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In Search of a Conceptualization of Multiple Sclerosis: A Historical Perspective

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A thorough understanding of Multiple Sclerosis (MS) is necessary to offer individuals informed options for treatment and planning. To assist in this quest, the following historical analysis examined how MS has been conceived from the 14th century through the early 20th century. Primary sources were consulted whenever possible, and many of the original archival materials were accessed by the first author (MB) during an on-site visit to the Rare Book Room of the New York Academy of Medicine. There is a striking similarity between how MS symptoms have presented throughout history compared with the 21st century. Sensorimotor and cognitive sequelae have been observed in patients since the 1800s. Cognitive symptoms were acknowledged in the 1800s, but disregarded in the early 1900s and were not given recognition again until the latter part of the 20th century. If conceptualizations of MS are inaccurate, patients will not be served well. In contrast to the shared symptomatology across time, early conceptualizations of etiology and treatment choices differed dramatically from today, a genuine reflection of the times in which they were created.

KEY WORDS: multiple sclerosis; history; demyelinating disease; cognitive deficits.

Historical analysis can be an invaluable contributor in developing a precise conceptualization of a disease process, including that of Multiple Sclerosis (MS). Having a proper conceptual framework of a disease is crucial in clinical practice to provide individuals with informed options regarding treatment and planning for the future. To assist in this endeavor, the following analysis examined how MS has been conceived from the 14th century through the early 20th century.

MS, also known as disseminated sclerosis in the historical literature, is a demyelinating disease of the central nervous system, which has been extensively researched since the mid-1800s. The symptoms cover a wide range, but are predominantly sensorimotor and cognitive in nature and are dependent upon the neuroanatomy that has been affected. As a result, symptoms are variable within and between individuals (Swiderski, 1998).

Collaborations between medical historians and physicians have been very useful in advancing conceptualizations of other diseases as well, such as Tourette Syndrome, a disease which shares a strikingly similar history to MS (Kushner, 1996).

As an example of how historical analysis can contribute to a more thorough understanding of a disease process, consider that in recent times the acknowledgment and legitimacy of the cognitive symptoms of MS has often been called into question. The dearth of studies, in the early to mid-1900s, investigating cognitive sequelae in MS, has been ample evidence for this trend. Yet, if one examines how symptoms presented in the 1800s, for example, it is apparent that the cognitive deficits, as well as the sensorimotor deficits, have been well documented in individuals that have experienced those difficulties. However, in the early part of the twentieth century, the focus was predominantly on sensorimotor deficits and consequently treatment options reflected this new belief system. The cognitive deficits and possibilities for intervention were disregarded for approximately 70 years and it would be detrimental to many individuals with MS if

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clinicians did not learn from previous errors or omissions. Historical analysis provides insight into the larger context in which some phenomenon has occurred so that we can more clearly reflect on where we have been and where we still need to go to reach our objectives. The time is ripe for MS to also be considered within this broader context.

SELECTED WORKS FROM THE HISTORY OF MS

Although historical analyses can meaningfully contribute to an enhanced appreciation for the nature of a disease, MS research has concentrated on etiology, treatments, symptoms, mechanisms of the disease process, and to a lesser extent on how the disease has presented throughout history. Notable exceptions are the works of Compston (1988), Medaer (1979), Murray (1999), and Swiderski (1998).

Swiderski has compiled an exceptional, comprehensive review of this history, albeit by reviewing the best secondary sources available. An exception to secondary source review would be his astute analysis of the archival documents of Carswell (as cited in Swiderski, 1998) and Cruveilhier (1840), two of the first pathologists to describe the histology of the MS lesion. Murray (1999) focused on the individuals that most likely had MS before MS had been identified as a disease. His strength is his enlightened interpretation of the original historical documents on Auguste d'Este, Grandson of George III of England. The materials he used to research additional individuals were some of the most reputable, secondary sources available.

