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Elected FRS 1983

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David Marsden was the most outstanding UK clinical neuroscientist of his generation, making key discoveries in the neurophysiology, neurochemistry and clinical aspects of diseases of the basal ganglia, and their normal function. His legacies are the establishment, with Stanley Fahn in the USA, of movement disorders as a subspecialty within neurology, of the international Movement Disorder Society, and of the journal *Movement Disorders*; his ex-students and fellows around the globe; and his research and teaching output embodied in his extraordinarily prolific publication record of more than 1360 papers, books and chapters, culminating in the posthumous completion and publication in December 2011 of *Marsden’s book of movement disorders*, a project he had started in 1984. All of these were achieved through the combination of his intellect and drive, his communication skills, and his forceful and charismatic personality.

BACKGROUND, EARLY LIFE AND EDUCATION

(Charles) David Marsden (‘CDM’) was born on 15 April 1938 at 4 Sydenham Road, Croydon, the elder of the two sons of Charles Moustaka Marsden CBE, a captain in the Royal Army Medical Corps, and Una Maud née Bristow. Charles Moustaka was born in Australia, the son of a New Zealander ear, nose and throat surgeon whose Australian wife was of Greek ancestry, her maiden name being Moustaka. Una Maud, a Guy’s-trained nurse in the Queen Alexandra Nursing Service, was born in India, where she met and married...

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David’s father. David was therefore an army child and a war child, despatched to English boarding schools while his father moved between postings in the Empire, and mainly looked after by a grandmother. He first attended St Peter’s preparatory school in Seaford, Sussex. His secondary education, from 1951 to 1956, was at Cheltenham College, although at the end of his last year he was suspended for smoking and had to sit his exams as a day pupil. He entered St Thomas’ Hospital Medical School in 1956. There, in addition to winning three scholarships, an exhibition, five prizes and two medals, he represented the hospital at cricket and rugby, having earlier captained England Schoolboys at scrum half. He was also a keen sailor, and crewed in two Fastnet races while a medical student. One contemporary described him as ‘a meteor’!

After preclinical training he obtained a first-class honours degree in his intercalated BSc in 1959, under Professor D. V. (Dai) Davis, formerly editor of *Gray’s anatomy*, who discovered, encouraged and fed his interest in the neurosciences. He went on to obtain an MSc in 1960, with a thesis on pigmentation in the substantia nigra that established his abiding interest in diseases of the basal ganglia of the brain, foremost among which is Parkinson’s disease (PD). He qualified MB BS in 1963, and obtained his MRCP in 1965. Within two years of qualifying he became a lecturer in medicine at St Thomas’ for two years. He then spent the following two years as a senior resident house physician at the National Hospital (for Nervous Diseases), in Queen Square in Bloomsbury (previously the National Hospital for the Paralysed and Epileptic, and today the National Hospital for Neurology and Neurosurgery).

**The Denmark Hill years, 1970–87**

In 1970, only seven years after qualifying, David was appointed Senior Lecturer in Neurology at the Institute of Psychiatry and Honorary Consultant Neurologist to the Maudsley and Bethlem Royal Hospitals and to King’s College Hospital. Two years later, at the age of 34 years, he was the first appointee to the newly established joint Chair of Neurology at the Institute of Psychiatry and King’s College Hospital Medical School, which straddled Denmark Hill.

The Maudsley was one of the so-called ‘special hospitals’ in the London area. To each was attached an institute of the University of London. Thus the Maudsley was the special hospital for psychiatry, to which was attached the Institute of Psychiatry, in a manner parallel to the National Hospital, to which was attached the Institute of Neurology. Moreover, like mirror images, the Institute of Psychiatry with King’s College Hospital Medical School contained the Joint University Department of Clinical Neurology, and the Institute of Neurology contained a Section of Neuropsychiatry.

These links were of particular importance given Marsden’s field of interest. First, many movement disorders, such as PD, Huntington’s disease and Tourette syndrome, encompassed both neurological and psychiatric or cognitive features. Second, the neuroleptic drugs widely used in psychiatry could themselves cause a variety of movement disorders, including drug-induced parkinsonism, acute dystonic reactions and delayed but chronic tardive dyskinesia and dystonia, and a state of motor restlessness called akathisia (‘not sitting’), all of which could be witnessed in the corridors and wards of the Maudsley. Third, some organic movement disorders, particularly the various presentations of dystonia, had hitherto been considered psychogenic. Conversely, there was also a significant number of patients who did have psychogenic
movement disorders. At this time the greatest challenge was the former, but late in Marsden’s life the pendulum swung when he, and others, realized how frequent the latter cases were in specialist movement disorder clinics. Fourth, the UK’s first Professor of Neuropsychiatry, Alwyn Lishman, was also at the Maudsley, and he and Marsden cross-referred patients and cross-fertilized ideas.

On the neurology side, there were three other consultants, two of whom, David Parkes (PD and narcolepsy) and Ted Reynolds (epilepsy), like Marsden, were academic clinicians with joint appointments at King’s and the Maudsley. The two Davids together established a specialist PD clinic at King’s, and Marsden established a clinic for other rarer and more esoteric movement disorders at the Maudsley.

On the laboratory side, Marsden set about recruiting promising young workers, including Peter Jenner and John Rothwell (see contributions below), to develop his interest and work in neuropharmacology and neurophysiology, respectively. Subsequently he recruited Richard Brown, later joined by Marjan Jahanshahi, to explore neuropsychological aspects of movement disorders.

He established a purpose-built unit in Windsor Walk, at one corner of the Maudsley estate, to accommodate his research team (figure 1). He co-founded and directed, with Andrew Lees, the UK Parkinson’s Disease Society Brain Bank, which subsequently moved with him to Queen Square and today thrives as the Queen Square Brain Bank for Neurological Disorders.

Marsden’s time at Denmark Hill really constituted his golden years of productivity and camaraderie with a host of fellows and visiting researchers drawn by his growing reputation. The first was Roger Duvoisin (USA), followed by very many others too numerous to name, but including Paul Bedard (Canada), Mark Hallett and Dan Tarsy (USA), Wolfgang Oertel and Reiner Benecke (Germany), Alfredo Berardelli, Alberto Albanese, Giovanni Abbruzzese and Fabrizio Stocchi (Italy), Tony Lang (Canada), Jose Obeso (Spain) and Philip Thompson (Australia), all of whom went on to become international leaders in the field of clinical and academic movement disorders (figure 2). A fuller list of 44 of them from 17 different countries who later went on to be appointed full professors is given in Appendix 1 in the electronic supplementary material online.

