the cat, he became a pioneer of the new field of motor control studied in human subjects, making seminal contributions on the control of muscle tone, reflexes and movement in healthy subjects and the pathophysiology of movement disorders in patients. At the same time he developed a clinical research program into the mechanisms and management of headache, in particular migraine. These studies evolved into parallel experiments in human subjects, cats and monkeys, probing the control of the cerebral circulation and the mechanisms underlying craniofacial pain, for which he received international acclaim in both fields. He received international and Australian honours and was the first practising clinician to be elected a fellow of the Australian Academy of Science. He is rightfully credited with leading the development of academic neurology in Australia and overseas.

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Overview

In 1980, James Waldo Lance (Fig. 1) became the first practising clinician to be elected to Fellowship of the Australian Academy of Science (AAS). The citation for the academy read:

> Professor Lance is noted for his contributions to neurology particularly in respect to disorders of the motor system and headache mechanisms. His specific attainments include the elucidation of the nature of myoclonus and akinetic attacks in epilepsy, the nature of the cogwheel phenomenon in Parkinson's Disease, the mechanism of reflex irradiation in spasticity and the description and investigation of the tonic vibration reflex that has led to a completely new method for investigating normal and disordered motor control. His contributions to our understanding of headache mechanisms include studies of vasoactive amines, hormones and prostaglandins in migraine. His monographs on the mechanism and management of headache, incorporating his own original contributions, have had a wide influence, being translated into French, Italian, Portuguese and Japanese.

It is only a slight over-statement to say that, in many areas of medicine, clinical practice in Australia was academically barren in the late 1950s, but enthusiastic young clinicians such as Lance brought to their teaching an understanding of the mechanisms of disease that inspired their pupils to enquire further and set in course the dramatic growth in medical research that sees Australia performing very well by international benchmarks.

Lance's career was devoted to taking the empiricism out of medicine and seeking a deeper understanding of the relevant biology. In an interview for the academy in 2010, he said, 'the guiding light of my research and clinical career has been to try to explain clinical phenomena in physiological terms and apply that to treatment'.[1] His personal research in two very different fields was paradigm-shifting, as detailed below, and has been documented in texts that have seen several editions.[2] He was a consummate communicator who could put complex concepts into words that lay people could grasp. His scientific writings were parallelled by

Fig. 1. James W. Lance at his election to the Academy in 1980. (From Mrs Judy Lance, with permission).

[1] Australian Academy of Science (2010).

[2] Lance (1969) and subsequent editions to the 7th, Lance and Goadsby (2005). Lance (1970). Lance and McLeod (1975). Lance and McLeod (1981). McLeod and Lance (1983) and subsequent editions, McLeod and others (1995).

books, pamphlets and seminars directed at non-medical audiences.[3] His clinical skill and these writings established his reputation as an authoritative clinician in Australia and overseas. He was driven by curiosity throughout his life: he needed to understand 'why', and was committed to passing on his new insights to colleagues and the lay public. In doing so, he set a benchmark for those who followed and cemented his place in neurology internationally. A bibliography of his published work accompanies this biographical memoir in Supplementary Material.

Early life and schooling

Jim Lance was delivered into the world by forceps on 29 October 1926 in the front bedroom of his family home in Wollongong, NSW. His father (Waldo Garland Lance, born in Mosman in 1903) was governing director of the family clothing and drapery business (Walter Lance & Co., subsequently renamed Lances Ltd, Crown Street, Wollongong). The company was acquired in 1965 by the David Jones empire along with the next-door Savoy Theatre. Jim Lance's paternal grandfather had emigrated from Birmingham, England in 1880. His mother was Jessie Forsyth Lance (née Stewart). She was the fourth child of James Douglas Stewart, who had been born in Windsor, NSW, in 1869. Stewart had trained in veterinary science at the Royal Dick School in Edinburgh (where his father had also trained before moving to Australia), and returned to Sydney to become the founder and inaugural dean of the first Faculty of Veterinary Science in Australia, at the University of Sydney. The university faculty building is named the J. D. Stewart Building.

