A tale of two books: milestones on the path to understanding multiple sclerosis

The publication of a new work is always exciting—whether this is a novel offering pathos, humor or other insights into the human condition, or a work of non-fiction whose object is to inform, stimulate or clarify. The recent publication of two landmark books on multiple sclerosis (MS), both very different in scope and objectives, but with many elements in common, provides an opportunity for personal comment and an historical perspective on the modern elucidation of this complex disease.

How do we conceptualize illness? This question has been at the centre of medical investigation over the millennia, and the issue continues today, at both individual disease and broad ethnoanthropological levels. Cultural differences in the approach to illness and wellness are most striking in considering differences in attitudes between 'developed and undeveloped' populations, and especially in the comparison of Eastern and Western traditional medical practices. These have seen subtle shifts in the relationship between what is considered normal and abnormal. Now, the process of ageing, accepted as an integral part of the human condition throughout the ages, has assumed in Western culture the status of a disease to be treated, modified and avoided. The more one investigates the practice of medicine, the more one is struck by how pervasive are these social and cultural influences on the fabric of clinical science.

Medicine has always hovered at the interface of science and the art of healing, and this duality has often created tensions for its practitioners. Most modern clinicians would like to believe that their practice is soundly based in science, and that the exercise of their healing arts is done in the setting of evidence-based knowledge and wisdom derived from experience. Similarly, basic and clinical scientists feel that they approach a given problem with open minds, and base their hypotheses and experimental plans purely on objectivity. These aspirations are most easily met in simple disease models, where there is a direct relation between cause and outcome. How different is the situation in complex conditions, where the described symptoms and signs may or may not be part of one disease, the aetiology that could possibly link these is unclear and the management is invariably uncertain? In this situation, differing scientific backgrounds and training may bias investigation and conceptualization, and social, cultural, political and economic factors start to influence medical behaviour. Many aspects of MS have been exquisitely detailed for >150 years, but the accounts have not always avoided these confounds, and the disease (or diseases) is still shrouded in mystery. Lest any of its practitioners or investigators believe this not to be the case, it would be well to review the evolution of neuroscience thought in the context of societal and cultural development and, more specifically, how concepts of MS have been subject to these influences. Critical study of this history helps to place our modern view of MS in perspective, and to judge how successful two new books that tell the contemporary story are in showing where we have come from, where
we are now and how we should go forward in a way that helps to eliminate some roadblocks of the past. The history of neuroscience reveals a marvelous amalgam of human discovery with all its genius and folly, insight and stubbornness, perceptiveness and blindness. With the distance of time, it is easy to see how this discipline was firmly embedded conceptually into the philosophy, culture, technology and art of each era in which progress was made. The development of studies and practice in MS has followed an analogous pathway, but this history is compressed, and the ideas are still in flux. Indeed, theories once discarded are now being rediscovered, and we are as yet not altogether clear where we stand on the evolutionary pathway towards a complete understanding and solution to the problem. That, ultimately, is why we write and read, and, each in its own way, these two books fulfill this mandate wonderfully.

The Greeks were the first seriously to study anatomy and physiology, including the brain, but their approaches to science and philosophy were indivisible. It is easy to forget that Aristotle, the philosopher, was also steeped in scientific practice, and his theories on the order of the universe were firmly rooted in personal scientific investigation. This Greek legacy persisted into the Roman era and was exemplified by Galen, the first towering figure in neuroscience. His studies were exhaustive and careful, although mostly based on animal dissection. It is not known whether he ever dissected the human body. The effects of this restriction to animal studies were profound: the benefit was that he confirmed the human body. The effects of this restriction to animal studies were profound: the benefit was that he confirmed the human body. The effects of this restriction to animal studies were profound: the benefit was that he confirmed the human body. The effects of this restriction to animal studies were profound: the benefit was that he confirmed the human body.