David’s most critical interaction and collaboration was with Stanley Fahn (figure 3), Houston Merritt Professor of Neurology at the Neurological Institute in Columbia Presbyterian Hospital in New York. They founded the Movement Disorder Society together with others (figure 4) in 1985, and shortly thereafter the journal Movement Disorders in 1986, of which they were co-editors for its first 10 years.

In 1987 two of us (N.Q. and P.J.) co-organized a Symposium on Movement Disorders at the Institute of Psychiatry, attended by 200 delegates and 33 speakers, all collaborators or former fellows, to celebrate David’s contributions to the field. Little did we know that there would never be the opportunity to organize a Festschrift at the end of his career. Gerald Stern, the senior Movement Disorder specialist at University College Hospital, speaking from the audience, famously prefaced a question with the observation that he must have been the only person in the room never to have written a paper with David Marsden! The speakers, and others in the audience, all willingly submitted 39 manuscripts for a volume of proceedings, which became known affectionately as the ‘butterfly book’ (we were interested to put a personal stamp on the cover and, Denmark Hill being in Camberwell, settled upon a picture of a Camberwell Beauty butterfly).
Figure 1. Opening of the UK Parkinson’s Disease Society-financed extension to the Windsor Walk Marsden Laboratories at the Institute of Psychiatry in May 1984. From left to right, front row: Dr Niall Quinn, Dr Giovanni Abbruzzese, Mrs Beth Williams (academic secretary), Dr Marie-Helene Marion, Professor David Marsden, Miss Pat Jenkins (Beth’s predecessor). Behind: Professor David Parkes, Dr Fabrizio Stocchi, Dr Brian Day, Dr Chris Carter, Dr John Rothwell, Dr Alfredo Berardelli, Dr Teruhiko Kachi.

Figure 2. Second meeting of the ‘CDM club’, at which clinical ex-fellows would gather to give talks and celebrate David Marsden, at the National Hospital, Queen Square, on 4 November 2003, almost 20 years after the photo in figure 1 was taken. From left to right, back row: Professor Jose Obeso, Professor Philip Thompson, Professor Alfredo Berardelli, Professor John Rothwell, Professor Yves Agid (collaborator), Professor Mark Hallett, Professor Brian Day. Front row: Dr Michael Sheehy, Professor Marjan Jahanshahi, Professor Tony Lang, Professor Fabrizio Stocchi, Professor Giovanni Abbruzzese, Dr Marie-Helene Marion, Professor Reiner Benecke, Professor Niall Quinn. (Reproduced courtesy of the National Hospital for Neurology and Neurosurgery/Institute of Neurology.) (Online version in colour.)
Return to Queen Square, 1987–98

After 17 years south of the river, Marsden moved back to Queen Square in 1987. At that time, Andrew Lees was the only card-carrying Movement Disorder specialist based at the National, and he and Marsden decided to keep their clinical and research teams separate, although they collaborated in many areas and particularly on studies based on brain bank material. On the academic side he succeeded Roger Gilliatt, who had been the first incumbent of the Chair of Clinical Neurology at the Institute of Neurology. Marsden held this chair until 1995, when he stepped aside to become dean of the institute. He was delighted that Anita Harding, with whom he had a close professional relationship, was appointed to succeed him, but was greatly
affected by her death at the age of 41 years, in September 1995 (only four months after being diagnosed with cancer), the month before she was due to take up the chair; Ian McDonald stepped in to run the department.

He did not greatly enjoy his three-year tenure as dean, but derived his satisfaction from his ongoing scientific and clinical work, continuing to do three clinics, a ward round and a ‘book round’, and Grand Rounds every week. However, he experienced bouts of depression, which led to difficulties with his home life and subsequently divorce from Jenny in 1998. In September of that year he started his first-ever sabbatical year, as a Fogarty Fellow at the National Institutes of Health in Bethesda, Maryland. However, on 29 September, only four weeks into his visit, he died suddenly and unexpectedly in Washington DC, at the age of 60 years (figure 5).

**HONOURS AND ACHIEVEMENTS**

Marsden was outstanding as a clinical neurologist and as a neuroscientist, and one of very few people to achieve eminence in both disciplines. He was a brilliant teacher and educator who inspired many trainee neurologists to sub-specialize in movement disorders.

He was awarded Membership of the Royal College of Psychiatry in 1978, elected a Fellow of the Royal Society in 1983, and received a DSc from London University in 1984. He was on the Council of the Royal Society from 1991 to 1993, of the Royal College of Physicians from 1995 to 1998, and of the Medical Research Council (MRC) from 1989 to 1994.

His lectures were marvels of lucidity and precision, and he was much in demand, leading to 40 visiting professorships in 18 countries. He gave 34 named lectures, including the Milton
Shy, Wartenburg, Geschwind and Merritt Putnam lectures in the USA, the Charcot Lecture in France, and the Aubrey Lewis and Maudsley lectures in the UK. Before his 10-year stint as co-editor-in-chief of Movement Disorders, he had edited the Journal of Neurology, Neurosurgery and Psychiatry for a decade, and was on the editorial boards of a further 21 journals (see his curriculum vitae in Appendix 2 in the electronic supplementary material online). His publication record was prolific, with 1368 publications (an average of one every week for the 24 years from 1975 to 1998), including more than 800 original papers, and a peak of double that rate in 1986. In Who’s who he listed his recreation as ‘The human brain’.

Contributions to Clinical Neurology (by N.Q.)

Like Peter Jenner and John Rothwell, I too first encountered David Marsden in the 1970s, during my first-ever neurology post, in 1976, as Senior House Officer, at the Maudsley and King’s College Hospitals. Here, because of Marsden’s inspirational teaching, I became ‘hooked’ on movement disorders. I returned in 1980 as a research fellow, then lecturer, later following him to Queen Square in 1988, where I worked with him, ultimately as a professorial colleague, until just before he died in 1998, so my personal experiences and recollections cover mainly the 18 years from 1980.

For the uninitiated reader, I should expand on the term movement disorders, which applies to the clinical conditions resulting principally from disease or dysfunction of several structures deep in the brain that are collectively called the basal ganglia. These include the dopaminergic substantia nigra in the midbrain (nigra because it contains the dark pigment neuromelanin), the noradrenergic locus coeruleus in the pons (another brainstem nucleus), and more rostrally the caudate nucleus and putamen (striatum) and globus pallidus (pallidum) and subthalamic nucleus (STN). Their connections and pathways are often referred to as the extrapyramidal system.