Compston (1988) also conducted a limited review of the history of MS, to determine who was the first individual to describe and depict the lesions of MS, Carswell or Cruveilhier. A review of the literature contained conflicting information, so Compston carefully reviewed the original anatomical atlases of these two individuals and determined that Carswell's description preceded Cruveilhier's by three years. Although, after the first author's (MB) review of the archives, it is clear that Charcot and his colleagues undoubtedly believed that Cruveilhier was a more significant contributor than Carswell.

Another limited analysis of the history of MS was done even earlier, in 1979, by Medaer, which focused exclusively on the frequently cited case of St. Lidwine of Schiedam. After reading the original documents pertinent to St. Lidwine, Medaer claimed that she suffered from MS in the 1300s–1400s. These documents included hagiographies and the original papers from the University of Leidan where her skeletal remains were examined. His methods are controversial because the original documents that he examined were written to support canonization, not to conduct a clinical diagnosis. Hence, the conclusions that can be drawn from them are circumspect.

METHODS

The goal of this research was to provide practitioners with a conceptualization of MS as it has been understood from the 14th century through the early 20th century. Special consideration has been given to the cognitive deficits that have been acknowledged at times and disregarded at others. Original sources were consulted whenever possible and included the procurement of several archival materials during an on-site visit to the Rare Book Room of the New York Academy of Medicine. When necessary, French documents were translated by MB. The categories of materials reviewed included: (1) biographies of the earliest recorded cases of probable MS; (2) diaries and autobiographical accounts of individuals with probable MS; (3) early scientific contributions in MS research, including works by Charcot, Carswell, and Cruveilhier (see Table 1 for major conclusions).

BIOGRAPHIES OF OLDEST RECORDED CASES OF PROBABLE MS

Historical accounts of MS often cite Auguste d'Este (1794–1848), Grandson of George III of England, as the first recorded clinical case of MS. This does seem to be the first nearly *undeniable* clinical account of MS. D'Este's diary provides autobiographical details rich in information about how MS presented in d'Este (Murray, 1999).

However, other historical accounts, indicate that MS may have existed as early as the 14th century. (This does not negate the possibility that MS also existed before the 14th century as well.) There are two cases that fit into this category. The first, more prevalently cited case, is the case of St. Lidwine of Schiedam. The second is of an Icelandic Viking woman named "Halla" who is cited less frequently than St. Lidwine in various literature reviews on the topic.

St. Lidwine of Schiedam

Lidwine (1380–1433) was born in Schiedam, Holland and experienced a healthy childhood up until the age of fifteen, when her medical difficulties began. The precipitating incident of the debilitating illness that was to follow seems to have been a skating accident in which she fell and broke her right rib. An abscess formed where the

Table 1. Major Conclusions

Source	Dates	Contribution	Confidence in findings based on source*
Biographies of earliest recorded cases of probable MS			
St. Lidwine	Late 1300s–early 1400s	Many have claimed that this is one of the first observed cases of MS	0 (need more evidence)
Halla	Early 1300s	Some argue that this is one of the first observed cases of MS	0 (need more evidence)
Diaries/autobiographical accounts			
Auguste d'Este	Early to mid-1800s	Many cite this as first recorded clinical case of MS	2.5
Heine	Early to mid-1800s	Had probable MS	2.5
Barbellion	Early 1900s	Had probable MS	2.5
Early scientific contributions			
Carswell	1838	First person to histologically document lesions	3
Cruveilhier	1842	First person to document MS with clinicopathological approach	3
Charcot	1868	First accurate and comprehensive clinicopathological description of MS; included cognitive deficits	3
Bourneville	Mid–late 1800s	Acknowledged cognitive symptoms and disconnect between cognitive and spinal symptoms; used clinicopathological approach	3
Babinski	Late 1800s	Acknowledged cognitive deficits; used clinicopathological approach	3
Malherbe	Late 1800s	Acknowledged cognitive deficits; recorded case of shortest duration (1 yr.); used clinicopathological approach	3
Moxon	Late 1800s	Spearheaded MS research in England; used clinicopathological approach; findings paralleled Charcot	3
Bouchaud	Late 1800s	Acknowledged cognitive deficits; used clinicopathological approach	3

**Note.* Confidence scale: 0 = no confidence; 1 = some confidence; 2 = reasonably confident; 3 = very confident.

fracture occurred and the wound was slow to heal. After this event, Lidwine's life was forever changed (Huysmans, 1923; Medaer, 1979).