As a child, Lance suffered from asthma, and he went to boarding school from age seven on medical advice. The first boarding school was Tudor House, an Anglican preparatory school at Moss Vale, with Mr 'Jack' Medley (later Sir John Medley, Vice-Chancellor of the University of Melbourne and Commissioner of the Australian Broadcasting Commission) as headmaster.[4] At age twelve he won an Exhibition for Geelong Grammar School that he attended from 1939. He called it 'a remarkable school which has not to my knowledge been equalled in Australia before or since'. His time at Geelong was interrupted by the Second World War, and from 1941 he completed his secondary studies at The King's School in Parramatta, his father's old school. The change was described by Lance as being 'a transition from Athens to Sparta' because of the latter's focus on physical activities (sport and the Cadet Corps) at the expense of academia. However at King's he was introduced to scientific method, logical thinking and deductive reasoning by a gifted physics teacher, Mr Bartlett, who had also taught Lance's father and who was 'the best teacher of science I encountered in my school career'.[5]

Medical education and postgraduate training

From the age of twelve, Jim Lance had ambitions to become a medical doctor and, in 1944, he started the undergraduate medical course at the University of Sydney at the age of 17. He always intended undertaking medical research during his career, but had no particular discipline in mind. Prior to graduation, his only research experience was a project on the erythrocyte sedimentation rate (ESR) in 1949. He graduated MBBS with honours in 1950, with an interest in internal medicine rather than surgery, but not specifically neurology. At that time there were no specialist neurologists with whom to identify in Sydney.

In 1950 and 1951 he worked as a junior resident medical officer and then a senior RMO at Royal Prince Alfred Hospital, under the tough conditions that were standard then but would not be tolerated today. At this time he and Henry Harris (later Sir Henry Harris, FRS, FAA)[6] sought advice on a research career from a distinguished visitor, Nobel Laureate, Sir Howard Florey, FRS, FAA.[7] On Florey's advice, Lance visited the University of Melbourne Department of Physiology headed by Professor (Sir) R. Douglas (Pansy) Wright,[8] but was not convinced to follow Florey's recommendation to enter medical research there. On the other hand, Harris moved to Melbourne, and subsequently joined Florey's laboratory at the Sir William Dunn School of Pathology in Oxford, UK, as a DPhil student, eventually succeeding Florey on his retirement.

In looking for a research mentor, Lance encountered Peter Bishop (later AO, FAA, FRS).[9] Bishop had just returned to Sydney and was setting up a 'Brain Research Unit' at the University of Sydney, having spent four years at Oxford with Professor J. Z. Young, FRS, said to be 'one of the most influential biologists of the twentieth century'.[10] Enthused by Bishop, Lance terminated his appointment at Royal Prince Alfred Hospital to become Bishop's first doctoral student. Other research collaborators in Bishop's unit were BSc (Med) candidates, Jim McLeod (later AO, FAA, FTSE) with whom Lance maintained a life-long friendship and collaboration, Bill Levick (later FAA, FRS) who moved to the John Curtin School of Medical Research with Bishop, and Dick Gye (later AO) who became the first full-time Dean of the Faculty of Medicine at the University of Sydney. Although primarily interested in the physiology of vision, Bishop supported Lance in his seminal studies on the pyramidal tract. While undertaking this research for the MD, he maintained clinical contact through a weekly clinic at the Northcott Neurological Centre with Dr George Selby, one of the founding fathers of the Australian Association of Neurologists.

Lance graduated MD (Sydney) in 1955 for a thesis that was based on four papers that defined the pyramidal tract of the cat.[11] The first studied the properties of pyramidal tract axons, stimulating the axons directly in the medullary pyramid, and recording

[3] Lance (1975). Lance (1977*a*). Lance (1986) revised and expanded from 1993 with a foreword by Oliver Sachs, Lance (2000).
[4] Serle (2000).
[5] Australian Academy of Science (2010).
[6] Gardner and Sidebottom (2018).
[7] Fenner (1996).
[8] McPhee (2012).
[9] Pettigrew and Dreher (2018).
[10] Boycott (1998).
[11] Bishop and others (1953). Lance (1954*a*). Lance (1954*b*). Lance and Manning (1954).