The clinical disorders of the basal ganglia can manifest as a combination of akinesia (poverty and slowness of movement, and fatiguing and decrement of repetitive movements) and rigidity (an increase in muscle tone evident on passively moving a joint), the so-called akinetic–rigid syndromes, the principal example being PD. Alternatively, there may be excessive movement (hyperkinesia or dyskinesia) of several types: tremor, a rhythmic alternating movement seen in essential tremor (ET) and in most patients with PD; dystonia, a syndrome characterized by sustained movements or postures, perhaps most familiar to readers as seen in athetoid cerebral palsy; and finally three types of jerky movement, namely tics, which are stereotyped movements seen classically in (Gilles de la) Tourette syndrome; myoclonus, brusque electric shock-like muscle twitches; and the unpredictable flow of movements of chorea, for example in Huntington’s disease. ‘Higher-order’ disorders of gait, and diseases of the balance organ or cerebellum, have also found a home under the rubric of movement disorders.

David Marsden’s laboratory work on the physiological and neurochemical bases of these disorders is outlined below by my co-authors. My task is to give some examples of the breadth and importance of his clinical contributions and collaborations.

PD was, and remains, the prototypic movement disorder, important because of the unraveling of its clinicopathological correlations and underlying neurochemical deficits and because it was one of the first, and few, neurological diseases with dramatically effective treatment. However, it is still not yet curable or preventable, and these remain the twin current goals of research.
It had been demonstrated that the nigrostriatal tract, which uses dopamine as its neurotransmitter, degenerates in human PD. In the 1950s and 1960s it was shown that drugs that depleted brain dopamine caused akinesia in rats, and that this could be reversed by the administration of the amino acid L-dopa (L-3,4-dihydroxyphenylalanine, the precursor of dopamine). In the 1960s it was shown that L-dopa gave striking symptomatic benefit in humans with PD, as vividly portrayed in the film ‘Awakenings’. However, L-dopa also had drawbacks: the drug has a very short half-life in the blood, and hence in brain also, so that sooner or later treated patients found that their 6-hourly doses lasted for progressively shorter periods (‘motor fluctuations’ or ‘end-of-dose deterioration’), sometimes precipitating them abruptly back to a state of severe immobility (the ‘on–off phenomenon’). At the same time, when L-dopa doses were working, patients experienced an overshoot from not enough movement to L-dopa-induced unwanted excessive involuntary movements (dyskinesias). These twin problems of the long-term L-dopa syndrome were elegantly chronicled by the two Davids (9)*.

In addition, David Marsden and his co-workers were among the first to stress the non-motor features of PD, in studies on pain, olfaction, bladder dysfunction, alertness and attention. With Anne Marie Gotham, Richard Brown, Marjan Jahanshahi and Trevor Robbins (at Cambridge University) he supervised studies of the prevalence and characteristics of depression, of dementia, and of more subtle, mainly frontal, cognitive deficits in patients with PD, with additional comparisons with patients with other atypical parkinsonian disorders such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) (53).

Throughout his career, David supervised numerous clinical trials in PD and other movement disorders. He trialled virtually every drug used in PD. In view of the short half-life of L-dopa, one focus was to achieve a more constant and continuous delivery of dopaminergic medication to the blood, and hence the brain. He supervised work on controlled-release oral formulations of L-dopa; on continuous intravenous infusions of L-dopa; on oral, intragastric and intravenous administration of L-dopa methyl ester, a more soluble pro-drug of L-dopa; and on the oral and subcutaneous delivery of lisuride, a soluble dopamine agonist. One particular drug development programme that exemplified his bench-to-bedside translational research was with the dopamine agonist PHNO that had potential for administration by transdermal patch, this parenteral route offering the promise of stable blood levels of the drug throughout the day and night. The compound was initially tested by Hiro Nomoto (35) in Peter Jenner’s marmoset model using methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), by oral and transdermal routes. It was then given in successively phased studies in a group of six fluctuating PD patients, first by single oral dosing, next by nasogastric infusion, then, to scale down the dose for more effective parenteral delivery, by intravenous infusion, and finally, and successfully, by transdermal skin patch delivery. Unfortunately the compound fell at the last pre-registration hurdle because of a toxicology issue, but this work presaged the successful introduction of the rotigotine transdermal patch 15 years later. David’s work on a range of dopamine agonists and antagonists led him to the conclusion that, as regards D-1 and D-2 dopamine receptors, it was D-2 receptors that determined motor and endocrine effects in PD (20).

When I first worked for David in 1976, computed tomography (CT) scanning was just beginning, and when I returned in 1980 magnetic resonance imaging (MRI) scanning had just been developed. Results from both, it turned out, were normal in PD patients (and also in patients with primary dystonia), although MRI was useful in diagnosing atypical parkinsonian

* Numbers in this form refer to the bibliography at the end of the text.
disorders and some of the dystonias secondary to other diseases. David capitalized on CT, and later the greater structural resolution of MRI, in clinic-radiological and clinic-pathological studies with Jose Obeso and Tony Lang (30), Myung Sik Lee (54), Kailash Bhatia (55) and others of correlations between focal structural lesions in basal ganglia and thalamus and their associated clinical syndromes.

In contrast, positron emission tomography (PET) scanning gave insights into the neurochemistry of the brain, and 18F-dopa PET scanning in particular could reveal in vivo whether or not a subject had a structural lesion of the nigrostriatal tract undetectable on CT or MRI. David collaborated with the MRC Cyclotron Unit at the Hammersmith Hospital, initially with Richard Frackowiak and David Brooks, and later with David Brooks and Paola Piccini. As well as using the technique to study PD and the results of transplantation in that disease, we also undertook several PET studies looking at patients with PD, MSA and PSP, revealing evidence of the known pathological lesions of substantia nigra in all three of these parkinsonian conditions, but normal findings in drug-induced parkinsonism, essential tremor and dystonia. In particular, 18F-dopa PET scans (46) could distinguish between young individuals with dopa-responsive dystonia (DRD) due to a metabolic block in the L-dopa synthetic pathway, who responded dramatically to low doses of L-dopa without developing the long-term L-dopa syndrome, and others with juvenile parkinsonism involving nigral cell loss, in whom treatment with L-dopa was best delayed because it would cause early motor fluctuations and dyskinesias. Marsden published several definitive studies of DRD in collaboration with Stanley Fahn and a young American fellow of his, Toby Nygaard, who visited our cases and examined virtually all the other cases hitherto reported in the world (47). The causative genetic defect was found in 1994 to be mutations in the GTP cyclohydrolase gene on chromosome 14.