Throughout the 37-year course of Lidwine's illness, she experienced a variety of different physical symptoms, some of which are reminiscent of MS today. Lidwine's deficits included sensorimotor symptoms, swallowing difficulties and pain. Her motor disturbances progressed from moderate to severe, presenting primarily as gait ataxia. At first, Lidwine could rely on furniture for support to move about a room, but then as the disease progressed, walking became impossible. She spent most, if not all, of her time in bed and needed to be carried to any other location (Huysmans, 1923; Medaer, 1979). Most accounts agree that she was paralyzed throughout her body except for gross head movements and movements of the left arm. This paralysis included her face as it is frequently cited that she had a "split face and hanging lip (Medaer, 1979)." She also suffered from general disturbances in sensation and visual deficits characterized by blindness in varying severity in both eyes, but no cognitive deficits were reported. (Medaer, 1979). It was a common belief that St. Lidwine's suffering and her experiences were miracles and this belief led to her eventual canonization (Huysmans, 1923). Clearly, the spirit and context of the times contributed to the interpretations that prevailed about her disease. The peak of the Renaissance and the medical model were still in the distant future. It seems then that it is a possibility that Lidwine had MS, but that considerable prudence should be exercised in this assumption.

In addition to the biographies of St. Lidwine, Medaer read the original papers from the University of Leidan where the skeletal analysis was performed. The pathology that was observed in the skeletal remains could be indicative of MS, but other interpretations are possible as well. Since Medaer was unable to physically examine the patient, he used modern criteria to diagnose the suspected MS as he worked through the above mentioned hagiographies and skeletal reports.

After Medaer's (1979) review of these documents, he concluded that, "Although discussion about the diagnosis still remains possible, we think that the aforementioned documents are sufficient proof that MS existed in the 14th century" (specifically in the case of Lidwine) and possibly before that time as well.

Kushner (1999), a historian of medicine, has remarked that clinicians face a daunting task while interpreting the meaning of the symptoms of a patient they actually *have* examined; imagine the challenge to judge a case, whose meaning has been interpreted to make a clinical argument (or in this case an ecclesiastical argument). The clinical case can become evidence for the author's conclusions. Medaer's conclusions may have been colored by his own perceptions but also undoubtedly by the hagiographers who preceded him. So although the case of St. Lidwine is cited in many introductions for journals and books as the first probable case of MS, skepticism is warranted when considering the validity of such analyses.

Halla, Icelandic Viking

The story of Halla is located in the Icelandic saga of St. Thorlaks. The story read that:

> ...a woman called Halla got such a bad illness that she lost sight of both eyes, and on the next day, she lost her speech, then she made a vow in her mind, with the advice of those who stood by, to almighty God for cure and to the holy bishop Thorlaks for intercession, to walk to Skalholt and fast on bread and water before Thorlaks mass, and some prayers in addition. On the third day, a candle wick was put around her head, and she then recovered the sight of one eye, and was able to open both. As the saga of St. Thorlaks suggests, she recovered her speech and on the feast of St. Michael during the elevation (of the host) she recovered the sight of the eye that had previously been blind. (as cited in Poser, 1995, p. 12)

The miracle is said to have taken place between 1293 and 1323. The only reference to Halla that was found during the present literature review was in Poser (1995) in which he hypothesizes about the Viking origins of MS. Here is a case of researchers in the 20th and 21st centuries, traveling back in time to the 14th century, reading miracle stories and hypothesizing about the medical condition which was cured by the supposed miracle. It would seem that some intelligent skepticism is warranted once again.

