# Paper bullets of the brain

## A neurologist's story

James W Lance

*Shall quips and sentences and these paper bullets of the brain awe a man from the career of his humour?*
— Shakespeare, *Much Ado About Nothing* (II.iii.260)

In 1993, when interviewing me for the archives of the Royal College of Physicians, Dr Max Blythe suggested that I write my autobiography. Never reluctant to take pen to paper, I put this suggestion to my family. Their answer was unequivocal — "No, Dad, no. Nothing exciting has ever happened to you. You've led a charmed life". However, as a person who even enjoys filling in questionnaires, I found it hard to resist the invitation of the Editor of the Journal to reminisce about my decision to undertake a medical career, the mentors who guided me and the influences in my chosen pathway to become a clinical investigator.

### Why medicine?

I wanted to be a doctor from the age of 12 years; why, I am not sure. I had no medical forebears but admired an uncle by marriage, Justin Markell, a physician at St Vincent's Hospital and a keen skier. As a boy I read everything medical I could lay hands on — "The Citadel", "Viewless Winds", "The Story of San Michele" and "The Healing Knife" come to mind — and many other books about the history and challenges of the medical life. I found their messages stirring and thought that this was the life for me.

I have never regretted my decision.

As a medical student I was fortunate in my introduction to clinical work at the Royal Prince Alfred Hospital (RPAH). Frank Mills, debonair and charming, was a kind and understanding tutor in surgery. Keith Harrison, our tutor in medicine, was a first class clinician, caring and courteous. The senior physicians included dedicated teachers such as Archy Collins, C G McDonald, Tom Greenaway and Bill Morrow, all of whom were later knighted, and Professor Lambie, who improved our history taking and physical examination with the rigour of the Scottish discipline he imposed. Cotter Harvey ran the only specialist medical unit in RPAH, the Thoracic Unit, which was of world standard.

### The pathway to research

After graduation I knew that I wanted to undertake research work. My uncle, Justin Markell, exclaimed "Why would you want to do research? You don't have any deformity or handicap. You could go into practice." I approached Hugh Ward, Professor of Bacteriology, to discuss my aspirations. When Sir Howard Florey visited Sydney, Professor Ward introduced Henry Harris, another recent graduate, and me to him as possible candidates for a research career.

Florey advised us to work in the Physiology Department of Melbourne University and then to do the honours course in physiology at Oxford. Henry Harris followed this advice, and eventually succeeded Florey as Director of the Sir William Dunn Institute in Oxford. I did fly to Melbourne, but was not excited by the work in progress. It was not until I met Peter Bishop, newly returned from London and setting up the Brain Research Unit in the Department of Surgery, University of Sydney, that I focused my research ambitions on neurophysiology. Peter was an enthusiast and transmitted that enthusiasm to others. I have written elsewhere about his influence on the development of neurology in Australia.[1]

*It is necessary not only to make a discovery but to repeat the findings at intervals to prevent the results from sinking into oblivion and to deter others from going through the same motions.*

While in Peter's laboratory I kept in touch clinically by seeing patients at the Northcott Neurological Centre, Cammeray, under the guidance of George Selby. George was a superb clinician and teacher who patiently imparted his art, which stood me in good stead when I departed for the then customary 2 years of postgraduate training in London.

### Marking time

On returning from Queen Square (now The National Hospital for Neurology and Neurosurgery) in 1956, I looked for an appointment combining clinical work with research. There were none. I was appointed Superintendent of the Northcott Neurological Centre and an Honorary Assistant Physician to the Sydney Hospital. I was one of a group of young specialist physicians who were astounded when informed that we could not conduct a clinic in our own speciality but had to rotate throughout all the clinics so that we could work in our own speciality clinic for 6 months every three years or so. We naturally rebelled against this mad manifestation of entrenched antagonism to specialisation until it was conceded that we could all work for a half day each week in our speciality, provided that we ran a general medical clinic on another half day and took fourth year students on physical examination 2 other half days in the week. As all hospital work was honorary this left three days a week to earn an income.