It was in the Renaissance, with its flowering of thought in art, science, architecture and geography, and with the first hesitant steps to break free from the confines of the Church, that neuroscience started on the modern path. Interestingly, it was artists who led the way. The revolution in painting by Leonardo da Vinci, whose realistic art mirrored an amazing capacity for understanding science, and Michaelangelo, who demanded realistic models for his portraits, forced anatomists to depict the brain accurately, which in turn shaped a re-evaluation of the way that it functions. The extraordinary partnership between Andreas Vesalius and the painter Titian led to production of one of the most influential medical texts of all time, De Humani Corporis Fabrica Libri Septem (1543), which laid the foundations of modern neuroscience. His accurate observations rejected the concept of the *rete mirabile* and the functional importance of the ventricles. Gone was the time when university Readers, beautifully depicted in many early woodcuts, merely read to their students from the great texts, perpetuating ancient myths. Vesalius set the stage for Thomas Willis, who depicted the circle of blood vessels, which bears his name, and emphasized the functional role of the cerebral convolutions. Concepts in neuroscience progressed over the next few centuries according to the social fabric of the times, the advent of new technologies and gradual freedom from ecclesiastical doctrines of medicine and science, especially during the Age of Enlightenment. But other institutions—governments, funding agencies, universities, learned societies and journals—have since imposed their own orthodoxies. During the Industrial Revolution, the introduction of parallel advances in technology and experimentation, and the increasing importance of public health, suggested a role for infectious and environmental agents in the generation of many diseases, and Robert Koch drew up his postulates. These trends have continued during the 20th and 21st centuries with the emergence of new disciplines such as immunology, neurochemistry, molecular biology and genetics and the introduction of animal experimentation to establish models of disease on which to base hypotheses. Clinically, the introduction of scientifically motivated therapeutic strategies has led to ever-increasing improvement in the practice of well-controlled clinical trials, and evidence-based prescribing and management.

Given these observations on social and cultural factors governing the conduct and interpretation of scientific investigation, which we see so clearly with the benefit of hindsight, it is reasonable to ask whether the study and concept of MS as a disease has been similarly constrained over the years, and continues to be influenced by these forces. Viewed from an historical perspective, it is obvious that, even though compressed into a relatively shortened period, theories of etiology, nomenclature and definition of MS have varied with the general theories and fashions of the times. Even the purists among MS researchers acknowledge that remarkable changes in medical fashion over the last 2 centuries have not spared their discipline. In a way this is to be expected. Scientists, although forever curious, generally tend to investigate along
directions that have been imprinted on them—consciously or subconsciously—by mentors, colleagues and (more subtly) societal influences. It is the rare individual who breaks free from ingrained thought and investigates a problem accordingly. Such individuals may miss the mark completely, or make major breakthroughs in conceptualizing a disease and explaining its mechanisms. It is sobering to consider that some of the key issues first raised by those who pioneered the study of MS remain unsolved. The basic concept of the disease make-up, including the scope of the condition and its classification, the aetiology, relative importance of separate pathological constituents and its treatment, are all still controversial. Current debates mirror those of our neurological ancestors.

What is MS? To most people, it is an autoimmune inflammatory demyelinating disease, occurring in people with a genetic predisposition, and triggered by some additional factor, environmental or perhaps even a second genetic step. How did this idea develop? Again, we note that the elements of this concept were imprinted many years ago. The early gross anatomical and microscopic examinations of the French and English schools demonstrated the lesions, but it was with the development of sophisticated microscopic techniques from the second half of the 19th century onwards that the composite elements were fully described. The perivascular inflammatory infiltrates, the role of macrophages, demyelination, reactive gliosis and even the axonal changes were beautifully depicted, but the independence or interplay of these elements and the sequence of events remained unclear. For Eduard Rindfleisch, the inflammation denoted a vascular problem, whereas Jean-Martin Charcot believed that the primary pathology lay in the abnormal glia. It is now clear that many of these early theories were not competing, but rather that the various components occurred as part of the general reaction to inflammation of the nervous system. In our current controversies, what are we similarly missing? Even in the earliest descriptions of the disease, a familial or genetic tendency was noted and, today, there are few who do not accept a genetic basis for susceptibility. Once again, this was only confirmed with the systematic introduction of modern molecular techniques and the concepts of genetic epidemiology from which the full dividend is yet to come.

