ABSTRACT

Multiple sclerosis has a long, fascinating, serendipitous, and well-documented history. The first recorded mention of the disease can be dated back to the fifteenth century, while a truly exhaustive investigation of the disorder began with the nineteenth century’s burgeoning neurologists. These records reveal a fascinating story of meticulous science aimed at comprehending a truly perplexing illness, one that even today is not completely understood. The great nineteenth century French neurologist Jean-Marie Charcot became very interested in studying this disease, and through his celebrity garnered much attention to a previously unknown affliction. Here we review a story of pioneering research that grants brief tribute to some of the more remarkable experiments, wondering if ideas born in the past may help develop solutions in the future.

A DUTCH SAINT, A BASTARD BRIT, AND THE FATHER OF NEUROLOGY

For half a millennium of documented effort, medical professionals have toiled in the attempt to alleviate their patients of multiple sclerosis. Today this illness afflicts about 400,000 people in the United States, and every week another 200 individuals are diagnosed with multiple sclerosis (MS). Scientific understanding of MS has evolved from utter bewilderment to an optimistic investigative insight with novel treatments in the pipeline. The story of MS is a fascinating journey of nineteenth and twentieth century medical ingenuity, a story with its humble scientific beginnings in the Middle Ages.

The first documented case of MS may be that of Saint Ludwina of Scheidam of the Netherlands at the turn of the fifteenth century. Obviously, the differential diagnosis of a 500-year-old case is fraught with the limitations of 500-year-old documentation. However, this particular individual, one eventually canonized as a saint, has a moderately descriptive biography drawn from such varied sources as a charter from the Count of Holland, early accounts of a close relative who lived with Ludwina for a time, and the copious writings of a Franciscan priest named Johannes Brugman. It is written and confirmed through the use of these multiple sources that on February 2, 1396, at the age of 16, Ludwina, a child of previously normal health, fell and broke one of her ribs while skating. It was soon realized that her healing was not progressing normally. Over the course of 37 years, what began early on as difficulties in walking degraded to partial paralysis as well as ocular deficits that perhaps can be attributed to optic neuritis, a common symptom and often a diagnostic characteristic of MS (Medaer, 1979). Interestingly, it seems that remyelination events during the course of MS illness may explain Ludwina’s periodic remission of symptoms that at the time were attributed to acts of God. Thus, it is not a far-fetched idea that MS had a hand in canonizing a saint.

If one is skeptical towards the belief of Ludwina of Scheidam as the first documented case of MS, then the story of Augustus d’Este, an illegitimate grandson of King George III of England, is probably the first undisputed illustration. In his diary, Augustus recorded his symptoms of MS that began with optic neuritis in 1822 and continued as a 26 year battle with the illness, complete with spontaneous remissions and a progression to paraparesis (Herndon and Rudick 1989). Clearly, MS has been with us for a long time.

FIGURE 1 I Original drawing by James Dawson from his seminal thesis on the central nervous system histology of multiple sclerosis.
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Another notorious neurological condition was also being hotly investigated during the nineteenth century. Upon the description by James Parkinson of the disease that was eponymously given his name, there arose confusion as to how to differentiate Parkinson’s disease from the “sclérose en plaques” of Charcot. The pronounced shaking tremor found in both diseases was the basis of this difficulty in establishing a differential diagnosis. It was through the creative and resourceful efforts of Charcot that these two neurological syndromes were distinctly classified. In addition to utilizing a bulky apparatus called a sphygomonograph to demonstrate the differences in frequency and amplitude in the tremors of both diseases, Charcot made the observation that extremely small handwriting, requiring a magnifying glass to be read, could be used to characterize Parkinson’s disease (Guillain 1959). Thus, one of Charcot’s greatest contributions to the understanding of MS was discriminating it from Parkinson’s disease.

The fact that such an eminent scientist of his day became involved in MS research and consequently brought great attention to it through the recognition of his name may interestingly have been an act of serendipity. It is recorded by two of Charcot’s protégés that their mentor became particularly interested in the neurologic disorder after his maid was afflicted by it (Dejong 1970). Charcot observed the woman’s motor and sensory functions deteriorate and diagnosed her with tabes dorsalis, a neurological disorder of the dorsal spinal cord commonly associated with syphilis. However, at the autopsy Charcot observed the sclerotic plaques that eventually came to characterize MS. By the turn of the twentieth century MS become one of the most common neurological admissions, due in no small part to the influence of Charcot. It is most likely that the rise in MS admissions resulted from an increase in clinical awareness rather than a natural epidemic.