DIARIES/AUTOBIOGRAPHICAL ACCOUNTS

d'Este

D'Este's autobiographical account includes a compilation of letters, diaries, account books and other manuscripts kept or written by Lady Augusta and her son. Combined, they provide what is possibly the earliest clinical account of disseminated sclerosis (Firth, 1948). (This diary can only be read in its entirety in Firth's book.) Murray (1999) recently visited the Royal College of Physicians in London and accessed the most primary documents available regarding this case. The next closest source was published by Cambridge University Press and edited by Douglas Firth in 1948, which was not long after the diary had been uncovered after the Second World War. Firth

provided the medical commentary to the diary, which helps the reader connect the reported symptoms with MS pathology. This information is a more reliable account than the work done by Medaer (1979) in which he connected ecclesiastical writings from the 1400s with MS criteria from the 1960s.

When considering the history of MS, diaries and autobiographical accounts add a level of legitimacy beyond biographies because they are written by the individuals suffering from the affliction. They write about how they are feeling, what they can and cannot do, and about how their lives are changing due to the disease process. Although, in some cases they do not know what the disease is that they have acquired. Unfortunately, an autopsy was never performed on d'Este, so the clinicopathological profile was incomplete. Beginning with the work of Cruvielhier, Charcot and many others, post-mortem techniques became more common. Even though autopsy data are unavailable, the detailed symptomatology leaves little doubt that d'Este's affliction was MS. This is in contrast to the stories of Halla and Lidwine for which more assumptions have been made.

Symptomatology

D'Este's diary was written with exceptional detail regarding the symptoms that he experienced. The following are quotations from the diary, which illustrate some examples of the symptomatology. D'Este experienced symptoms that are frequently reported by individuals with MS today, i.e., visual disturbances, paresis, Ulthoff's phenomenon (heat sensitivity), bladder and bowel control problems, paresthesias, tremors, spasms, and impotence. The language and spelling used are Old English.

One of many accounts of his visual impairment was noted in 1823.

> In the month of December, I traveled from Ramsgate to the Highlands of Scotland for the purpose of passing some days with a relation for whom I had the affection of a son. On my arrival I found him dead. I attended the funeral, there being many persons present I struggled violently not to weep, I was however unable to prevent myself from so doing; shortly after the funeral I was obliged to have my letters read to me, and their answers written for me, as my eyes were so attacked that when fixed upon minute objects indistinctness of vision was the consequence . . . soon after, I went to Ireland and without any thing having been done to my eyes, they completely recovered their strength and distinctness of vision. In 1825, I sometimes saw imagined spots floating before my eyes . . . In 1826, my eyes were again attacked as they had been in Scotland . . . In 1827 I began to suffer from a confusion of sight . . . the malady increased to the extent of my seeing all objects double. (Firth, 1948, p. 25)

Additional symptoms were noted in 1843.

> What I complain of now is...that sitting produces a numbness all down the back part of my thighs and legs, and gives me a curious numb sensation in the lower region of the belly.... When standing or walking I cannot keep my balance without a stick.... I sleep well when I am not annoyed with little nervous twitchings in my legs and feet...for the first time in my life I was attacked by giddiness in the head (vertigo), sickness and total abruption of strength in my limbs (p. 36). ...the attack came on whilst I was in my phaeton. I was able to drive to my own house, but totally incapable of getting out of the phaeton. I was carried up to my bedroom where I was sick as a dog, and broke out in the most perfuse perspiration. (Firth, 1948, p. 39)

In summary, the symptomatology that d'Este endured is parallel to the sensorimotor symptomatology that many individuals with MS report today. Depending upon the anatomy involved, it is not unusual for some individuals to have predominantly sensorimotor symptoms while some individuals have predominantly cognitive symptoms and some individuals clearly have both. These symptoms can also fluctuate during the course of the disease in a given individual. So d'Este may never have had cognitive symptoms or he may have had them at some other time during the disease process but did not document them. In addition, the pattern that d'Este depicted is similar to the relapsing-remitting pattern that most individuals with MS experience today (Chelune, 2002).