David was intimately involved in an important and fruitful long-term collaboration on the surgical grafting of human fetal nigral cells into the striatum of PD patients with the Swedish team headed clinically by the neurologist Olle Lindvall and the neurosurgeon Stig Rehncrona, and scientifically by Anders Björklund, at the Wallenberg Neuroscience Centre at Lund University in Sweden. They had undertaken a great deal of preclinical work before, in the early 1980s, grafting the first two (of an ultimate total of 16) patients with PD. The results were negative in these two cases, so the team went back to the drawing board to see what elements of the procedure could be improved on, and approached David to enhance the scientific and intellectual input to the project, and subsequently to widen it to include five of our own patients. Neuropsychological and neuropsychological assessments were done on all patients operated on in Lund, by John Rothwell and Marjan Jahanshahi at Queen Square, and PET studies of 18F-dopa uptake in striatum (where the nigral grafts were placed) were done by David Brooks and Paola Piccini at the Hammersmith MRC Cyclotron Unit. Lund patients 3 and 4 were the first clinically successful graft recipients (43). Subsequent patients received grafts unilaterally either into putamen alone, or into putamen and caudate if there was enough tissue, and followed closely for a year, after which they received grafts on the second side, and were again followed up indefinitely (57). A subsequent small cohort had almost synchronous bilateral grafts, separated by two weeks, and a further small group received preoperative experimental treatments of both subject and grafted tissue before implantation, intended to enhance grafted cell survival. Overall the results were variable between patients, but some, including two of our five patients from Queen Square, operated on in 1993 and 1996, improved markedly in all respects (clinical, physiological and PET scanning of dopaminergic function in grafted neurons). At the time of completing this memoir in 2012, these two individuals have...
been completely off dopaminergic medication for a decade and are still remarkably mildly
affected 19 and 16 years after grafting, after 28 and 27 years of disease respectively, dem-
onstrating that, if the conditions are right, fetal nigral grafting can be strikingly successful in
some, but not all, recipients. David would have been fascinated to learn that, when one of our
other patients died 12 years after grafting, his brain showed the presence of Lewy bodies, a
pathological hallmark of PD, in 5% of the surviving fetal nigral neurons (Li et al. 2008). This
has opened fascinating new possibilities of mechanisms by which the disease process can be
transmitted from cell to cell, and from host to grafted tissue.

After PD, David Marsden’s main interest was in dystonia, which had for many years
been poorly understood, and often misdiagnosed as psychogenic. For example, the move-
ments in patients with adult-onset focal dystonias such as blepharospasm (contractions of
orbicularis oculi muscle causing involuntary eye closure) and spasmodic torticollis (caus-
ing neck rotation), were interpreted by many as being due to the patient’s not wishing to
see something psychologically distressing. David firmly established these conditions as
organic, and clearly demonstrated the division between patients with adult-onset focal
dystonia, who only occasionally gave a positive family history, and others with the rarer,
more severe, young-onset progressive generalized primary dystonia, who frequently had
other similarly affected relatives. With Anita Harding, then recently appointed Professor of
Neurogenetics at Queen Square, he launched family genetic studies of generalized dystonia
with Nick Fletcher (44) and focal dystonias with Heather Waddy (48), which helped to set
the scene for the subsequent linkage and identification by Stan Fahn’s group of the DYT1
dystonia gene (now called TOR1A) responsible for primary generalized (Oppenheim’s)
dystonia.

Until the early 1980s there was no effective treatment for these conditions. However,
David, together with John Lee and John Elston at Moorfield’s Eye Hospital, was the first to
introduce botulinum toxin injections in the UK to treat blepharospasm, and later, with Rick
Stell and Geoff Sheean, spasmodic torticollis, long before their wholesale adoption as vanity
treatments by legions of private cosmetic surgeons, and even dentists!

In addition to these areas highlighted above, David also published many key papers on
(besides other topics) other aspects of dystonia, on Huntington’s disease and other causes of
chorea such as neuroacanthocytosis, on essential tremor, on the extrapyramidal side-effects of
neuroleptic drugs, on the stiff person syndrome and allied disorders, on gait disorders, and on
progressive myoclonic ataxia. He also wrote several influential papers on hysteria, and then
on apraxia, a difficult topic that he planned to further elucidate during his sabbatical at the
National Institutes of Health.

**CONTRIBUTIONS TO NEUROPHYSIOLOGY (BY J.R.)**

David Marsden’s superb clinical skills were supported by his deep understanding of the basic
physiology and pharmacology of the motor system. It was an infectious combination that
attracted young scientists and clinicians from all over the world to work with him and imbibe
his philosophy of science. He believed that clinical problems inspired good science, setting
questions that had to be answered either by combining different branches of current knowl-
edge or by searching for insights from new experiments. Over the 22 years that I worked with
him, starting as a neurophysiology PhD student in 1976 until his death in 1998, I saw regularly
how he could transform his clinical experience into formal scientific questions that could be tested directly by available science.

To him, movement disorders were the outward expression of a disordered physiology, and when physiology was not capable of explaining what he had observed, then ‘nature was speaking’ to us and demanding an answer. It was a highly infectious philosophy.

David’s own physiological investigations began with tremor, first as a medical student with the later Labour politician and Foreign Secretary David Owen (now Lord Owen), and then later with John Meadows, who became a consultant at St George’s Hospital. They illustrate how he would search for new methods to address clinical questions, and for tremor this involved both the measurement and analysis of tremor itself. In 1966 this required devising (with T. K. Howell, an engineer at St Thomas’ Hospital) a mechanical integrator to quantify tremor amplitudes that he and David Owen used to assess the effect of propranolol on tremor in PD (2, 3). Three years later he was spending nights at the National Physical Laboratory, using the computers there to perform frequency analysis of tremor and even coherence analysis between tremor records obtained simultaneously from both sides of the body. This is a form of processing that is available these days in most clinical neurophysiology laboratories, but 40 years ago it demanded the full power of some of the best computers in the country. It showed that physiological tremor, the very small amplitude tremor of the outstretched fingers that we all have, was not coherent on both sides of the body and hence was not driven by some central oscillator in the central nervous system (4). At the time, the most likely explanation was that this form of tremor was due to local oscillations in the spinal stretch reflex, in which stretch of a muscle (signalled by receptors called muscle spindles) is transmitted to the spinal cord, where it activates outputs back to muscle to produce contraction and oppose the stretch. However, because he also found that physiological tremor of the same frequency could be observed in a patient with a severe sensory peripheral neuropathy, in whom the spinal cord was deprived of muscle spindle input, this was clearly not the only cause of tremor (5).

During his time on the computers in Teddington, he met Pat Merton (FRS 1979; Rothwell & Glynn 2006), who was analysing the frequency components of electroencephalogram (EEG) records. It was a happy meeting of minds that led to the ‘3 Ms’ collaboration of the 1970s that revitalized the study of neurophysiology in humans. The ‘3 Ms’ (figure 6) were Marsden, Merton and an engineer, Bert Morton, who had worked in radar during World War II. The combination of a cutting-edge clinical mind with the classical neurophysiology of Merton and the technical genius of Morton was a remarkable success. They could only work together at weekends and on some weekday afternoons, but over 15 years wrote 24 papers, mainly addressing the stretch reflex and its role in movement.