Of interest is a re-examination of how MS stands up as an example of an autoimmune disease. From the 1930s, the emerging science of immunology attracted MS researchers who were quick to grasp its ideas and apply new techniques as these developed. The identification of immune markers for myelin-specific T cells and antibody-producing B lymphocytes in the blood, cerebrospinal fluid and brain parenchyma have been well demonstrated. Together with the extensive use of animal models of immunity, especially experimental allergic encephalomyelitis (EAE) and with lessons from the response to immune-mediated therapies, the groundwork for current dogma was laid down and, until recently, accepted without question. Again, we should note that this evolution of evidence and concepts matches trends and opportunities seen with respect to other immune diseases over the same era. The parallels between Crohn’s disease and MS are striking, and this author is fond of referring to Crohn’s as ‘MS of the gut’. Many autoimmune disorders share immune-related abnormalities, and present pathologically as a chronic scarring disorder, punctuated by episodes of acute inflammation. Rheumatoid arthritis has a specific immune-related marker, and Crohn’s has a specific genetic marker. In addition, there is a spontaneous animal model for inflammatory bowel disease in which infection of the gut serves as the trigger. None of these features are present in MS, although whether they are present but are as yet undiscovered remains to be seen. Skeptical authors point to the presence of myelin-specific T cells in the blood of normal individuals, non-specificity of the oligoclonal or other antibodies in the cerebrospinal fluid or blood of patients with MS and the low efficacy of immunosuppressive and other disease-modifying agents. They warn against the dangers of extrapolating conclusions from an artificial immune-mediated animal model of autoimmunity to such a complex disorder. It is well to remember the mistakes of Galen who confined his work to anatomical dissections on animals, making incorrect conclusions that misled investigators for centuries. The overwhelming body of evidence does point to a role for immune factors in the evolution of MS, although whether the pathogenic immune reaction is a cause or consequence of the primary disease process continues to be hotly debated. Bernhard Hemmer and Hans-Peter Hartung have suggested ways in which tissue damage in the brain may release antigens that, in turn, cause a secondary immune reaction. Indeed, in their recent study of acute cases, Michael Barnett and John Prineas noted the absence of significant inflammation in areas where oligodendrocyte apoptosis and demyelination are present, suggesting that inflammation is indeed a secondary reaction to tissue damage. The fact that this does not occur in patients with other destructive brain lesions, such as stroke, calls this hypothesis into question.

Does infection trigger the disease process in MS, as is the case in inflammatory bowel disease? When the infectious theory was in fashion, millions of dollars were spent in an unsuccessful attempt to isolate an agent or agents that cause MS. The theory of molecular mimicry begs the discovery of such agents. Again, fashion rears its alluring head. Charcot and others wondered about syphilis as a cause during the era when the effects of this disease were being examined; and over the following 150 years, bacteria, viruses, spirochaetes, prions and other agents have all been suggested. Against this background, it is salutary to look at the investigation of the putative role of retroviruses. The lack of success, thus far, in finding an infectious agent in MS has prompted many, sometimes vehemently, to deny such a role. Indeed, those other arbiters of fashion, the granting agencies, today look on this kind of work somewhat unsympathetically. History warns us not to be too hasty in judgement; our concepts of subacute sclerosing panencephalitis, Creutzfeld–Jakob disease, progressive multifocal leukoencephalopathy and other
enigmatic conditions changed when new techniques led to the demonstration of defective viruses and prions. We remain dogmatic at our peril. The postulate of environmental toxins surfaces every now and then, but especially when public concern over these becomes marked. This was seen in the early 20th century when the clustering of MS around the Great Lakes was related to rising public concern over the level of chemical toxins, anxieties that are at times reactivated nowadays.

The defining feature of MS is demyelination. Well described by our predecessors, most workers in the field did not initially think much about the mechanism of myelin injury in MS. Once the notion that the disease is autoimmune in nature was accepted, views were extrapolated from the experimental immune model, where we knew that lymphocytes and macrophages activated by exposure to myelin antigens attack either the sheath itself or the oligodendrocyte. Many other forms of primary demyelination were known, both in the clinical and experimental situation. These included destruction of the oligodendrocyte by toxic agents such as ethidium bromide, Cuprizone and by ischaemia, as well as viruses, or following direct destruction of the myelin sheath, as in lysolecithin administration. Together, these provided useful information about some aspects of demyelination and remyelination, but the direct relevance to MS was less certain. This concept changed when Claudia Lucchinetti and co-workers at the Mayo clinic, in Germany and in Vienna, using material from acute cases, demonstrated evidence arguing for the existence of multiple pathways to demyelination and subsequent remyelination. They described four patterns in a large series of patients, each of whom showed only one such type in all their lesions. Whereas some of the patterns resembled the inflammatory reaction seen in EAE, consistent with an autoimmune basis, others showed destruction of the oligodendrocyte, suggestive of the dying back process seen in ischaemia among other causes.