Treatments

Although the mid-1800s marked the beginning of the development of an accurate conceptualization of the symptoms of MS, the treatments were still light-years behind. Some of the treatments used on d'Este included leeches for diplopia, eating beef steaks with wine twice a day, backrubs with alcohol, opium and oils, and being slapped by his servant to regain his strength. For pain, plaster was applied and he would take extremely hot baths (we now know the heat probably exacerbated symptoms). Bathing, in sulfate of zinc, hot springs, vapor caves or the sea, was also used for its potential therapeutic properties. Frequently, d'Este would be vigorously rubbed with a wet sheet and sometimes he wore a wet band of material around his waist. He ingested many different substances as treatments throughout the course of his illness, some with active properties and some inert. These included valerian, strychnine, quinine, nitric acid, ammonium carbonate, mercury, cinnamon, healing waters, rhubarb, and iron oxide. Galvanism (direct current electricity) was applied to his muscles and healthy activities were encouraged such

as horseback riding and walking (especially in the mountains) (as cited in Firth, 1948).

Heine

Heinrich Heine was an internationally acclaimed poet in the early 19th century whose poems and songs inspired music by such classical artists as Schubert, Schumann, Mendelssohn, Wagner and Strauss to name a few. Some have said that he is second only to Goethe among the great German poets and, like d'Este, he most likely suffered from MS. In a collection of poetry, Heine included an autobiographical essay entitled *Self-Portrait: Lazarus*. Within it are many letters that he wrote to his family and other acquaintances, many of whom were prominent Europeans. In these letters, he reveals with impeccable detail, how his disease was progressing and affecting him. Although, neither he nor his physicians were certain about the diagnosis. Throughout the letters, it is apparent that he strived to maintain an attitude of tranquility amidst his suffering and anguish, but this was no small task. The excerpts that follow are from a collection of Heine's letters that was republished without modifications in 1948.

> To Heinrich Laube
>
> Paris, January 25, 1850
>
> Dearest Laube: Only a few days ago I learned that you had become theatrical director in Vienna, and that made me so happy that I could no longer put off writing you at once. The reason I was silent was that I had the painful feeling that I had nothing pleasant to tell you. I was always waiting for a sound hour and for some good news before writing you. But the hours and the news have since become worse. The rumors concerning my state of health are unfortunately more than true. For the last year and three-quarters, I have been tortured day and night by the most horrible agonies, confined to my bed, and paralyzed in all my members. Incessant cramps, most insufferable spasms, practically total blindness-a calamity rarely met with in the annals of human suffering-an unheard of, horrible, and insane calamity. (Heine, 1948, p. 460)

In addition to the above-mentioned symptoms, Heine also had a constellation of many other symptoms, which are frequently reported by individuals with MS today. All of these symptoms followed a relapsing-remitting pattern except as he neared his death at age 59, 24 years after the onset of his symptoms. At this time, they became progressive. Symptoms included: severe migraines, recurrent depressions, facial paresis, diplopia, perceptual and color distortions, eye pain, numbness, impotence, ptosis, facial hyperesthesia, blindness, paralysis, gait disturbances, ageusia, difficulty swallowing, dysarthria, muscle spasms, incontinence, weight loss, constipation, respiratory complications, L'Hermitte's Sign, and Ulthoff's Phenomenon. The depression may have been reactive to his circumstances or itself may have had an organic basis. In these letters, Heine often discusses the various treatments that were prescribed for him (Heine, 1948).

Heine says that he was treated with overdoses of opium and morphine, which often led to a "desolate narcosis" or a "doped wildnerness." The other treatments that were attempted are strikingly similar to those used on d'Este, such as leeches, bloodletting, sulfur baths, etc. Physicians at the time were not certain of the diagnosis. They entertained diagnoses of neurosyphillis, amyotrophic lateral sclerosis, encephalomyelitis, spinal muscular atrophy, and spinal tuberculosis. Heine himself believed that it was neurosyphillis due to his promiscuity in his youth (Murray, 1999). It was not until later that writers who were familiar with disseminated sclerosis started researching the possibility of this diagnosis for Heine. No autopsy was performed on Heine to clarify the pathology of this illness.