Their main insight was to show that the stretch reflex in hand and arm muscles could also involve a pathway to the brain in addition to the spinal reflex that had been known since the late nineteenth century. Using a combination of clever arguments about latencies, bolstered by careful studies of neurological patients with localized lesions in particular parts of the postulated pathways, they showed that muscle stretch produced sensory input that travelled quickly and directly to the sensorimotor area of the cerebral cortex, where it connected to fast conducting motor outputs back to the muscle that was stretched (6, 7, 11, 12). They termed this the ‘long latency stretch reflex’, and the pathway was termed the ‘transcortical loop’. Later work extended the range of these reflexes to muscles distant from the site of muscle stretch: in this case, if the muscle that was stretched was being supported in position by other muscles (for example, if a hand muscle was stretched while it was being held in position by other muscles
that extended the arm), then reflexes would also appear in the postural arm muscles so as to support the extra force that was being exerted by the hand (21, 25). These ‘anticipatory postural reflexes’ were remarkable in that they appeared before any mechanical disturbance had arrived at the postural muscle in question. In addition they were highly sensitive to context and were switched off immediately that support was available from an external object.

The concept of the transcortical reflex was an important advance because it showed how sensory inputs from the limbs could interact directly with cortical processes involved in voluntary movements. Long latency stretch reflexes became one of the first new windows into the operation of the cerebral cortex since the discovery of the EEG in the 1930s. Although it is probably fair to say that the long latency concept was driven mainly by Merton, who had first worked on the stretch reflex in the 1950s, in typical fashion David Marsden realized its enormous potential for informing clinical questions in movement disorders. He used the new discovery to show how increased gain of the reflex was responsible for certain forms of myoclonus, a condition in which patients have involuntary jerking movements in response to sensory stimulation or during voluntary movement (16). He also examined how the postural component of the reflexes was impaired in cerebellar disease and PD, suggesting that they could contribute to the postural instability in these patients (18).

As David took up a greater and greater administrative role, his direct involvement in physiological experiments became rarer, but his influence was no less than ever. With Mark Hallett, who later became a clinical director at the National Institutes of Health in the USA, and David Chadwick, his work laid the foundations for the now widely accepted physiological classification of myoclonus into cortical, subcortical and spinal types (13, 16, 32). They described the physiological features of subcortical myoclonus, a form of muscle jerking that
seemed to arise from a site in the lower brainstem. Careful study of these jerks showed that each started by recruiting muscles innervated by a lower cranial nerve (sternocleidomastoid, innervated by the XI nerve), spreading up the brainstem over the next few milliseconds to the higher cranial nerves (mentalis, VII, and masseter, V) while at the same time descending to spinal cord (arm then leg). The topic returned in the early 1990s when the laboratory began to study the syndrome of hyperekplexia (excessive startle).

Towards the end of the 1970s David began to recruit a young team to carry forward his interests in physiology. I started my PhD there in 1976, immediately after Mark Hallett had returned to the USA, and was joined in 1980 by Brian Day. Both of us followed him to the Institute of Neurology when he was asked to set up the MRC Human Movement and Balance Unit in 1988. Neither of us was a clinician, but over the next 20 years we were joined by a series of extremely talented young neurologists who later set up their own groups around the world on the same model as David’s. Among these were Jose Obeso from Pamplona, Spain; Philip Thompson, now in Adelaide, Australia; and Peter Brown, now a professor of experimental neurology at Oxford. David inspired the work of our small group, always prodding us intellectually with his astute clinical observations. He was instrumental in guiding the huge range of the output from this group.

I remember in particular how he came across a man with a severe sensory peripheral neuropathy, similar to the patient he had studied with tremor many years previously, and insisted that we do more than he had done to investigate how this individual could manage to move so well despite having no sensation in his arms and legs (23). In fact the man could perform a range of tasks quite well, even when he closed his eyes and was no longer able either to see or feel what he was doing. For example, he could touch his thumb to each of the fingers of his hand in turn and outline numbers in the air with the tip of an outstretched finger. As David noted, this was an example in nature that illustrated how well controlled the motor output from the brain could be in the absence (at least when the patient closed his eyes) of any sensory information from the periphery.

David led us to investigate the neurophysiology of a variety of movement disorders that were at the time sometimes suspected of having a psychological origin. With Jose Obeso we showed that the jerks in Gilles de la Tourette syndrome were not accompanied by the EEG changes that precede volitional movements (the Bereitschaftspotential) and hence were likely to be involuntary rather than mimicked (22). He presented us with the mystery of dystonia, particularly the focal dystonias such as blepharospasm, torticollis and writer’s cramp (involuntary contraction of hand and forearm muscles when trying to write or manipulate small objects). Together with Alfredo Berardelli from Rome and Kenji Nakashima from Japan, in all cases we were able to document abnormal physiology in the blink reflex, or spinal reciprocal inhibition and in cortical motor output (see below) that were strong proof that the symptoms were organic rather than psychogenic (31, 38, 45).

In the 1980s Merton and Morton described a new method for stimulating the human brain through the intact scalp (Merton & Morton 1980). Although the brain had been known to be electrically excitable since the second half of the nineteenth century, it had never been possible to stimulate it in an intact conscious human because of the high electrical resistance of the skull and scalp. Merton and Morton showed that with the correct design of stimulator this was possible with very brief pulses at very high voltage. David was fascinated by this advance and we immediately had to incorporate it into all possible investigations. The work focused on stimulation of the motor cortex, because this produced a twitch of muscles on the contralateral
side of the body that was easily measured and quantified with electromyogram (EMG) electrodes. David encouraged us to show delayed conduction in central motor pathways in multiple sclerosis and intact motor output pathways in PD (26, 27). He also encouraged us (as did Pat Merton) to try to stimulate other parts of the motor system, in particular the cerebellum. Eventually, with Yoshikazu (Kaz) Ugawa, we were able to do this, and even to show that with even higher stimulus intensities it was possible to activate corticospinal motor fibres in the brainstem at the level of the pyramidal decussation (49, 50).

With the introduction of transcranial magnetic stimulation (TMS) in 1986 (Barker et al. 1985), this work moved forwards very rapidly indeed. TMS was virtually painless, whereas Merton and Morton’s electrical method caused scalp muscle contraction that some people considered uncomfortable. With TMS we began slowly to study neural connections within the cortex itself, eventually being able to identify particular intracortical and corticocortical connections (51, 52).