MULTIPLE SCLEROSIS AND AN EMERGING FIELD

Though there is a wealth of literary resources available on the esteemed Charcot, it is equally important to recognize the contributions of his German contemporaries. In 1849, Friedrich von Frerichs first recognized the pattern of remissions, symptom of nystagmus, and the effects upon mental state that all were characteristic of MS (Raine, 1997). Contributions of the German School to nineteenth century neurology also included the identification of the focal vascular dissemination of MS lesions by Rindfleisch in 1863 and the identification of demyelination in MS by Fromman in 1864 (Compston, 1999). At the turn of the century, Otto Marburg put together a comprehensive clinical picture of acute MS including the understanding of its myelinotoxic inflammatory pathology. At the same time Charcot and the French school were piecing together the MS neurolog-
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HISTORICAL PERSPECTIVE

The nineteenth century neurologists made great strides towards composing a clinical picture of MS as well as associating the correct post-mortem pathology with the disease in life; however, little was known about the underlying cause of MS. Even Charcot admitted that he did not know what caused the disease, though he did speculate that MS may have been provoked by an acute infection, citing associations with cholera, typhoid fever, and small pox. Pierre Marie, Charcot’s pupil, became the greatest nineteenth century proponent for the role of an infectious cause in MS. The idea of an infectious etiology in the late 1800s may have been inspired by the recent microbiological revolution stirred by the work of Louis Pasteur. Interestingly, even though the definitive cause of MS remains unknown to this day, the concept of an acute initiator, such as infectious challenge, remains accepted by most specialists in the field. Perhaps the microbial doctrine originally proposed by nineteenth century neurologists was not as far off as one might have expected.

At the turn of the twentieth century, the prevailing theory for the etiology of multiple sclerosis was not the infectious cause emphasized by Charcot and Marie. Rather, the scientific community preferred the explanation that MS resulted from an inborn error in myelin metabolism, and this belief remained dominant until the conceptualization of autoimmunity early in the twentieth century.

The advent of photographic technology revolutionized the way that medical pathology was recorded, and consequently had a profound impact on the study of MS. Charcot, a strong proponent for the importance of medical illustration, was very much involved in the publication of the third volume Nouvelle Iconographie in 1890, which most likely included the first photographs of multiple sclerosis (Compston, 1999). These photomicrographs presented the spinal cord pathology of MS in series, and seemed a natural predication for even greater understanding of the disease’s progression. One would probably expect that improved diagnostic success was destined to follow as the photographic technology evolved. However, it was not until the development of magnetic resonance imagery (MRI) in the late twentieth century that photographic or radiologic techniques played any routine role in the diagnosis and treatment of MS.

One of the most interesting issues arising out of nineteenth century MS research was the absence of a single nomenclature. While Charcot and the French used the term “sclérose en plaques,” the English called the same disease “disseminated cerebrospinal sclerosis,” and the German School referenced the term “multiple sklerose” from nearly the outset. Reports on the subject of MS in the United States began to emerge during the 1870s, and an American, Hammond, coined the term “multiple cerebral sclerosis” in 1871. This neurological disease was also referred to invariably as Charcot’s disease when Julius Althans named the condition after the French neurology pioneer in 1877. Curiously, it does not appear that there was a consistent nomenclature utilized worldwide until the emergence of patient support groups in the 1950s.

In addition to the previously established infectious and inborn error of myelination theories, the turn of the twentieth century saw other explanations begin to appear in an attempt to explain the onset of MS. Adolf Strumpell, in 1896, championed the idea that the pathology of MS was secondary to glial overgrowth. Yet others, like Hermann Oppenheim in 1911, looked to a toxic etiology for an explanation, pointing to tin, carbonic oxide, and mercury as potential culprits. Some investigators simply looked for more definitive data in the hopes of finally proving one theory over the others.
NEUROLOGY IN THE TWENTIETH CENTURY

In the early twentieth century, many insightful advances in the study of MS came from James Dawson through his work published in the thesis “The Histology of Disseminated Sclerosis.” Dawson utilized extensive histological study to construct a sequential model for MS progression. He noted the process began with degradation of the myelin sheath, involved glial cell proliferation, included a fat granule cell formation and ‘fat granule cell myelitis,’ and culminated in progressive sclerosis (Dawson 1916). Dawson’s thorough pathological analysis helped significantly advance the field, and his comprehensive summary of the current body of research did much to consolidate and focus the efforts of other researchers.

A particularly interesting hypothesis came from Richard Brickner in 1931, with the belief that an abnormal lipase was to blame for the pathology of MS. Brickner utilized an acid titration assay to measure differences in lipid hydrolysis between the contents of serum taken from MS patients and those not afflicted with the illness. Though his work did not produce any conclusive data in support of an abnormal MS lipase, Brickner did contribute to the understanding of MS disease progression. He was among the first to assert that even though the areas surrounding the destruction of myelin were filled with immune cells, their presence “was not the result of an inflammatory process to an infectious agent” (Brickner 1931). Brickner’s abnormal lipase work illustrates that the twentieth century brought new efforts to understand the underlying disease process that could not be simply explained by infection or congenital myelin malformation.