Having completed training in neurology, I had thought that I might reasonably be asked to lecture in this discipline. I gave a

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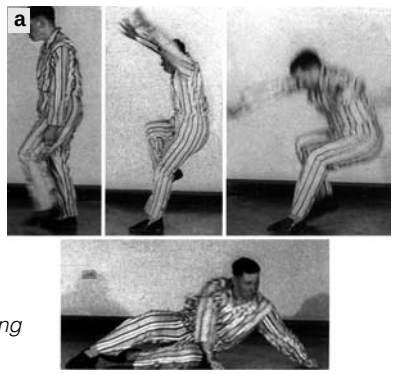
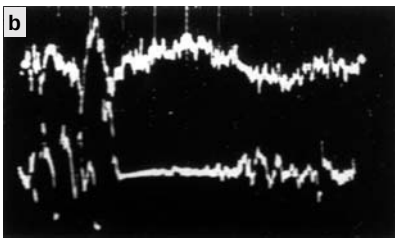
**1: Myoclonus**

In 1960, the cause of myoclonic falling attacks was not understood. Our investigations established that it was not the violence of the myoclonic jerking that caused the fall, but the following period of silence in all muscle groups.




*(a) Myoclonic jerk and falling attack.*




*(b) Sharp and slow wave seen in an electroencephalogram (upper trace) and myoclonic jerk followed by a silent period in an electromyogram (lower trace). Reproduced with permission from* Brain.[4]

series of lectures in physiology at Sydney University but the task allocated to me at Sydney Hospital was to give lectures to nurses on hygiene. The neurological topics were covered by the senior general physicians. When the opportunity arose for Sydney Hospital to be rebuilt on the Prince of Wales site at Randwick, the main teaching hospital of the new University of New South Wales Medical School, my spirits rose. They were dashed when the honorary staff voted by a small margin in favour of the status quo. I decided to jump ship.

Sir Kenneth ("Bob") Noad, senior physician at Sydney Hospital, kindly wrote to Dr Raymond Adams in Boston on my behalf and supported my application for a Lilley Travelling Fellowship. Dr Adams was the Bullard Professor of Neuropathology and Chief of the Neurology Service at the Massachusetts General Hospital. I was accepted to start there in August 1960.

There were 2 events worth recording in my four years as an "Honorary" before going to Boston. Bob Noad had looked after four members of a family with epilepsy that he passed on to my care. They had myoclonic jerks and falling attacks with cerebellar signs, known then as the Ramsay Hunt syndrome (a form of familial myoclonic epilepsy). Bob Noad and I reported the family in *Brain*.[2] This experience aroused my interest in myoclonus, which I was later able to investigate in Boston. The second was the suggestion by George Selby that we analyse the case histories of patients with migraine headache. The resulting article[3] was published in 1960 and is still quoted today. That work started me on the headache road.

My wife Judy and I arrived in Boston with our daughter Fiona in September 1960. While I was working in the centrally heated comfort of the Massachusetts General Hospital, Judy trudged through the snow of a cold New England winter, dragging one reluctant daughter and pregnant with another.

While in Boston I followed up my interest in myoclonus, working and publishing with Ray Adams on a group of patients with myoclonus after hypoxia, and on the cause of myoclonic falling attacks (Box 1).[4]

I completed another interesting project with Dr Robert Schwab, who ran the Parkinson's disease clinic at the Massachusetts General Hospital, on the relationship between action and resting tremors and cogwheel rigidity.[5] Neurological grand rounds were held in the Ether Dome, where ether was first used as a general anaesthetic in 1846 (Box 2). Foremost among the clinicians were Raymond Adams, Miller Fisher and Maurice Victor.

From Boston, I applied for the position of Chairman of Neurology at the Prince Henry and Prince of Wales Hospitals, which were to become the teaching hospitals of the Medical School of the University of New South Wales. To my great joy I was appointed. There are many legacies of the year in Boston — a lasting friendship with Raymond Adams, one of the great neurologists of the twentieth century, continuing contact with my colleagues in training at the Massachusetts General who went on to chair most of the major neurology departments in the US, honorary membership of the American Neurological Association, being a foundation member of the editorial board of *Annals of Neurology* and becoming the proud father of our second daughter, Sarah.

