W. Ian McDonald, MB, ChB, PhD (1933-2006): The Multiple Sclerosis Physician-Scientist of the 20th Century

On December 13, 2006, the neurology community lost one of its most influential physician-scientists, W. Ian McDonald, MB, ChB, PhD. Dr McDonald’s name has become recognized around the world for his seminal insights into the underpinnings of multiple sclerosis (MS) and for the application of novel technologies to reveal the diagnosis of this fiendishly challenging disorder of the brain and spinal cord.

Ian McDonald was a native of New Zealand, where he obtained his medical school training and a doctorate at the University of Otago. His graduate work focused on the pathophysiology of axonal demyelination; the functional effects and mechanisms of demyelination and remyelination were topics that remained the focus of his entire professional career. He moved to London, England, in 1963 and continued his clinical training at Queen Square between 1963 and 1966, with a year serving as a research fellow to Derek Denny-Brown, MD, DPhil, FRCP, at Harvard University (1965-1966). He became a consultant neurologist at the National Hospital for Neurology and Neurosurgery in 1966 and professor of clinical neurology at the Institute of Neurology at London University in 1974; he continued in these posts until his retirement in 1998.

To fully appreciate the magnitude of Dr McDonald’s achievements, one must first put the field of MS into historical context. His predecessors deserve credit for setting the scientific scaffolding on which Dr McDonald would launch his monumental research. Armed with the insights of others, he was able to formulate some of the most important hypothesis-driven, testable questions of the 20th century relating to elucidating the underpinnings of MS. Those who work tirelessly in the clinic and laboratory on behalf of our patients with MS and their families will forever be indebted to Dr McDonald for providing us with many of the tools that we now use to strategically and practically approach the diagnosis and management of the disease.

Multiple sclerosis is the most common disabling neurologic disease among young people. While accounts of what most likely constituted MS date back to Viking Norse stories of the eighth century, it was the Scottish physician Robert Carswell who pathologically described the plaques of MS as “firm spots” in 1830, signifying the yet-to-be-discovered fibrous and sclerotic nature of the disease.1 Jean Cruveilhier in France described the degeneration of the white matter columns of the spinal cord derived from a patient at the Salpetrière Institute in Paris.2 The most exacting histopathologic description of spinal cord MS was provided by the German Carl Frommann in 1867.3 Frommann recognized the role of glial elements as a critical component of the lesion substrate (ie, gliosis). Without a doubt, however, it was Jean-Martin Charcot4 in 1868 who assembled all of the clinical, neuroanatomic, and pathological elements into the first comprehensive framework of MS (sclérose en plaques). Charcot recognized the cardinal elements of MS: the history of disease-related relapses and remissions, producing a myriad of symptoms derived from a diversity of potential lesion localizations (dissemination of disease in time and space). Siemerling and Raecke5 recognized in 1914 that MS plaques could be disseminated throughout white matter but also in the cerebral cortex, an observation now receiving greater attention by contemporary workers. In 1916, James Dawson6 refined the gross pathology of MS lesions by drawing attention to the fingerlike projections arising from the ventricular lining, an observation that would later represent a classic magnetic resonance imaging signature of MS, as demonstrated by Dr McDonald; this observation also had implications for understanding postcapillary venular trafficking of circulating mononuclear cells.

A quantum leap forward was provided by the discovery of myelin by Louis Ranvier in 1878 and by Pierre Marie,7 who first suggested in 1892 that demyelination represented a critical element in MS pathology. In 1925, Lord Edgar Douglas Adrian8 reported the first electric recordings of nerve transmission. Ultimately, 6 Nobel Prizes were awarded for contributions directly related to the characterization of the nerve impulse and the role played by myelin, a monumental achievement of modern biology.

The first diagnostic criteria for MS were proposed by Charcot himself in 1868; the criteria suggested that an intention tremor, nystagmus, and scanning speech were characteristics of this newly defined disorder. Many different criteria were established during the decades since, with varying degrees of acceptance by neurologists. However, the first consensus of clinical criteria for the diagnosis was provided by a 10-member working group headed by George Schumacher in 1965 and sponsored by the National Multiple Sclerosis Society.9 This first criteria were principally focused on the historical and clinical elements of diagnosis and the exclusion of mimicking conditions. Notwithstanding this important milestone, the diagnosis of MS could only be precisely confirmed at biopsy or autopsy.

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While working at the University of Otago and later at the Institute of Neurology in London, Dr McDonald was the first to provide objective evidence that demyelination in the peripheral and central nervous system was associated with a corresponding change in the transmission of electrically coded messages within nerve axons.\textsuperscript{10-12} He noted that the disruption of myelin led to a reduction in the axonal cross-sectional area and conduction velocity, with loss of saltatory conduction and a prediction to conduction block. Understanding this conspicuous aspect of MS pathophysiology allows us to predict many of the symptoms described by our patients, particularly those symptoms provoked or intensified by exercise, elevated core body temperature, and infection. Such processes appear to lower the safety threshold for high-fidelity nerve transmissions (this was also recognized clinically by Wilhelm Uhthoff\textsuperscript{13} in 1899).