In parallel with all these new technical advances, David’s mind always came back to simple but unsolved clinical problems that demanded a back-to-basics approach. When Reiner Benecke arrived from Germany, he was given the task of understanding why it was that patients with PD had such difficulties in making two movements at the same time. This inspired the ‘flex and squeeze’ task, which could easily quantify the additional deficit seen when patients had to both flex the elbow and squeeze an object in their hand simultaneously (33, 36, 37). On another occasion he had read about a newly described condition, ‘orthostatic tremor’ in a US journal; he identified a case in a clinic he held a few weeks later, and then presented us with the task of discovering the mystery of the physiology. Orthostatic tremor occurs in the legs, but only when patients stand still; when they walk, the tremor lessens. There is often no visible tremulous movement, but just a feeling of unsteadiness that grows stronger the longer that patients have to stand. According to David’s advice we began simply by recording the EMG of the tremor in the legs, something that the previous report had omitted. Immediately it was clear that this was a novel form of tremor, with a frequency that was roughly double (16 Hz) the usual tremors seen in the hand, which are about 8 Hz (34). In fact, this high frequency also explains why there is little visible movement, because activity at such high rates causes the individual contractions to fuse and seem almost continuous.

Perhaps David Marsden’s fundamental contributions to the pathophysiology of movement disorders are best summarized in his famous Wartenberg Lecture (24) of 1982, in which he concluded from a vast summary of clinical and recent scientific work (mainly from his own laboratory, which at that time was leading the field) that the basal ganglia were responsible for the ‘automatic execution of learned motor plans’. It was a remarkably prescient observation that has since been explored in enormous detail by new work on the role of the neurotransmitter dopamine in learning via reward and many other mechanisms. Yet it was a conclusion reached from careful observation and a small number of clever, yet simple, critical experiments.

David’s name is on more than 175 physiology papers. I have highlighted only some of the vast range that he covered. Despite other tasks, he was involved in, read and corrected all those papers, many times telling us which direction to take next or which new disease to study. His curiosity was insatiable and his enthusiasm infectious, waning only later in his life when he suffered from depression. David Marsden established an environment that encouraged questioning and careful observation. Because he wanted difficult questions solved, it was always a matter of doing first and then using the results to stimulate further enquiry. He often said
that human physiology and its disorders were so underinvestigated that we were lucky to be able to take the pick of the sweetest fruit and leave the remainder to others. We were only in that position because we followed so closely the clinical expansion that he led in the field of movement disorders.

**Contributions to Neurochemistry and Neuropharmacology (by P.J.)**

David Marsden’s fascination with the biochemistry of the basal ganglia started as a medical student when, through examination of pathological specimens, he mapped the pigmentation of substantia nigra across a range of species (1). Even more remarkable was that he published this as a single author paper in *Journal of Anatomy* when aged 23 years. This fascination with events occurring in substantia nigra that cause cell death in PD led quickly to studies of oxidative enzymes involved in melanin formation and the measurement of ascorbic acid levels. This interest in oxidative stress as a cause of PD lasted for the next 35 years. His involvement in pharmacology started with studies of the use of beta-blockers in the control of essential tremor.

Marsden and I became a team when, in 1973, I was appointed Lecturer in Biochemistry in his newly opened University Department of Neurology at the Institute of Psychiatry. He was the youngest-ever professor of neurology in that era, and the stature of the man shone through from the moment that I met him. My appointment was typical of David, as I came from a background of studies in drug metabolism and pharmacokinetics; I had never heard of PD and scarcely knew anything about the brain. The interview was short and sharp. He took me to Golla Ward and showed me patients with PD and explained, as only he could, the problems they faced. So, spellbound by his charismatic personality, I changed fields and joined him in his quest. In the period between 1973 and his death in 1998, we undertook work that led to more than 400 publications.

David understood the value of experimental models of PD, and so we started by using the reserpinized mouse as a testbed for examining the actions of L-dopa and measuring the increase in locomotor activity (8). This was at first the blind leading the blind (a sort of double-blind study!) because neither of us had any experience of laboratory studies of this kind. However, in a recurring theme that continued throughout his career, David was joined on sabbatical by his great friend Roger Duvoisin and by Dan Tarsy, and between us we mapped out new ideas on how L-dopa might be so effective in treating PD. David hit immediately on the loss of noradrenaline occurring through degeneration of the locus coeruleus as being a key neurotransmitter deficit in PD, over and above the nigrostriatal deficiency of dopamine, that could be counteracted by L-dopa administration. Indeed, we showed that blocking the formation of noradrenaline from dopamine or manipulating noradrenergic receptor function did alter motor activity. The efforts of Annette Dolphin, another of Marsden’s first PhD students, expanded these studies and showed that significant amounts of noradrenaline were indeed formed from L-dopa. This became a Marsden fascination, and with the appointment of Chris Pycock and the sabbatical of Ivan Donaldson from New Zealand, another era started, using stereotaxic surgery in the rat with electrolytic lesions or the toxin 6-hydroxydopamine to destroy dopaminergic neurons in the substantia nigra and to destroy noradrenergic neurons in the dorsal and ventral bundle that innervate the forebrain and arise from the locus coeruleus (10). Again, as David had suspected, clear evidence emerged of a functional interaction between the noradrenergic
and dopaminergic systems in the control of motor function relevant to PD. Another PhD student, Sarah Rose, extended David’s interest in the mode of action of L-dopa, setting up a range of experimental models of PD and then moving us on to pharmacokinetic analysis of the time courses of effects in plasma and brain; this would eventually lead to the use of in vivo microdialysis as a key method of studying the biochemistry of basal ganglia and drug action (39).

The final part of the basal ganglia story started with David’s need to know about the organization of the output pathways from basal ganglia that led to the control of voluntary movement. We had by this time forged links with Robert Naylor and Brenda Costall at the University of Bradford, who became close colleagues and friends. An unbelievably dynamic duo and productive team, they led us to many new ideas on stereotaxic lesioning of basal ganglia and the focal infusion of drugs into key nuclei. Joined by a research student, Charlie Reavill, and by a young neurologist, Nigel Leigh, we spent many years knocking out individual nuclei around the basal ganglia, thalamus and brainstem, building up a map of how dysfunction in basal ganglia caused PD. These studies led us to areas of the brain that seemed to have no name, so in true Marsden fashion he invented one; for example, we worked on an area in the reticular formation that he designated the ‘angular complex’. This field of research led to a tremendous rivalry with an Italian group in Sardinia that we lovingly referred to as the ‘mafia’. Gessa, Spano and DiChiara were both loved and hated as we agreed and disagreed over findings, and David pushed us on and on to be first and to publish ahead of them. The Italians organized many meetings on their beautiful island at which we fought and cursed over science and then drank our way into the night, led by David, and sang with our arms round our competitors.