## Re-entry

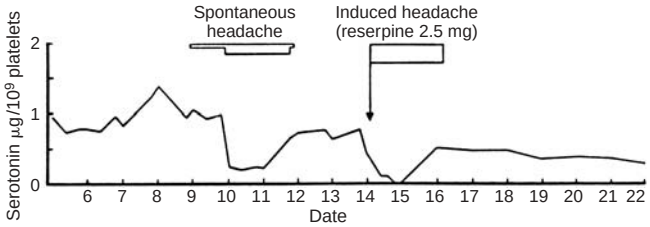
The task of creating a teaching hospital out of a run-down infectious disease hospital (Prince Henry) and a collection of wooden huts dating back to the First World War (Prince of Wales) was challenging. The great merit of Prince Henry was that it was a very happy hospital, superbly situated between the Pacific Ocean and Botany Bay with its own golf course. I set up a modest laboratory in a disused ward where our work on the neurophysiology of movement disorders began.

In investigating reflex actions we discovered that it was the vibration wave set up by percussion which was the essential trigger for tendon jerks, and this led to the discovery of the tonic vibration reflex, which had important clinical implications, and which led to collaboration with Karl-Erik Hagbarth in Sweden, who had recently discovered the same phenomenon.

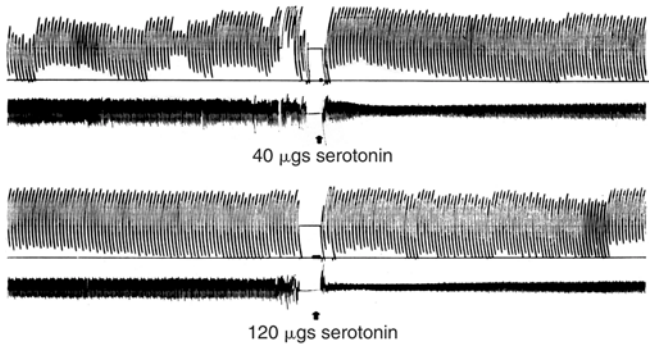
***2:*** *The Ether Dome of the Massachusetts General Hospital. Dr Miller Fisher on my right and Professor Raymond Adams on my left during a lecture visit in 1989.*

### 3: Serotonin and migraine

Our investigations of migraine in the 1960s clarified the role of serotonin and paved the way for others to find serotonin analogues that would be safe and effective in treating and preventing migraine.




*(a) Levels of platelet serotonin in a migrainous patient. The injection of reserpine releases serotonin from body stores. Platelets discharge serotonin at the onset of a migraine headache, whether spontaneous or induced. Both spontaneous and induced headaches were relieved by intravenous infusion of serotonin. Reproduced with the permission of the Editor of* Archives of Neurology.




*(b) The vasoconstrictor effect of intracarotid serotonin on the superficial temporal artery pulsation. The upper trace in each pair shows respiratory function, the lower, arterial pulsation. Reproduced with the permission of Karger Publishers (New York, Basel).*

Studies on the mechanism of spasticity and the control of movement were carried out with David Burke, David Gillies, Colin Andrews, Carlo Tassinari (visiting from Marseilles) and Peter Ashby (from Toronto). I have summarised the early motor studies and their clinical implications in the Wartenberg Address that I gave to the American Academy of Neurology in 1980[6] and in my book on clinical neurophysiology in which I collaborated with Jim McLeod.[7] I wish that the findings were more widely known to guide clinical neurologists today. It is necessary not only to make a discovery, but to repeat the findings at intervals to prevent the results from sinking into oblivion and to deter others from going through the same motions.

David Burke and Simon Gandevia later joined Ian McCloskey in founding the Prince of Wales Institute of Medical Research. The motor program, which started in a disused ward and moved to a basement under the EEG Department and then to an abandoned operating theatre at Prince Henry Hospital, now resides in handsome villas on the Prince of Wales site at Randwick.

## Headaches and serotonin

My interest in headache was reignited by observations made in 1959 and 1961 by Federigo Sicuteri in Florence and by a group at the Montefiore Hospital in New York in 1960. It appeared a paradox that a serotonin antagonist, methysergide, could prevent attacks of migraine and yet an infusion of serotonin itself could ease the headache. We had the good fortune to have a biochemist at Prince Henry Hospital, Herta Hinterberger, who was an expert amine chemist, to teach Don Curran (our first Research Fellow), and then Michael Anthony (our second), the mysteries of estimating serotonin (5-hydroxytryptamine, 5-HT) in blood. We found that serotonin was discharged from blood platelets at the onset of migraine headache. An intravenous infusion of serotonin would constrict cranial blood vessels and relieve the headache (Box 3).[8]