The fundamental observation that myelin loss was germane to understanding the pathophysiology of MS led Dr McDonald to collaborate with Martin Halliday and Joan Mushin in the development of visual evoked potentials.\textsuperscript{14} Armed with this powerful physiologic technique, they were able to demonstrate that patients with optic neuritis exhibited prolongation in event-related latencies, consistent with demyelination and his principal hypothesis of conduction slowing (or block) in denuded axonal segments. The application of this technology constituted the first noninvasive diagnostic capability for the neurologist to document the pathology of MS. It was certainly not the last.

The third major, and perhaps most far-reaching, contribution made by Dr McDonald to MS was his systematic application of magnetic resonance imaging technology to the noninvasive profiling of the disease process in patients suspected of having MS. Starting in 1984, and supported throughout by the Multiple Sclerosis Society of Great Britain and Northern Ireland, he organized the first dedicated MS magnetic resonance imaging center at the National Hospital for Neurology and Neurosurgery at Queen Square in London. His enormous energy and commitment to this discipline, combined with a deep understanding of the pathobiology of the disease, elucidated the importance of inflammatory lesions in acute relapses\textsuperscript{15} and axonal loss in disease progression and disability,\textsuperscript{16} and culminated in the development of the current diagnostic criteria for MS: the McDonald and the modified McDonald criteria.\textsuperscript{17,18} Incorporating the historical, clinical, and laboratory elements of preceding criteria (including cerebrospinal fluid analysis and evoked potentials), the National Multiple Sclerosis Society-sponsored working group integrated the systematic use of magnetic resonance imaging (the 2005 modified criteria integrated both the brain and spinal cord) to derive a highly specific and sensitive method to help physicians confirm or refute the diagnosis of MS.

The McDonald Criteria was the culmination of 40 years of dedicated effort to bring MS from the disease of his predecessors (who described it as peculiar, unseen, enigmatic, and humbling) to an entity that could now be systematically evaluated with noninvasive means to confirm the diagnosis, even shortly after the time of the sentinel neurologic event, a time when perhaps the implementation of disease-modifying therapy has its greatest impact on modifying the disease process and its resultant disability on patients, their families, and our communities.\textsuperscript{19}

During Dr McDonald’s lifetime, MS became a partly treatable disease. Presently, 6 immunomodulatory agents are approved for the treatment of relapsing forms of this disease, after they were found to positively alter the natural course of MS. While the availability of pharmacotherapies for patients was a welcome change, it also resulted in a new ethical challenge: how to conduct future clinical trials without the use of a placebo group? Henry McFarland, MD, and John Noseworthy, MD, initiated the Sylvia Lawry Center for MS Research in Munich, Germany, a new database that is composed of the placebo groups of numerous MS treatment trials. Dr McDonald was instrumental in establishing this research program.

It is a challenge to summarize the achievements of someone who contributed so much and had such influence, and mentored so many. At the time of his death, Dr McDonald was Emeritus Professor of Clinical Neurology at the Institute of Neurology at University College London. He also held academic appointments at the Heinrich Heine University of Dusseldorf and Yale University. Dr McDonald served as the editor of Brain (1991-1997) and was on numerous editorial boards of many of the most prestigious scientific journals. He was the president of the 2001 World Congress of Neurology and past president of the European Neurological Society, and the Association of British Neurologists. He authored and coauthored hundreds of peer-reviewed research articles, scientific reviews, book chapters, and monographs. His outstanding contributions to MS were recognized in 1991, when he received the Charcot Award, and in 1999, when the National Multiple Sclerosis Society and the American Academy of Neurology awarded him with the John Dystel Prize for MS Research.

He also had many interests outside of medicine. His cultural interests included music; he was an accomplished pianist and very recently described his temporary loss of the ability to read music and play the piano following an infarct of the right angular and supramarginal gyri in 2004.\textsuperscript{20} His knowledge of and passion for medical history was honored with his appointment as Harveian Librarian at the Royal College of Physicians (1998-2004). His personal attributes included an abundance of wisdom, kindness, modesty, and elegance; he was, to so many, a wonderful colleague, friend, and mentor.

Aspiring junior neurologists may wonder about the qualities that make an outstanding physician-scientist and an academic leader. Is it intellectual curiosity? Perseverance? Clinical skills? Scientific instincts? An ability to formulate key ideas to create purposeful achievements? An unrelenting enthusiasm for learning and teaching? The ability to mentor gifted junior physicians and scientists? The combination of all these qualities enabled Dr McDonald to penetrate the entire world of neurology education and to remain at the forefront of MS research for many decades.

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REFERENCES


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