The implications of this heterogeneity, if validated, are profound, not only for dissecting out disease mechanisms but also for defining the disease, or diseases, and ultimately in formulating a rational approach to differential therapy and diagnosis.

Few aspects of the disease better emphasize the dangers of ignoring the past and adhering slavishly to fashion, than does the tale of the role of the axon in MS. Although well described in both the German and French literature of the 19th century, as well as by James Dawson in Britain in the early 20th century, it was left to Hugh Perry and then, in a definitive study, Bruce Trapp and associates in the 1990s to bring the attention of the community back to this phenomenon. This neglect can only be explained by a collective closing of the mind to the written historical record, as well as an inability to break free from the predominant concept of MS as an autoimmune disease only affecting myelin. The repetition of the mantra of MS as a disease with ‘relative sparing of axons’ served only to reinforce the perceived primacy of the reaction against myelin. This may still be valid aetologically, but ignores the enormous and probably pre-eminent effect of axonal loss on the clinical symptomatology, as well as converting the course of the disease from a relapsing–remitting to a progressive chronic deterioration, resistant to disease-modifying agents. In distinguishing the early inflammatory (demyelinating) phase from the later ‘neurodegenerative’ phase, some authors have gone so far as to suggest that MS is in fact a primary neurodegenerative disease. The evidence for this is very weak. Uncertain as the evidence is for an immune reaction against myelin, it still far outweighs the very slender case for MS as a primary neuronal disease. These semantics are most important. Axons and neurons may be damaged in a number of neurological disorders, and even in MS may be the chief source of symptoms and outcome. However, in designating a disease as primarily ‘neurodegenerative’, the perception is created of similarity to diseases such as Alzheimer’s and Parkinson’s, with all the attendant implications for investigation and therapy. There is no solid evidence to support this position. Of great importance, however, both for understanding the aetiology and evaluating therapeutic potential, is the debate on why the axonal degeneration occurs. Two possible major factors exist: axonal damage secondary to persistent inflammation, or degeneration secondary to a lack of trophic influence from the myelin sheath and other elements. These are not necessarily mutually exclusive. Each might require a separate therapeutic approach—anti-inflammatory agents in the first, and growth factors and other trophic support in the second. However, it would seem to this reviewer that at least some elements of the inflammatory process are present chronically, and it is difficult for me to believe that they do not play at least some part in the pathogenesis. Two aspects of modern studies have caused surprisingly little controversy: the growing appreciation of widespread clinical symptomatology, affecting cognition and behaviour, often in the absence of a significant white matter plaque load, and the focus on involvement of the cortex and so-called normal appearing white matter. Appreciation of these changes has been considerably aided by sophisticated imaging techniques. Once again it is surprising how these cognitive and cortical features described many years ago, were ignored for so long.

Consideration of all these questions and controversies brings us back to the fundamental unresolved issue—what is MS? Is it a single disease or many? I like to use the analogy of stroke in framing the problem. A stroke can be caused by vasculitis, carotid embolus or a drop in blood flow, amongst many causes. Yet how do we conceptualize it? Is it a single disease with multiple aetiologies, or is it the common outcome of multiple causative conditions? The studies of Lucchinetti and colleagues cited above suggested heterogeneity, but Barnett and Prineas argue for a single disease, varying in intensity or stage in evolution. Again, we realize that we are as yet not in a position to settle this debate. However, personally I believe that at present the clinical, pathological and diagnostic literature on MS shows too much diversity and variation to be dogmatic in ruling out the concept of
heterogeneity, which is an attractive hypothesis demanding further investigation. This concept should spur investigators to look for meaningful correlations between the described four patterns (or any others still to be described) and the clinical management, diagnosis, genetic susceptibility or response to treatment. Ultimately, however, many diseases are defined as much by aetiology as by any other factor, and until we go beyond mechanisms to find the root cause or causes, we are bound to remain unsure. Historically, there are many precedents for these crises of identity in MS. Schilder’s disease was thought to be a form of childhood MS, until most cases were shown either to be viral in origin or due to inborn errors of metabolism. The relationship of acute disseminated encephalomyelitis (ADEM) to acute MS is uncertain. The fact that it most closely represents the human equivalent of EAE makes it tempting to include it in the MS spectrum, although there are some major differences. Nevertheless, major paediatric prospective studies are currently under way, designed to answer among others, the question of whether ADEM is related to, or progresses into, MS. Neuromyelitis optica is currently the best example of a disease whose putative place within the MS spectrum has been weakened following the demonstration of a specific biomarker. The discovery of an antibody to aquaporin 4, present in cases of neuromyelitis optica but not MS, points to the fact that it is a different disease, potentially ending years of controversy. Conversely, many cases of Balo’s concentric sclerosis also have features of more typical MS. Indeed, Balo’s concentric sclerosis virtually defines pattern 3, placing it firmly in the (heterogeneous) family.