8–12 mm distally. There were two populations with a similar pattern of recovery after a single impulse, but the first had a shorter absolute refractory period (0.45 ms versus 0.8 ms) and faster conduction velocity (35–40 ms^{-1} versus 12–16 ms^{-1}), values that were recognised as probably underestimating the true velocities due to the short conduction distance. In a subsequent study he demonstrated a projection of the lateral corticospinal tract, uncontaminated by a significant homolateral projection, to the lumbar region (to L4 but not below) with faster conduction velocities than he had previously calculated, at least for the fastest axons. The pyramidal tract axons were traced antidromically and orthodromically to and from cortex to define their origin—two thirds from pre-Rolandic cortex, and almost one third post-Rolandic, the average conduction velocity slightly slower for those from parietal cortex. He then went on to determine whether pyramidal tract axons regenerated over up to 170 days after section in the medulla, but could find no electrophysiological or histological evidence for this. These studies were published in major international journals, introduced novel techniques (see comment from Professor T. A. Sears below), and established his reputation in England for science and particularly motor control neurobiology, before he travelled there to undertake clinical training.

In 1954, Lance travelled to England as a ship's surgeon in *SS Orcades*, and in 2010 he reminisced that he was unable to receive the miserly stipend for being the ship's doctor because the payment was available only to union members and the obligatory union fees were greater than the stipend! He trained as a physician, working at the Royal Postgraduate Medical School at Hammersmith Hospital and then at the National Hospital for Nervous Diseases at Queen Square, gaining specialist qualifications as a physician (MRCP London) in 1955. The publication of his thesis studies attracted some interest at Queen Square. A former post-doctoral student of Sir John Eccles in Canberra, Professor Tom Sears, founder of the Sobell Department of Neurophysiology at Queen Square, wrote:

> Among the papers I read was one published in the Journal of Neurophysiology by this Australian Jim Lance. What had attracted my attention was his use of 'killed end recording' from the pyramidal tract. This transformed the otherwise complex multi-phased low amplitude compound action potential recorded by a microelectrode to an overall monophasic wave with distinct components travelling at different velocities. He achieved this by the use of a large electrode which severed the fibres in the cortico-spinal tract so simulating monophasic recording from a peripheral nerve. Sometime in the mid 1950's I heard that Jim was at Queen Sq. pursuing his training in Clinical Neurology so I sought him out and enjoyed our many chats about neurophysiology … .[12]

Subsequent scientific life

On his return to Australia in 1956, there was little opportunity for Lance to develop a career specialising in neurology rather than a career in medicine 'with an interest', so he became an assistant physician at Sydney Hospital and Superintendent of the Northcott Neurological Centre in Cammeray. During this period he wrote a seminal paper, co-authored with mentor Dr George Selby, analysing five hundred cases of migraine.[13] This work helped define one of his two major research themes. Supported by Sir Kenneth Noad, with whom he had written a major report on familial myoclonic epilepsy, called the Ramsay Hunt syndrome,[14] he won a Lilley Fellowship to work at the Massachusetts General Hospital in Boston. Here he was influenced by Raymond D. Adams, Bullard Professor of Neuropathology at Harvard University and chief of the neurology service at Massachusetts General, a man considered by his peers as the pre-eminent neurologist of the twentieth century. He was also influenced by the legendary New Zealand-born Derek Denny-Brown, OBE, James Jackson Putman Professor of Neurology at Boston City Hospital. From his time in Boston, Lance authored two seminal papers, one on what is now known as the Lance-Adams Syndrome of post-hypoxic myoclonus,[15] and one on the action tremor of Parkinson's disease.[16]

In 1959, the University of New South Wales set up a new School of Medicine at the Prince Henry Hospital under the Foundation Professor of Medicine, Ralph B. Blacket. While in Boston, Lance applied for and was appointed to the position of senior lecturer and head of neurology in the new medical school at the Prince Henry and Prince of Wales Hospitals. He returned to Sydney to develop the Department of Neurology, which he chaired for nigh on thirty years. In that time, he worked tirelessly to develop the speciality, not just at the Prince Henry Hospital but also throughout the country. At Prince Henry, he had the good fortune to be associated with Dr Alec Gonski (AM) who arrived in 1961 from South Africa. Born in Łódź, Poland, Gonski attended medical school in South Africa, trained as a neurosurgeon in Edinburgh, and from 1952 practised as a specialist in Cape Town. Gonski was recruited to set up the Department of Neurosurgery at the Prince Henry Hospital, sharing the same ward with neurology.[17] Lance was promoted to associate professor in 1964 and to the first Chair of Neurology in Australia in 1975. In 1989, the Departments of Neurology and Neurosurgery were linked administratively as the Institute of Neurological Sciences, with Lance as the inaugural director, and in 1991 the Prince of Wales Medical Research Institute (now renamed Neuroscience Research Australia) was created, the first medical research institute devoted exclusively to neuroscience in Australia.

