THE BEGINNINGS OF SLEEP MEDICINE AT THE ALFRED HOSPITAL

The year 1969 saw the beginnings of what would become the new discipline of Sleep Medicine at the Alfred Hospital and Monash University Medical School. This involved a pioneering research program, based at the Alfred Hospital, Department of Surgery. Between 1969 and 1973, many different aspects of sleep physiology were investigated in healthy volunteers and in hospital patients, particularly looking at the effect of major surgery with cardio-pulmonary by-pass on patients' sleep. This meant making 24-hr recordings in the ward before surgery and in the Intensive Care Unit during the post-operative period. This had never been done before.

It was John Masterton who initiated this research, with the strong support of Hugh Dudley, the foundation Professor of Surgery at Monash. John had done some sleep research in Greenland when he joined the British North Greenland Expedition as Medical Officer and Physiologist in 1952-54. He was then in the Royal Navy for his national service. He investigated changes in the duration and timing of sleep, reported in sleep diaries, as a result of prolonged daylight and dark in the artic summer and winter. This kind of sleep research was done then by physiologists, influenced heavily by the pioneering work of Nathaniel Kleitman at the University of Chicago.

It was in Kleitman's department that rapid-eye-movement (REM) sleep was first described in 1953. That was also where William Dement demonstrated the relationship between dreaming and REM-sleep in adults. Dement suggested that a temporary psychosis could result if subjects were deprived of REM-sleep (but still having non-REM sleep) for several nights. This was later proven to be wrong. Nevertheless, because of this pioneering research, wakefulness, non-REM sleep and REM-sleep were recognized as three distinctly different states that we alternate between regularly. This provided a great stimulus around the world for sleep research.

By 1965 it was becoming clear, particularly from Ian Oswald's sleep laboratory in Edinburgh, that many drugs, including the barbiturate and other sedatives and hypnotics that were widely used then, inhibited REM-sleep at first and caused an excess of REM-sleep (REM-sleep rebound) upon drug withdrawal. Alcohol ingestion had a similar effect on REM-sleep. Rapid withdrawal from alcohol after acute intoxication could also cause delirium tremens, a relatively common cause of acute brain syndrome in hospital wards. Delirium tremens was shown to involve an excess of highly fragmented REM-sleep, as if this were a REM-rebound phenomenon. Questions arose therefore about the possible role of sleep fragmentation and of REM-sleep in other forms of acute brain syndrome. This was a particular problem for about 20% of patients who had cardio-pulmonary by-pass surgery, and who were in the intensive care ward for several days. They developed a temporary psychosis which resolved after a few days or weeks. Preliminary observations suggested that the sleep of such patients was interrupted frequently by the staff and procedures involved in their 24-hr care.

After his years as Junior (1967) and then Senior (1968) Resident Medical Officer at the Alfred Hospital, Murray Johns took up the challenge of investigating the sleep of patients in those very difficult circumstances. He became an NHMRC Research Scholar in the Department of Surgery (1969-71) and then Edward Wilson Research Scholar, Alfred Hospital, in 1972. During that time he completed the first PhD on clinical sleep medicine in Australia. He did this from the point of view of an applied human physiologist who happened to work in a Department of Surgery. This was very unusual in itself, but entirely consistent with the ideas of Hugh Dudley and John Masterton, whose thinking about the care of surgical patients was many years ahead of its time.

By 1968 there was an international consensus about defining and monitoring sleep in its various stages (Rechtschaffen & Kales, 1968). A combination of EEG, electro-oculogram (EOG) which recorded eye movements, and electromyogram (EMG) recorded from under the chin, was advocated then and is still used today. With help from Ian Oswald, a psychiatrist and pioneer of sleep research in Edinburgh, a sleep laboratory was set up in the Monash Department of Surgery, Alfred Hospital, in 1969.

There was also a biomedical engineering laboratory in the Department of Surgery, with Bruce Cornell the Technical Officer. Because there was no one in Melbourne that knew much about sleep, Murray Johns, Bruce Cornell and John Masterton taught themselves by spending many nights in the sleep laboratory observing the sleep recordings of healthy volunteers on an oscilloscope. Other sleep laboratories around the world at that time used ink-writing polygraphs to record the masses of data on hundreds of metres of paper for one night. However, to monitor the sleep of patients in surgical wards, unique technology was required, with a transportable magnetic tape recording system that could be housed under the patient's bed. This was made in the Department of Surgery.

Incidentally, Bruce Cornell went on to do a PhD in physics at Monash, investigating the interaction between anaesthetic agents and cell membranes, an interest kindled by John Mainland who was Senior Lecturer (anaesthetics) in the Department of Surgery. Bruce later worked at CSIRO, and in more recent years at Ambri Ltd in Sydney, applying that knowledge to become a world authority on nanotechnology relating to membranes, both natural and synthetic.