So what do these two new books contribute to our knowledge and real understanding of MS? It is interesting to note that, in the evolution of medical and scientific publishing, books are now increasingly supplanted by journal articles or abstracts when it comes to the presentation of new discoveries. However, their role in accumulating a body of information remains indispensable for education of the relevant readership. Moreover, the role they play in directing future study is potentially even more important. Creating a thought-provoking text therefore involves wisdom in interpreting the past, preparedness to challenge prevailing ideas, and an academic call to action for the future.

The fourth edition of McAlpine's Multiple Sclerosis, written by Alastair Compston and seven colleagues is a monumental work. It deals in great depth with all of the issues mentioned above, with meticulous detail and referencing. Although it is naturally based on previous editions, it is entirely rewritten and breaks new ground in its scope, ambition, and sheer volume of information. At close to 1000 compactly printed pages, it is surely the most complete work on the subject extant. The sheer size and density of the content is at first blush intimidating. This is not a book for the faint-hearted. It does not give out its information easily—it requires dedicated reading by the serious reader, who is ultimately rewarded and taught so much more for the effort. The information is all there but one has sometimes to search through more than one
Multiple Sclerosis as a Neuronal Disease, edited by Stephen Waxman, is likewise a work of the highest quality, although its ambition is more limited. The title indicates from the start that is it not a comprehensive text laying out all the options for the aetiology and pathogenetic mechanisms of the disease, but rather has an agenda to push, which is to influence perceptions of the primacy of the axonal changes in MS. Indeed, many chapters are just as informative for other non-MS diseases that affect the axon. In this way, the book represents an update of the editor’s previous works on the subject—in this volume heavily weighted toward MS. In contrast to McAlpine’s Multiple Sclerosis, it has multiple international authors, each contributing a different aspect of neuronal and axonal anatomy, physiology and pathology, relating them to the events occurring in MS. It is of interest that there are authors in common between the two books. The flow of chapters is excellent; the book, because of its circumscribed mandate, is more immediately readable and succinct than its companion. Each chapter stands alone. This book too is an outstanding and comprehensive text, exhaustive and beautifully illustrated. The effects of disease on the axon are wonderfully depicted, and the authors clearly point out the membrane changes, the reorganization of channels, the physiological blocks and other axonal changes seen in clinical and experimental disease. Many of the same mechanisms damaging myelin can concurrently cause damage to the axon. Indeed, knowledge of how to protect the axon with trophic and growth factors, as well as the enhancement of remyelination, will I am sure, one day be a standard part of the therapeutic armamentarium. Does this make it a neuronal disease? Again, semantics are important. If the intent of the provocative title is to swing the pendulum, this is legitimate. If, however, the intent is to switch the primary target, then the evidence, to my mind, is not there. Most of the data still favour the theory that the primary target in MS is the myelin sheath. The chapter on the consequence to the axon of non-inflammatory demyelination in mice with myelin mutations highlights the integral importance of a myelin sheath for the axon, just as we accept that the integrity of the sheath depends on axonal influences and viability. If this is so, we should continue to regard MS as a myelin disease, and look for ways to prevent its attack by immune cells or any other agents, and thus prevent axonal damage. Unless this is done, we risk trying to find an aetiology for a secondary problem. Of course, given the historical precedents, I would be very wary of excluding any reasonable hypothesis, unless supported by reasonable evidence. This may be lacking because the evidence is not there, or because we lack the tools to see it, or the wisdom to recognize it.

The MS community is fortunate to be presented with these two texts. Each in its own way has provided us with a milestone in the understanding of the disease, and each, if read carefully and with thought, will provide a direction to the path ahead.

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doi:10.1093/brain/awl195