In the 1960s, research on clinical topics in medicine was hampered by restrictions on resources, and it was not until the late 1970s and 1980s that opportunities for regular funding through the National Health and Medical Research Council began to open up. To fund equipment and the salaries for research fellows and technicians required persistence and persuasiveness. Lance set up his enterprise and kept it afloat by fund-raising in various ways: talks to community organisations such as: Lions Club and Rotary; gifts from grateful patients, among the first being Edwin Street, OBE, and his wife Daisy, from Wollongong, and subsequently

[12] Thomas Sears, personal communication, 1 March 2019.
[13] Selby and Lance (1960).
[14] Noad and Lance (1960).
[15] Lance and Adams (1963).
[16] Lance and others (1963).
[17] Ward 4, run by the indomitable nursing sister-in-charge, Mary (Jo) Loder (OAM).

others including the J. A. Perini Family Trust and businessman Warren Anderson; approaches to charitable foundations, for example the Basser Foundation; and even his parents in Wollongong. He undertook clinical trials, and turned the proceeds into support for research. With students and visiting overseas collaborators, he developed research programs in two areas. The first was motor control, with a combination of experiments on human subjects and patients, supported and illuminated by parallel experiments on reduced animal preparations. The second, the mechanisms and management of headache, was triggered by his studies with George Selby on migraine.[18] This became his enduring interest. His initial studies documented the clinical features of headache and craniofacial pain and the biochemical and neurophysiological mechanisms underlying vascular headache, as described below.

Motor control

As mentioned above, Lance's research for the MD degree had resulted in four landmark papers on the pyramidal tract of the cat, and this underpinned his interest in the control of muscle tone and the pathophysiology of disorders of movement. In the early 1960s, the mechanisms underlying muscle tone, posture and movement were only just beginning to be studied in human subjects. Lance achieved an enviable reputation in this growing field, becoming internationally renowned in the field of 'neurophysiology studied in man' (as it was then known). He began investigating disorders of motor control in patients when in Boston, publishing a landmark study of tremor in Parkinson's disease.[19] For the first time it was demonstrated that, in the majority of patients, voluntary effort brought out an action tremor (an exaggerated physiological tremor) which was faster (7–12 Hz) and of lower amplitude than the classical resting 'pill-rolling' tremor (3–6 Hz). He found that the action tremor more commonly determined the rate of the 'cog-wheel' phenomenon than the resting tremor.

Back in Sydney, his initial experiments revolved around muscle vibration. He demonstrated that the abnormal spread of tendon jerk reflexes in spastic patients was not due to intraspinal spread of a normal afferent input to the produce heteronymous reflex contractions in muscles remote from the stimulus, but rather to spread of the percussion wave through bone to excite muscle spindle endings in multiple muscles, thereby triggering homonymous reflex responses. He then applied a vibrator to his thigh in the expectation that it would produce a tendon jerk, but found to his surprise that it produced a slow tonic contraction of the vibrated muscle. During the vibration the tendon jerk of the vibrated muscle was suppressed, as was the H reflex. He presented these findings in 1964 to the Australian Association of Neurologists in Canberra, and Nobel Prize Laureate, Sir John Eccles,[20] commented that similar findings had been presented that year at a Nobel Symposium in Stockholm by Karl-Erik Hagbarth. Hagbarth was soon to become Professor of Clinical Neurophysiology at the University of Uppsala, Sweden. He was a pupil of another Nobel Laureate, Ragnar Granit who, like Eccles, had been a student in the 1930s of the doyen of motor control neurophysiology, Nobel Laureate Sir Charles Sherrington. This triggered a life-long collaboration, with mutual visits and exchange of postdoctoral students. Lance pursued the mechanisms of the paradox that, while the vibration could produce a tonic reflex contraction of the vibrated muscle (the 'tonic vibration reflex', TVR), it suppressed phasic reflexes such as the tendon jerk in the same muscle. He and his team—Peter Neilson, David Gillies, and Carlo Tassinari (from Italy)—produced convincing evidence from experiments in the cat that the suppression of the monosynaptic reflex was a pre-motoneuronal phenomenon due to a vibration-induced decrease in the group Ia excitatory postsynaptic potential. The mechanism was thought to be classical GABergic presynaptic inhibition. The finding by Paul Delwaide (Belgium), confirmed by Lance's group and subsequently by others, that the reflex suppression produced by vibration was less in spastic patients was taken as evidence that presynaptic inhibition was suppressed in spasticity. His team then studied the supraspinal pathways controlling the tonic vibration reflex, and used the findings to clarify abnormalities of muscle tone in patients.