These and other of our observations on blood vessels in migraine came to the attention of Dr Patrick Humphrey in the Glaxo laboratories in England. He set out to find an analogue of serotonin that had its beneficial effects without its side effects of chest tightness and lightheadedness. At the time of our early studies, there were only 2 receptors known for serotonin. Now there are at least seven main groups with many subdivisions. Patrick Humphrey came up with a substance that was active at the B and D subtypes of the serotonin$_1$ receptor and named this sumatriptan. This and the other triptans developed later have proved to be highly effective agents in cutting short or preventing the development of migraine headache. It is gratifying that our observations qualify us to be godfathers to the triptans.

Our initial concentration on the vascular aspects of migraine was carried on by Ewan Mylecharane, pharmacologist, with Paul Spira, John Duckworth, Michael Welch (from the UK and US) and Jusef Misbach (from Indonesia) who quantified the effects on the monkey cranial circulation of various vasoactive agents and their antagonists with a potential use in migraine. Geoff Lambert took over the pharmacological reins in 1978 as the emphasis in migraine research moved to determining the cerebral mechanisms

***4:*** *Members of the headache research team, 1987, in front of the Clinical Sciences Building, Prince Henry Hospital. From left to right: (front row) Professor Michael Anthony, Professor James Lance, Mr. Mark Hellier (Technical Officer), Mr. Basil Daher (Biochemist); (middle row) Mrs Patricia Miller, Mrs Francine Skane (Secretaries), Mr Paul Charalambous (Histology Technician); (back row) Dr Geoff Lambert (Pharmacologist), Dr Peter Goadsby, Dr Alessandro Zagami (Research Fellows), Mr John Duckworth (Technical Officer).*

that could underlie vascular changes and be of significance in the genesis of migraine. Some of the headache research team are shown in Box 4.

Peter Goadsby and Richard Piper joined the team as BSc(Med) students in the early 1980s, followed by Rick Adams and Sandrino Zagami as Higher Degree candidates. A series of papers established the way in which the cerebral circulation of cat and monkey could be controlled by brainstem structures,[9] thus filling a gap in the hypothesis of migraine mechanisms.[10] Peter Goadsby continued research as a PhD and MD candidate investigating the pathophysiology of migraine, including a collaborative study of peptide neurotransmitters with Lars Edvinsson of Lund, thus forming our second Swedish connection. Peter later accepted an invitation from the Wellcome Foundation to set up a research department at the National Hospital, Queen Square, London. He joined me as a co-author for the sixth edition of my headache book,[11] which outlines the research that has led to the current hypothesis of the mechanism of migraine.

We have participated in many therapeutic trials including the triptans. Two early publications are worth mentioning. Don Curran and I conducted a double-blind controlled trial of amitriptyline for chronic tension headache in 1964,[12] which has been accepted as a main line of treatment since then. Michael Anthony and I[13] reported in 1969 on a successful open label trial of phenelzine for migraine patients resistant to other treatment which opened the door for the use of monoamine oxidase inhibitors when all else had failed.

## Odd neurological syndromes

In parallel with the research programs, our clinical work grew apace. We had close relationships with our neurosurgical colleagues under the leadership of Alex Gonski.

Among the routine case load unusual problems appeared from time to time.[14] We studied patients with phaeochromocytoma[15] to define the headache and "funny turns" of this disorder, as well as benign sex headache, "neck–tongue syndrome", visual hallucinations and paroxysmal dystonia.[16]

The arrival of Dr Peter Drummond, an experimental psychologist, brought a new dimension to our group's studies of the autonomic nerve system. He worked out the part that the sympathetic nervous system played in facial flushing and the mechanism of the unilateral flushing in harlequin syndrome[17,18] and clarified the nature of autonomic deficits in migraine and cluster headache.