These memories of Italy evoke another facet of David. Sociable and gregarious, he led from the front and would have everybody from the newest PhD student to the most distinguished professor dancing into the night. He excluded nobody, and his ability to team build and to inspire was phenomenal although, as with most geniuses, there were ‘black’ days, and dismay at any form of rejection. But build he did, and from the science perspective his sociability had a deep purpose to it. Being summoned to a meeting with him at 5 or 6 o’clock in the afternoon invariably meant walking up the hill to the George Canning pub or a short distance along Windsor Walk to the Phoenix and Firkin (a brewery and pub established in the still-functioning Denmark Hill railway station), and downing pints of beer, which, like most things, he did far better than us mere mortals. Surrounded by students, fellows, staff and visitors, he would expound at length about his latest ideas and then map out, on the back of a beermat (figure 7), complete research programmes, grant applications and schemata of how the basal ganglia worked. We would show him puzzling results from some complex experimental study that had taken months to perform and where no one could see meaning and, with one sweep of his hand, he would remove the dross and clear a path with absolute brilliance that captured the key findings and explained all. However, sometimes this approach did not work, as for example when, after one evening during which we had spent hours discussing the mechanism of action of the dopamine agonist bromocriptine and reached a stunning ‘discovery’, on the following day not a single person could remember what it was.

David’s vision also meant that he did not let us forget that we were based in a neurology department. Through Brian Meldrum and Ted Reynolds there was an interest in epilepsy, and David also had a keen interest in myoclonus. Consequently, with David Chadwick and Judith Pratt we undertook studies on the neurochemical effects of some anticonvulsant drugs, notably in relation to the involvement of 5-hydroxytryptamine (serotonin) systems. Similarly, with
Graham Luscombe and Mark Hallett from the National Institutes of Health we established models of a variety of forms of myoclonus seeking to establish testbeds in which more effective treatments could be devised (15). David recognized that we were based at the Institute of Psychiatry and that we were, in many ways, a small and peripheral unit in comparison with the huge Departments of Psychiatry and Psychology, and this made him aware that we had to be involved in studies that would be of interest to the psychiatric world. This led us to an era of studying typical and atypical neuroleptic drugs and their relationship to the development of extrapyramidal side effects. David led us in to this area through a side door by wanting to understand how the antiemetic metoclopramide could cause parkinsonism in some individuals. We showed it to have central dopamine antagonist actions in a range of behavioural models, but then he wanted more direct proof of its effects. This period in the 1970s, going on to the mid 1980s, was the era of the identification of dopamine receptors and their subtypes and the introduction of receptor binding assays using radioactive ligands for assessing interaction and change in response to drug exposure. So I was dispatched to Janssen Pharmaceutica in Beerse, Belgium, to work with Josee Leysen and Pierre Laduron, who were pioneers in the field, and to bring the technology home. We showed that metoclopramide interacted directly with postsynaptic dopamine receptors. At that time all dopamine receptors were thought to be linked to adenylyl cyclase as the second messenger system. I was then dispatched to Cambridge to look...
at the interaction of metoclopramide with this enzyme, in collaboration with Richard Miller and Les Iversen (FRS 1980), and to our surprise no effect was found. At this point we came to an example of how even the best could get it wrong. In my enthusiasm, I suggested that there might be another dopamine receptor that was not linked to adenylate cyclase, but the others were cautious, questioning the results of the ligand binding assay. A few weeks later, rivals published a paper on the new non-cyclase-linked dopamine receptor that subsequently formed the basic classification of dopamine receptors into D-1 and D-2 classes. As a result of the work on metoclopramide, we became aware of other drugs that were from the same chemical class known as substituted benzamides, and that one in particular, sulpiride, was used as an atypical antipsychotic in France. We showed, along with Costall and Naylor, that these drugs were less able to block motor function than typical neuroleptics and that they were very specific D-2 receptor antagonists. For many years Marsden’s team reigned supreme as the world experts on the pharmacology of substituted benzamides (14).

David’s appetite for the antipsychotic field continued unabated through his fascination with the cause of extrapyramidal side effects, most notably tardive dyskinesia. Indeed, Marsden and Jenner wrote one of the few mechanistic concept papers on the cause of parkinsonism, acute dystonia, akathisia and tardive dyskinesia to enter the psychiatry literature at that time (19). His interest was timely, because there had been a recognition from the work of Phil Seeman and Ian Creese that tolerance developed to the acute dopamine-receptor blocking effects of neuroleptic drugs, and that adaptive change over a period of three weeks’ treatment led to the onset of supersensitivity, as judged by alterations in motor behaviours and receptor binding assays. For most people this would have been sufficient to explain tardive dyskinesia, but not for Marsden, who wanted to know why tardive dyskinesia occurred only after months or years in humans. So we embarked on a series of experiments using typical and atypical neuroleptics that was of such duration and magnitude that it was a major logistical challenge even to set up. David wanted colonies of up to 1500 rats to be treated with neuroleptic drugs in their drinking water for periods of up to 18 months, and to undergo biochemical and behavioural analysis at intervals to study how basal ganglia function changed as intake progressed. A battery of PhD students undertook these studies over many years, most notably Angela Clow (who married John Rothwell), Kamala Muragiaha, Nadia Rupniak, Andreas Theodorou and Simon Fleminger. These were unique studies and highly rewarding, in that they exposed tolerance to acute drug effects, functional supersensitivity that occurred even while drug administration continued, and marked differences between typical neuroleptics associated with a high incidence of tardive dyskinesia and atypical neuroleptics where the incidence in humans was low (17, 28). Most importantly, we showed the emergence of vacuous chewing movements that looked like the rat equivalent of oro–buccal–facial–mandibular dyskinesia. Like all hot areas, this was another highly controversial field, with keen rivalries with the groups of John Waddington and Phil Seeman, but everybody came down on the same side in the end through David’s diplomacy.

There is a final chapter that perhaps represents the most important contribution from Marsden’s laboratories, one that went back to the very start of his career. His desire to know the cause of neuronal death in PD led us to the study of pathogenic mechanisms in human post-mortem tissues. Collaborations with Yves Agid and France Javoy-Agid in Paris allowed us to measure indices of oxidative stress in substantia nigra and to show elevations in the levels of lipid peroxidation and iron content in PD through the efforts and achievements of David Dexter, who initially joined the team as a PhD student and subsequently as a post-
doctoral fellow (40). Subsequently, Jeswinder Sian and Bali Saggu demonstrated decreased levels of reduced glutathione and increased levels of manganese-dependent superoxide dismutase in the parkinsonian nigra (56). Typical of the collaborations that Marsden engendered, work on tissues from cases of incidental Lewy body disease provided by the Austrian Brain Bank allowed us to show that the change in glutathione content was one of the earliest markers of pathogenesis that we could locate. David realized the value of the Brain Bank philosophy and, as usual, decided that we needed a facility in the UK. He persuaded the UK Parkinson’s Disease Society to provide funds, and in the newly built extension to his department he appointed Raymund Wells to coordinate the donation of brain material that continues to this day through the collections created by Andrew Lees, Sue Daniel and David Dexter.