In parallel, Lance and his students (David Burke, Colin Andrews, Peter Neilson) introduced techniques for documenting the clinical abnormalities in patients with motor disturbances, such as spasticity, Parkinson's disease, athetosis, dystonia and cerebral palsy. They developed new approaches to investigating these clinical signs, explaining their pathophysiology on the basis of current knowledge. One of Lance's highly cited writings is his definition of spasticity, advanced at a scientific meeting on this topic in Scottsdale, Arizona in 1979: 'Spasticity is a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motoneuron syndrome'.[21] This definition was based on detailed experiments clarifying the abnormal muscle tone of spastic patients who were at rest. The work on spasticity and their studies of muscle tone and tremor in Parkinson's disease, athetosis and cerebral palsy were reviewed in a prestigious Wartenberg Lecture to the American Academy of Neurology.[22] This paper summarised his research activities in motor control, and has been cited 404 times (to January 2021). Thereafter he passed on the motor control baton to his students, Peter Neilson, David Burke and Simon Gandevia. Although no longer active in motor control, he continued to draw on his research experience to illuminate clinical phenomena.

While the insights into clinical signs in neurological disease were of profound importance when made, some have not survived the efflux of time in the precisely the same format. The findings remain valid, but their interpretation has changed. For example, (i) presynaptic inhibition was invoked to explain the inhibition of so-called monosynaptic reflexes by vibration. As noted above, this inhibition is less in spastic patients, leading to the belief that suppression of presynaptic inhibition was the driving force responsible for spasticity. It is now well documented that the inhibition is

[18] Selby and Lance (1960).
[19] Lance and others (1963).
[20] Curtis and Andersen (2001).
[21] Lance (1980*a*).
[22] Lance (1980*b*).

not due to primary afferent depolarisation at a GABergic axo-axonal synapse, but largely due to another pre-motoneuronal phenomenon, 'post-activation depression' of the release of transmitter at the synapse between group Ia afferents and the motoneuron. (ii) The tonic reflex contraction (the TVR) was attributed to polysynaptic spinal pathways from group Ia afferents, but it is now known that prolonged high-frequency inputs can trigger 'plateau potentials' in motoneurons, and this provides a better explanation of the tonic contraction. (iii) The 'clasp-knife phenomenon' in spastic patients was attributed to an inhibitory effect of group II afferents from muscle spindles on extensor motoneurons, a 'flexor reflex afferent' effect, as documented in studies in spinal cats. However, there is no evidence that group II muscle afferents produce inhibition of extensors in humans. The effects noted by Lance's group are now attributed to other 'flexor reflex afferents', non-spindle stretch and tension receptors with group II and III afferents. (iv) Muscle tone in healthy subjects was thought to be based on a tonic contraction mediated through spinal reflex pathways (hence the relevance of being able to produce a tonic contraction using muscle vibration). It is now appreciated that healthy subjects can relax limb muscles completely, so that muscle stretch does not produce a reflex contraction. The resistance to passive movement is largely musculo-skeletal, not neural and, accordingly, hypotonia in cerebellar disease is not due to hypo-active stretch reflexes.

Headache

When working as Superintendent of the Northcott Neurological Centre after his return from London in 1956, Lance noticed that only a minority of patients with migraine were taking specific therapy for their condition. This led to a detailed prospective survey of the clinical feature, demographics and precipitants in 500 patients, undertaken with his clinical mentor, Dr George Selby.[23] That paper defined the syndrome and distinguished it from mimics, and has been cited 515 times. Similar detailed analyses (accompanied by biochemical studies) subsequently led to the definition of other conditions: cluster headache, lower-half headache, and their distinction from tension headache and tension-vascular headache.