Barbellion

Like d'Este, Barbellion wrote his autobiography in diary format in *Journal of a Disappointed Man* in 1919 and also suffered from probable MS. According to the journal, neither Barbellion nor his physicians were certain of his diagnosis. Since no autopsy was performed on Barbellion, this case is lacking in additional corroborative evidence compared with techniques that incorporated pathological information. The title of Barbellion's journal is an accurate reflection of its content. In this autobiography, Barbellion, a zoologist by trade, is brutally honest about coping with this illness, which caused the progressive deterioration of his sensorimotor functioning and his eventual death at the age of 28. Barbellion suffered from a profound depression in reaction to living with this devastating illness. In fact, he had contemplated suicide as a solution for achieving freedom from the disease. He believed that each hour was a conquest and that stated that there were several times he had gone to bed and hoped he would never wake up. Barbellion wrote that he believed that he was developing locomotor ataxy (a condition often confused with MS at that time). He experienced ipsilateral paresis, paralysis, paresthesias, visual disturbances, and dysarthric speech. His had impaired writing; he stuttered when excited and his head movements were difficult to control. No cognitive symptoms were noted. A comment that is revealing about how etiology was understood at that time occurred when a nerve specialist examined

him. When the specialist could not find any symptoms of a definite disease, he asked Barbellion suspiciously if he had ever been with women (Barbellion, 1919).

Although not an inspirational book for individuals with MS, it is brutally honest and realistic regarding Barbellion's experience. He was a keen observer of that experience and was able to effectively portray the story of his life with MS.

EARLY SCIENTIFIC CONTRIBUTIONS

By the 1830s, new scientific methods were being implemented by physicians to better understand disseminated sclerosis. Interestingly, many of these physicians also shared an artistic prowess, which allowed them to also recreate their observations with great precision. (Carswell, Cruveilhier, and Charcot were all accomplished artists.) At the minimum, the methodology involved post-mortem pathological analysis of the nervous systems of individuals who were suspected of suffering from disseminated sclerosis. At their best, the physicians had known the patients for several years before their passing, thereby gathering a plethora of clinical and diagnostic information before death. They then followed up with dissection post-mortem and correlated the clinical profile with that pathological data. This method was later called the clinicopathological approach by Charcot, and it proved invaluable in terms of medicine gaining firmer ground as researchers attempted to reveal the nature of disseminated sclerosis. This method certainly added more validity to our understanding of this disease compared with the biographical and autobiographical sources mentioned previously.

Carswell and Cruveilhier: Earliest Depiction of MS Lesions

Two of the first scientists to research disseminated sclerosis were Robert Carswell and Jean Cruveilhier, although their path to learn more about this disease is not without controversy. There is some debate shrouding the determination of who should receive credit for first identifying the lesions of MS. These two scientists are the two contenders for this distinction, although many casual readers of the MS literature might assume that it was Charcot in 1868. Although Charcot was the first individual to masterfully describe MS using his implementation of the clinicopathological approach, he was not the first to describe these lesions, nor was he the first to use this approach. Carswell and Cruveilhier were both physicians, pathologists and medical illustrators, both experts at their craft. Many sources cite Cruveilhier as first because the date of the first volume of his pathological atlas was dated 1829, while Carswell's was 1838. However, the second volume of Cruveilhier, the one that pertains to MS, was not written until approximately 1841. This would make Carswell the first person to depict the lesions of MS.

Compston (1988) examined the originals of each atlas and arrived at this same conclusion. However, it is also well documented that many eminent neurologists, such as Charcot and his students, who were pursuing the study of this disease, always credited Cruvielhier with this distinction. This might have been because Carswell focused on the specimen post-autopsy without much knowledge about the living patient, and Cruveilhier, pioneering the clinicopathological approach, emphasized both the living patient and his symptoms along with the pathological anatomy. It seems likely that these neurologists, also proponents of the clinicopathological approach, valued Cruveilhier's work more than Carswell's and it is for this reason that they credited Cruveilhier as the first individual to depict the lesions of MS and not Carswell (Cruveilhier, 1829–1842; as cited in Swiderski, 1998).

MB accessed the original French version of Cruveilhier's pathological atlas printed as two volumes from 1829–1842 while conducting this archival study in the Malloch Rare Book Room at the New York Academy of Medicine. The pages were yellowed and brittle, but despite this, the text and the color plates were remarkably well preserved. As MB searched through each individual case, she finally came across the case of Josephine Paget, fascicle 38, plate 5, the first case of MS documented using the clinicopathological approach (Cruveilhier, 1829–1842). (The first depiction of the lesions of MS using the clinicopathological approach can be seen in the online version of this article in *Neuropsychology Review* in Issue 13, Number 2, 2003.)