In the meantime, another breakthrough in studies of the cause of PD had come through the discovery by Bill Langston in California of the selective toxicity of MPTP (a by-product of attempts in California to produce a ‘designer drug’ for recreational use that instead caused permanent parkinsonism in the mostly young addicts exposed to it) to nigral dopaminergic neurons in humans and non-human primates. David immediately saw the need to establish an MPTP-treated primate model of PD in the UK, and chose the common marmoset for this purpose because a colony already existed at the Institute of Psychiatry. He saw MPTP as a clear clue to an environmental cause of the disease and used our strong collaborations with Costall and Naylor and the Agids as a means of studying its mechanism of action and effectiveness in mimicking PD in experimental animals. This started a phase of research that continues to this day with the demonstration of the ability of the MPTP-treated common marmoset to show motor features of PD and to develop, on chronic l-dopa treatment, the complications of motor fluctuations and dyskinesias that also occurred in patients with PD (29, 41). However, it was Marsden’s ability to think laterally that led us to another major finding. We knew that MPTP acted as a toxin to dopaminergic neurons by conversion to 1-methyl-4-phenylpyridinium (MPP+) by the enzyme monoamine oxidase B, and that MPP+ then impaired mitochondrial function at the level of complex I. So Marsden, Dexter and I approached a mitochondrial specialist at Queen Square, a then young Tony Schapira, and we asked the key question: does the deficit in complex I activity form a component of pathogenesis in PD? A complex I deficiency is now an accepted part of the neuronal death process in classical PD, and it also transpires that many other causes of PD, including gene defects, have been linked to dysfunction at the mitochondrial level (42).

Marsden’s legacy in pharmacology and biochemistry resides in the dynasty that he spawned on a global basis, and many of his students have continued as key researchers in the neuroscience field. His amazing ability to move seamlessly from one field of science to another was a gift that others envied. A mental agility that allowed him to grasp the key literature at a stroke meant that he could discuss cutting-edge science with experts in other specialities at their level. He had a clarity of mind that gave him the gift of speaking and writing about complex scientific issues with ease and of translating the findings to an improved understanding of his beloved basal ganglia. Scientists were drawn to working with him by his insistence that clinical neurology and laboratory-based science needed to be integrated for progress to be made. He was never constrained by accepted wisdom, instead continually challenging current belief and pushing the boundaries of knowledge to new limits. David led by example, charging forwards to unknown territory, fearless and with a certainty in his invincibility. He did not take fools lightly; you quickly learnt that when his only reply to your latest ideas was ‘fascinating’, you were clearly talking rubbish. He engendered loyalty and was loyal, but bluntly honest, in
return. He ensured that the careers of others progressed alongside his own and, despite all of his success, he sometimes shunned the limelight and chose to sit quietly with a pint of beer and a cigarette and talk science with young people. David Marsden was one of a kind, and the global movement disorders community is a poorer place with his passing.

FAMILY

On 7 October 1961, as a medical student still two years away from qualifying, David married Jill Slaney, a physiotherapist, the daughter of William Bullock, a general practitioner. They had three daughters (Anna, Abigail and Amy) and two sons (Andrew and Adam), the second of whom predeceased him in 1985. This marriage broke down in 1978, and he became partner to Jennifer (Jenny) Mudditt (née Sandom), his former ward secretary. After divorce from his first wife he finally, on 26 July 1989, married Jenny, with whom he had three daughters: Lucy, Alice and Jessica. This marriage also ended in divorce in 1998.

PERSONAL CHARACTERISTICS

As might be expected, David’s character and attributes were complex and somewhat paradoxical. He was part English public school, part Greek, part British colonial Antipodean, leading Andrew Lees to call him ‘archetypically British with a Gipsy streak’. He was handsome, in a slightly Mediterranean way, with luxuriant dark eyebrows. He was also rather short in stature, as befitted a former scrum half, but such was his presence and charisma that few noticed this.

Besides sailing, and his abiding interest in the human brain, he enjoyed gardening, bird-watching, good food and wine, and opera, particularly Wagner.

Intelectually he was not just bright but brilliant, and impressed everyone with his ability to digest and clarify difficult and complicated data or concepts, and make them appear simple and even obvious, making him greatly in demand to distil significance and meaning after a couple of days packed with talks at one conference or another. He was a very organized and articulate teacher and lecturer, and his writings were models of clarity. He was meticulous and thorough, and consumed with his search for scientific truth. All papers leaving his stable were closely scrutinized through numerous versions so that when they reached a referee they were perfect or near-perfect. His chapters took form in his head, and they were then dictated into a machine while strolling in his garden.

He was ‘driven’; what in others might be called workaholism was in fact an intense fascination with the brain and its workings and a need to communicate this to others.

He was determined, and always convinced that he was right (which in matters of science he usually was). He had high expectations of those who came to work with him, and they in turn developed a fierce loyalty.

David was courteous, diplomatic and fair, with considerable powers of persuasion, which helped in numerous situations. In some ways he was rather shy, and very much a private person. However, he also liked to play hard, and had a reputation for being able to consume copious amounts of wine or beer on social occasions with little apparent effect, although those making this judgement were not in a great position themselves to assess such matters, and his
fondness for partying was probably less appreciated at home. He loved grilling his young, usually foreign, fellows of both sexes about their lives, and had a flirtatious streak. He was also an inveterate smoker of Marlboro cigarettes, and after work at Queen Square, or away at conferences, could often be found under a haze of smoke with his co-addicts Anita Harding and Philip Thompson.

He was sometimes moody and reclusive, and during his last few years he experienced periods of quite severe depression preceding and following the breakup of his marriage to Jenny. All who knew him held him in awe and respect, and greatly missed him when he died. With the passage of time, however, one might reflect that he would perhaps not have relished experiencing the ravages of old age, and the indignity of standing on the pavement outside to smoke, as he would have had to do today.

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The frontispiece photograph was taken in the Institute of Neurology in about 1988 by the Medical Illustration Department of the National Hospital for Neurology and Neurosurgery/Institute of Neurology, Queen Square.

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