In the early 1960s Frederigo Sicuteri and colleagues in Florence, Italy reported that the urinary excretion of serotonin metabolites was increased during the headache of migraine, and that methysergide, thought to be a serotonin antagonist, was effective in the prophylaxis of migraine.[24] This triggered Lance to focus on the biochemical changes in migraine, cluster headache and other headaches with biochemist Herta Hinterberger and doctoral students, initially Don Curran and then Michael Anthony. In a paper cited 286 times (to January 2021), they reported that platelets discharged their serotonin content at the onset of the migrainous headache, whether the headache was spontaneous or induced by the injection of reserpine, and that intravenous infusion of serotonin could alleviate the headache.[25] These and subsequent studies on the biochemical changes associated with the onset of the migrainous headache contributed to the development and marketing of sumatriptan by a scientific team, led by Dr Patrick Humphrey, OBE,[26] at Glaxo (UK). Sumatriptan is a serotonin agonist without the unwanted side-effects of serotonin itself, and was the first of several 'triptans' now available for treatment of the acute attack of migraine.

However humoral changes and the resulting extracranial vasodilatation are not sufficient to explain migraine, and the scope of the headache research expanded to encompass central factors. Lance's headache research unit grew with many local students and research fellows, such as Brian Somerville, Paul Spira, Peter Drummond, Ewan Mylecharane, Geoff Lambert, Peter Goadsby, Alessandro Zagami, George Lord and Rick Adams, to name a few. With the arrival of Michael Welch (from the UK), attention turned to the humoral control of the cerebral circulation in primates, with studies in cats and monkeys into the nociceptive afferent impulses from extracranial vessels, and the pathways involved in headache and cranio-facial pain. A key development was an animal model that could be used to test potential therapies. Throughout his research career Lance and his team undertook clinical trials, illuminated by their research, to improve patient treatment.

Many factors are involved in the acute attack of migraine. There seems to be a polygenic 'migraine threshold' susceptible to external and internal triggers and to fluctuations in hypothalamic function (resulting in cravings and alterations in mood). Serotonin remains a central factor in the acute migraine attack: 'Receptors for 5-HT are present in cranial arteries and are also widely distributed in the central nervous system, where they play a role in the neural control of the cranial circulation and endogenous pain control system. The pathophysiology of migraine involves interaction between these central pathways and cranial blood vessels. It is probable that many prophylactic agents exert their action by central 5-HT_2 antagonism, whereas termination of an established attack of migraine depends upon constriction of cranial vessels mediated by 5-HT_1 receptors.'[27] The scientific and clinical insights gained into these mechanisms have been documented in a major text,[28] now in its seventh edition and co-authored by former student Peter Goadsby, currently Professor of Neurology and Director of the National Institute for Health Research–Wellcome Trust King's Clinical Research Facility at King's College London, and one of the foremost experts on headache in the world.

Lance drew on the understanding derived from his clinical research studies for the International Classification of Headache Disorders, initiated when he was President of the International Headache Society (1987–9). The third edition of this classification has become a citation classic, cited 3,242 times (to January 2021). In 1998 a phase I clinical pharmacology unit, the James Lance GlaxoSmithKline Medicines Research Unit was developed at the Prince of Wales Hospital as part of the Institute of Neurological Sciences to undertake early-phase clinical trials, a crucial step in assessing the safety and efficacy of new medicines before marketing.

[23] Selby and Lance (1960).
[24] Sicuteri and others (1961). Sicuteri (1976).
[25] Anthony and others (1967).
[26] British Pharmacological Society (2020).
[27] Lance (1991).
[28] Lance (1969).