There are always new diagnostic and therapeutic challenges arising from our patients' histories. Recent examples are the red ear syndrome[19] and the "blip" syndrome.[20]

## Epilogue

Surely neurologists must have one of the most exacting and exciting occupations in the world. I have been fortunate in being able to set up the first Academic Department of Neurology in Australia and being appointed a Professor of Neurology rather than Professor of Medicine. The struggle to have neurology regarded as a discipline separate from general medicine has been long, hard and eventually rewarding. I want to emphasise that the research described here is very much the result of a team effort, and I regret that I have not had enough space to record all of it or to mention here all those that have been involved. I am indebted to my wife Judy for so many things, not least for her tolerance of my deskbound habits. I have been shielded from the uglier side of paperwork and helped over the years by three wonderful secretaries — the late Margaret Kendall, Patricia Miller and Carol Flecknoe.

New techniques of studying cerebral function and dysfunction are granting us deeper insight year by year. I have no wish to be young again, but would not object to a 20 per cent discount so that I could observe further into the future. I am cheered by the fact that bright eyes and brighter minds are carrying on the exploration of the unknown.

## Acknowledgement

I am grateful to the Medical Illustration Unit of the Prince of Wales Hospital for preparation of these figures and for their constant support of our work over the years.

## References

1. Lance JW. Mentors in neuroscience. Peter Orlebar Bishop. *J Clin Neurosci* 2002; 9: 125-126.
2. Noad KB, Lance JW. Familial myoclonic epilepsy and its association with cerebellar disturbance. *Brain* 1960; 83: 618-630.
3. Selby G, Lance JW. Observations on 500 cases of migraine and allied vascular headache. *J Neurol Neurosurg Psychiat* 1960; 23: 23-32.
4. Lance JW, Adams RD. The syndrome of action or intention myoclonus as a sequel to hypoxic encephalopathy. *Brain* 1963; 86: 111-136.
5. Lance JW, Schwab RS, Peterson EA. Action tremor and the cog-wheel phenomenon in Parkinson's disease. *Brain* 1963; 86: 95-110.
6. Lance JW. The control of muscle tone, reflexes and movement: Robert Wartenberg Lecture. *Neurology* 1980; 30: 1303-1313.
7. Lance JW, McLeod JG. A physiological approach to clinical neurology. 3rd ed. London: Butterworths, 1981.
8. Anthony M, Hinterberger H, Lance JW. The possible relationship of serotonin to the migraine syndrome. *Res Clin Stud Headache* 1969; 2: 29-59.
9. Goadsby PJ, Lance JW. Brainstem effects on intra- and extracerebral circulations. Relation to migraine and cluster headache. In: Olesen J, Edvinsson L, editors. Basic mechanisms of headache. Amsterdam: Elsevier, 1988: 413-427.
10. Lance JW, Lambert GA, Goadsby PJ, Zagami AS. Contribution of experimental studies to understanding the pathophysiology of migraine. In: Sandler M, Collins GM, editors. Migraine: a spectrum of ideas. Oxford: Oxford University Press, 1989: 21-39.
11. Lance JW, Goadsby PJ. Mechanism and management of headache. 6th ed. Oxford: Butterworth-Heinemann, 1998.
12. Lance JW, Curran D. Treatment of chronic tension headache. *Lancet* 1964; 1: 1236-1239.
13. Anthony M, Lance JW. Monoamine oxidase inhibition in the treatment of migraine. *Arch Neurol* 1969; 21: 263-268.
14. Lance JW. Unusual syndromes in neurological practice. *Med J Aust* 1984; 140: 409-416.
15. Lance JW, Hinterberger H. Symptoms of pheochromocytoma with special reference to headache correlated with catecholamine production. *Arch Neurol* 1976; 33: 281-288.
16. Lance JW. Familial paroxysmal dystonic choreoathetosis and its differentiation from related syndromes. *Ann Neurol* 1977; 2: 285-293.
17. Lance JW, Drummond PD, Gandevia SC, Morris JG. Harlequin Syndrome : the sudden onset of unilateral flushing and sweating. *J Neurol Neurosurg Psychiat* 1988; 51: 635-642.
18. Drummond PD, Lance JW. Mechanisms of normal and abnormal facial flushing and sweating. In: Low PA, editor. Clinical autonomic disorders. 2nd ed. Philadelphia: Lippincott-Raven, 1997: 715-726.
19. Lance JW. The red ear syndrome. *Neurology* 1996; 47: 617-620.
20. Lance JW. Transient sensations of impending loss of consciousness (the "blip" syndrome). *J Neurol Neurosurg Psychiat* 1996; 60: 437-438.

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