The experiment on the sleep of surgical patients was completed successfully. Six patients were studied, five of whom had either aortic or mitral valve replacement with cardio-pulmonary by-pass, and one had major abdominal surgery after a large-bowel obstruction. Two patients had "post-cardiotomy delirium" after being lucid for the first two or three post-operative days. They did not show any localizing neurological signs, but did have retinal microemboli, with platelet and crystalline (?cholesterol) aggregates demonstrated by Ilsa Williams, a neuro-ophtahlmologist in the Department of Medicine. She performed pre- and post-operative fluoroscein retinal angiography on the same patients as a parallel study. The by-pass machine did not have a blood filter on it then that might have reduced this problem.

The patients' sleep was frequently disturbed during their stay in the ICU because of medical, nursing, and physiotherapy requirements. REM-sleep was absent during the first few post-operative days and nights, and for much longer in the patients who became

delirious. There was no REM-sleep rebound later, which was quite unexpected. It was concluded that cerebral dysfunction because of "microembolic encephalopathy" was a more important cause of "post-cardiotomy delirium" than was sleep fragmentation and REM-sleep deprivation. The latter were more the result than the cause of the central nervous system disturbance, during which patients were unable to maintain either wakefulness or sleep, even when undisturbed. Their acute brain syndrome was quite different from that in delirium tremens. It was more than a decade before another research group, this time from Scandinavia, repeated this difficult experiment with essentially the same results.

Other important aspects of sleep physiology and pharmacology were investigated for the first time in Australia in the Sleep Laboratory at the Alfred Hospital. For example, experiments done in collaboration with Brian Hudson's group at the Monash Department of Medicine, Prince Henry's Hospital, investigated the episodic secretion of many hormones (cortisol, growth hormone, TSH, LH, FSH, estradiol, testosterone) and their relationship to sleep and wakefulness. The first sleep laboratory study in Australia of a new benzodiazepine hypnotic drug, flurazepam, was carried out at the Alfred in 1971. The sleep habits of medical and surgical patients when at home were described in detail for the first time. The psychophysiology of insomnia was investigated, the role of psychological distress was highlighted, and relationships between sleep and thyroid function were demonstrated.

Sleep research often involves multi-disciplinary studies, with physiologists, clinical psychologists, psychiatrists, endocrinologists, neurologists, etc, collaborating. That was certainly true of the first sleep laboratory at the Alfred Hospital. For example, David Bruce collaborated as a clinical psychologist, and Allan Large as a Psychiatrist. What is of some interest now is the fact that the importance of sleep-disordered breathing was not recognized then. There had been early reports of respiratory irregularity and apneas occurring even in "normal" subjects during REM-sleep, but the enormous clinical and public health significance of obstructive sleep apnea was yet to be grasped.

It was not until after 1981, when Collin Sullivan at Sydney University developed nasal CPAP as a successful treatment for sleep apnea, that respiratory physicians became heavily involved in sleep medicine worldwide. Glen Bowes began this second phase of sleep medicine at the Alfred Hospital from the mid 1980's, treating patients with obstructive sleep apnea in the Department of Respiratory Medicine.

Since then, Sleep Medicine has become a separate discipline with its own Board examinations in the USA. In Australia, there are about a hundred sleep clinics now, investigating and treating sleep disorders, particularly obstructive sleep apnea and snoring. Sleep Medicine is now practiced by specially trained physicians who are often trained in Respiratory Medicine too, although there are also some neurologists, pediatricians and others. ENT surgeons are also involved, with palatal and nasal surgery for sleep-disordered breathing. Specially trained clinical psychologists have an important role to play, particularly in the behavioural treatment of insomnia. The Alfred Hospital continues to play a major role in Sleep Medicine, providing a much-needed clinical service and because of the outstanding work by Matthew Naughton and his group of researchers and clinicians on the role of sleep-disordered breathing in heart failure.

Murray Johns left the Alfred Hospital in 1973 and went on to do further sleep research at the Brain Research Institute, University of California Los Angeles, and later at the MRC Environmental Physiology Unit in the UK. After a stint in general practice in Melbourne, he set up the Sleep Disorders Unit at Epworth Hospital in 1988, diagnosing and treating patients with the whole range of sleep disorders. This was the first sleep laboratory in the world that used only digital methods for polysomnography. Murray designed that equipment in conjuction with David Burton of Compumedics Pty Ltd, who manufactured it in Melbourne and later supplied it to many other sleep laboratories in Australia and overseas.

Based on his broad experience of Sleep Medicine at the Alfred and elsewhere, Murray created the Epworth Sleepiness Scale in 1991 which has become the world standard for measuring a person's general level of sleepiness in daily life. It appears that 10-15% of

the whole adult population are chronically too sleepy as a result of insufficient sleep and a variety of sleep disorders. Murray retired from the Epworth Sleep Centre in 2002. Because of his concerns about the public health problem of excessive daytime sleepiness, he is developing a new method (Optalert™) for monitoring the drowsiness of active people, such as drivers. It is estimated that about 20% of highway crashes are caused by the drowsiness of drivers, in Australia and elsewhere. The word drowsiness still does not appear in text books, whether of general medicine, neurology or psychology, and is seldom used in clinical practice. However, it is a word that we can expect to see and hear much more frequently in the future as the role of Sleep Medicine becomes more established.

Murray Johns
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