Fig. 2. Speakers at the Symposium in his honour on his retirement (24–26 October 1991). Front row: Dr Frank Clifford-Rose (Secretary-General of the World Federation Federation), Professor Richard T. Johnson (Johns Hopkins, Baltimore), Professor James W. Lance, AO, CBE, FAA, Lord Walton of Detchant (then President of the World Federation Federation), and Dr Stanley Fahn (Columbia University, New York). Second row: Dr Keith Lethlean, Assoc. Professor Paul Spira, Assoc. Professor Michael Anthony, OBE, Professor Jim Colebatch, Assoc. Professor Peter Neilson and Professor Simon C. Gandevia, FAA, FAHMS. Third row: Professor David Burke, AC, FAA, FTSE, Professor Peter Goadsby, Professor Robert Porter, AC, FAA (past Director of the John Curtin School of Medical Research), Dr David Gillies, Dr Rod Mackenzie, Dr Ewan Mylechrane, Professor John Morris, AM. Fourth row: Dr Richard Piper, Professor Peter O. Bishop, AO, FRS, FAA (Lance's mentor), Professor D. I. McCloskey, AO, FAA, FTSE (Director, Prince of Wales Medical Research Institute), Professor Peter Ashby (Toronto, Canada), Professor Jes Olesen (Rigshospitalet, Copenhagen) and Professor K. Michael Welch (Henry Ford Hospital, Case Western Reserve University), Professor James G. McLeod, AO, FAA, FTSE. Absent: Professor Nikolai Bogduk (Newcastle), Dr Nick Francis-Jones (Sydney), Professor Peter Drummond (Curtin University), Dr Patrick Humphrey, OBE (Director, Glaxo Research, UK), Dr Geoffrey Lambert (Sydney). (David Burke).

Serendipity

'One patient with a new syndrome is interesting, two is a coincidence and three is a paper',[29] and Lance seized the opportunity to investigate patients with unusual conditions, to clarify the underlying pathophysiology. Perhaps the first such example was familial myoclonic epilepsy.[30] Myoclonic jerks and falls, dystonic seizures and other movement disorders remained an interest throughout his life. Indeed his last paper in 2019 was a commentary on falling attacks in the elderly, in which he drew a parallel to his studies on negative myoclonus in the 1960s.[31] This paper was the last of many published over sixty years in the *Journal of Neurology, Neurosurgery, and Psychiatry* after his initial, landmark paper on migraine in 1960,[32] and it is notable because it was written with his granddaughter, a neurologist-in-training. Another early example is action myoclonus in post-hypoxic patients, studied in Boston with Raymond Adams, and now known as the Lance-Adams Syndrome, detailed in a paper cited 362 times to date.[33] Studies on patients with the adrenaline-secreting tumour, phaeochromocytoma with Herta Hinterberger, preceded and led to his biochemical studies of serotonin and other amines in migraine.

Lance and his colleagues defined a plethora of unusual neurological conditions (such as sensory loss in poliomyelitis, formed visual hallucinations, familial cerebellar ataxia, familial paroxysmal dystonic choreoathetosis), often applying attractive names when describing them for the first time: the 'Harlequin' syndrome (a condition to which his daughter Fiona first alerted him), the neck-tongue syndrome, red ear syndrome, 'blip' syndrome, sex headaches.

Awards, honorific appointments and scientific recognition

James W. Lance received considerable national and international recognition for his scientific and clinical contributions, as detailed

[29] J. W. Lance, personal communication 29 January 2010.
[30] Noad and Lance (1960).
[31] Lance and Waller (2019).
[32] Selby and Lance (1960).
[33] Lance and Adams (1963).

in the Supplementary Material. Particularly notable are those associated with the development of academic neurology in Australia (such as appointment in 1975 to the first Chair of Neurology in Australia, and the creation of named lectureships in his honour). He was appointed Commander of the Order of the British Empire in 1977 and Officer in the General Division, Order of Australia 1991. In recognition of his seminal role in the development of triptans for the treatment of the acute attack of migraine, a phase I clinical trials unit was opened at the Prince of Wales Hospital in 1998 as the James Lance GlaxoSmithKline Medicines Research Unit.

Retirement

In 1991, age discrimination was still the rule in Australian universities, and Lance retired from his University and hospital appointments on attaining sixty-five years, on 26 October 1991. He moved sideways into consultant practice, with emeritus appointments at the hospital and university where he continued to contribute to the academic activities of his former department. A symposium, *The Changing Face of Neurology*, was held on 24–26 October 1991 to honour him, and it attracted many overseas and local attendees. Some of the guest speakers are in Fig. 2.