It is extremely difficult to summarize all of the pertinent discoveries of the twentieth century relating to multiple sclerosis within a short review. For the sake of brevity, this paper will focus on a few of the more profound and seemingly karmic findings. One of these experiments of serendipity was conducted by Rivers and Schwentker in 1935, and may have laid the groundwork for an autoimmune model of MS. They demonstrated that injections of normal, sterile rabbit brain tissue could produce a myelin-destructive response in monkeys (Rivers and Schwentker, 1935). Though they still are unwilling to rule out an infectious etiology in their paper and do not offer an autoimmune explanation themselves, Rivers and Schwentker’s work not only presented some of the earliest data in support of an autoimmune process but also established a laboratory standard for studying autoimmunity in the experimental autoimmune encephalomyelitis model.

Remission of symptoms had been observed in MS perhaps as early as the case of Saint Ludwina of Scheidam. However, a mechanism for the cycling of symptoms in MS had yet to be devised. The work of Mary Bunge, Richard Bunge, and Hans Ris in 1961 demonstrated for the first time the process of remyelination, and offered a convincing new explanation for the spontaneous remission of symptoms in MS (other theories suggest spontaneous down-regulation of inflammation within the CNS). Bunge, Bunge, and Ris introduced lesions into the subpial spinal cord through repeated injection and the withdrawal of cerebral spinal fluid. By sixty-four days after CSF exchange, regions of damaged myelin were at least thinly remyelinated (Bunge et al., 1961). Now that remyelination had been firmly demonstrated and the spontaneous remission of signs could be at least in part explained neurologically, the scientific community moved even further along in understanding the pattern and progression of MS.

THE QUESTION OF TREATMENT

For a disease whose underlying cause is as mysterious as that of MS, it is not surprising that effective treatments have been just as elusive. Charcot, in 1866, held a pessimistic view of potential treatment:

Need I detain you long over the question of treatment? The time has not yet come when such a subject can be seriously considered. I can only tell you of some experiments which have been tried the results of which have, unfortunately, not been very encouraging.

This statement could be used to characterize much of the treatment attempts up until the 1950’s, when significant progress began to manifest. Throughout the nineteenth century searches for a vaccine, antidotes for toxins, and chemical therapies such as barium chloride treatments and carbonic acid baths were all attempted with little success.

Novel therapies were continually developed in the mid-1900s, but still less than desirable effects were achieved. In 1934 an initiative spearheaded by the American Neurological Association looked to fever therapy, previously shown to be successful in the alleviation of malaria symptoms, as an answer to multiple sclerosis. Perhaps focusing on the vascular orientation of MS pathology, Horton and Wagerer developed histamine-induced vasodilation therapy in 1948 (today it is understood that such therapy could potentially exacerbate the disease by compromising the blood-brain-barrier even further). Though such novel ideas were based upon what was believed to be pertinent data, they still did not offer long-term solutions for disease treatment.
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Not until the use of corticosteroid therapy to control the immune process of MS in the 1960s and 1970s was there a treatment that was at least mildly beneficial. The effectiveness of immunosuppressive therapy is not surprising, as it has been shown in recent years that the invasion of lymphocytes into the CNS via α4-integrin expression causes influx of myelin-antigen-specific T cells into the CNS and ultimately destruction of the myelin sheath. However, it has yet to be established whether such neurological destruction is the primary disease process or rather a secondary response. One of the hopes in unraveling this paradox lies in transcriptional analysis (Steinman and Zamvil, 2001). Using such analysis, potential therapeutic targets implicated in the CNS immune invasion, such as IL-23 and osteopontin, have been identified.

The complexity of MS has made drug design particularly perplexing at times, perhaps best illustrated by the failure of inhibition therapy of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α). While shown to be profoundly efficacious in rheumatoid arthritis patients in one trial, anti-TNF-α therapy worsened disease in MS patients in another trial (LMSSG, 1999). This paradoxical result perhaps best exemplifies the unconventional and heterogeneous nature of this disease. It is likely that a relatively large number of genes contribute to MS quantitatively (Martin et al., 2001), and one specific gene target or therapy is unlikely to be the ultimate answer.

Most recently, developments within the field of MS have become increasingly numerous while the areas of research have broadened. Some of the most significant breakthroughs of the late twentieth century in the realm of MS include: identification of genetic predisposition at the level of class II MHC, the role of leakiness within the “blood-brain barrier”, the role of myelin-specific T cell subsets, importance of changes in adhesion molecules (especially α4 integrin), evidence that myelin-specific antibodies are produced early in the disease course, limits of remyelination, presence of oligodendrocyte precursors, and the potential of cytokine therapy. Time will tell which of these areas of advancement hold the greatest therapeutic value.

CONCLUSION

Today, the science of MS includes theories of molecular mimicry, talk of superantigens, and clinical trials with inhibitors of immunologic adhesion molecules. MS research has certainly come a long way from its humble nineteenth century beginnings, but some of the same questions posed by Charcot still exist today. What is the acute event that underlies the induction of MS? Will we ever have a truly effective means of treating the neurodegeneration of this disease? Scientists today are still investigating Charcot’s “sclérose en plaques” at the laboratory bench and in clinical trials. However, today in an age of molecular medicine we can beg to differ with Charcot’s pessimistic nineteenth century outlook on multiple sclerosis therapy. Perhaps the time has finally come to “seriously consider the question of treatment.”

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REFERENCES