Personal attributes and community service

Lance gave his time generously to medical charities, such as the Brain Federation, to the Australian Academy of Science and to professional organisations. Above all, however, he was an enthusiastic teacher and inspirational mentor. To quote from an obituary in *Cephalalgia*: Jim was, as his daughter described him at his memorial service, unfailingly polite. This was applied to all he met, in all circles, at all times. It is said one mark of a person is how they behave to those who can do them no advantage; by this mark, Jim Lance passed muster at the highest level. He was always considerate and thoughtful even when faced with braggadocious assertions, politely suggesting further reading or the possibility of another interpretation. He had a wonderful sense of humour; especially quick-witted, his quips are now legend. When the term 'short-lasting neuralgiform headache attacks with conjunctival injection and tearing' was first mooted, it was he who remarked 'the names get longer as the attacks get shorter'.[34]

He was the compleat neurologist. He could speak authoritatively on areas outside his own personal focus, and international colleagues were frequently impressed by the depth and breadth of his knowledge of general neurology when he was a visiting professor. His clinical consultations were an opportunity for teaching: they provided carefully thought-through guidance and the reasons behind his recommendations. Coupled with his research activities and his publications, this resulted in his influence being felt throughout the world, and inevitably drew clinical and research fellows from throughout the world to the Prince Henry Hospital to work with him.

Jim Lance served the academy on council from 1982 to 1985, as vice-president 1984–5. He was a member and chair from 1985 to 1989 of Sectional Committee 8 (Applied Sciences), and served on the National Committee for Medicine 1981–3 and the Vice President's Committee (as chair and member) 1985–7.

[34] Edvinsson and others (2019).

Fig. 3. Judy and Jim, relaxing. (From Mrs Judy Lance, with permission).

Having served the Australian Association of Neurologists for some years on council and on committees, Jim Lance was elected president in 1978, serving a three-year term. In recognition of his contributions to the growth of neurology in Australia, the Association created the James W. Lance Young Investigator Award to be presented at the association's Annual Scientific Meeting and, in 2019, the James W. Lance Award and Lecture for a neurologist member for excellence in academic career achievement. Other major roles included inaugural President of the Australian Headache Society (1987–91), inaugural President of the Australian Movement Disorder Society (1991), 4th President of the International Headache Society (1987–9, having served as vice president 1985–7), and Vice President of the World Federation of Neurology (1989–93), the first Australian to hold these international positions.

Lance was a director for some decades and a life-long supporter of the Brain Foundation (originally set up as the Australian Neurological Foundation). This foundation raises money for research into neurological diseases, and his commitment stems from his own activities to find funding support for research in his early years. In recognition of his service, the Brain Foundation created the James Lance Award for research into migraine and other headaches in 2016.

Family life

Jim first met Judy Logan when she was studying physiology as a medical student, and then for the second time at a dance at St Paul's College after he had returned to Sydney from the UK. They married on 6 July 1957, and have five children, Fiona, Sarah, Jenny, Robert, and Sophie, 19 grandchildren, and a great grandchild (Fig. 3).

Fig. 4. Jim Lance, relaxing. (From Mrs Judy Lance, with permission).

Lance was an avid family man, who published a children's book, *The Golden Trout*, a compendium of stories that he made up as bedtime reading for his own children.[35] For sport, he enjoyed skiing and fishing (Fig. 4). He is survived by a loving family, and he leaves an academic legacy that lives on through his grateful pupils and his pupils' pupils.

Jim suffered from myelofibrosis for some years, and required regular transfusions (Fig. 5). As is commonly the case, the terminal event was the development of acute leukaemia, which he, Judy and the family elected to take as it came, rather than embark on debilitating chemotherapy. He died in Sydney on 20 February 2019.

Concluding remarks

Jim Lance did not wait patiently at God's gate: he embraced life fully, was never idle, a man of boundless enthusiasm who saw challenges as opportunities. He took on tasks without demur, and he made a difference. He has had a lasting impact on neurological thought and neurological practice throughout the world, and he will be forever recognised as the 'father of academic neurology' in Australia. Ever modest, always supportive, he has been an exemplar of what is meant by 'clinician scientist'.

Fig. 5. James W. Lance in retirement, 2018. (From Mrs Judy Lance, with permission).

[35] Lance (1977*b*).

Conflicts of interest

The author was a student, colleague and friend of James W. Lance and, on his retirement, his successor as departmental head. Lance inspired him to undertake medical research and has encouraged and supported him throughout his career.

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