Charcot, Babinski, Bourneville, and others all referred respectfully to the case of Josephine Paget. It was included in a section entitled *Maladies de la Moelle Epiniere,* translated *Diseases of the Spinal Cord.* Josephine Paget, 38 years old, was in the hospital La Charite on May 4, 1840. She had bronchitis when Cruveilhier first examined her and was quite weak. She could hold herself upright and walk with assistance, although her legs trembled in the process. Her left leg was weaker than her right and after 18 months, this became more pronounced. Paget dropped her bread, her spoon, anything she tried to hold. Cruveilhier diagnosed an illness of spinal tissue and since there was no serious pain, a paralysis due to fluid compression of the spinal nerves. By March 9, 1841, she was feeling pain on her left side and greater numbness, though she retained the ability to

Table 2. MS Symptomatology of Charcot Compared with Symptomatology in 2002[a]

Charcot's symptomatology	Symptomatology—2002
Visual Function: diplopia, amblyopia, nystagmus, optic neuritis	Similar findings
Motor Function: ataxia, dysarthria, paresis, intention tremor; final stage: permanent contracture of limbs	Similar findings
Other Sensory Function: vertigo ("giddiness"); less of a problem than other symptoms, sometimes formications, numbness, pain	Paresthesias consistently reported; acknowledged more frequently than in Charcot's time
Cognitive Function: intellectual decline, memory deficits, "total and complete blunting of intellect and emotional faculties", "stupor"; final stage: dementia, "unintelligible grunting"	Rao states that 45%–65% present with cognitive dysfunction (subtle to moderate) absence of dementia in most; occurrence and pattern of dysfunction are variable; might include information processing speed, memory, problem solving, visuospatial abilities, attention, language
Bladder/Bowel Function: incontinence, rare but possible	More frequently reported than in Charcot's time
Emotional Function: pathological laughing and weeping	Similar findings; also frequently includes depression
Vital Function: swallowing, respiration, circulation	More typical toward final stages
Etiology: "moist cold, problems of moral order; grief, vexation"	Prevalent theory: Slow virus/autoimmune disorder
Prognosis: "has hitherto been of the gloomiest", fatal ailment, significantly decreased life expectancy	Not a fatal disease; can expect 90%–95% of the normal life expectancy
Treatment: "the time has not yet come when it can be considered," trial and error, few successes	Symptom management agents: Disease modifying agents: immunomodulators, immunosuppressants, cytotoxic agents
Gender Distribution: higher prevalence in females	Similar findings: Of people with MS, approx. 73% female and 27% are male
Disease Course: relapses and exacerbations	Relapsing-remitting: 55% Secondary progressive: 31% Primary progressive/progressive relapsing: 14%
Comorbidity with Psychiatric Illness: depression, paranoia, bipolar disorder	Similar findings
Speed of Processing: slow formation of ideas	Similar findings
Age at Onset: 25–30; "a disease of youth"	Similar findings
Facial Expression: "vague, uncertain expression, hanging, half-open lips"	No mention of this
General persistent weakness	Fatigue

[a]Current information from "Multiple Sclerosis and Neuropsychology in the 21st Century," by G. Chelune, 2002, in a workshop conducted at the meeting of the 22nd Annual National Academy of Neuropsychology, Miami Beach, Florida.

move her fingers. Her skin had lost feeling, but her muscles were highly reactive. He was sure this was an acute spinal arachnitis, an infection of the arachnoid layer of the spine. By March12, the pain had grown so severe she cried out, "Dogs are gnawing at me." She died on March 20 from a bronchial blockage (Cruveilhier, 1841; Swiderski, 1998).

Most of the cases that were cited earlier in this paper, including d'Este and Heine, were not autopsied. So at this point, another level of investigation was being explored. Cruveilhier performed an autopsy on Paget, which revealed pleurisy of the left lung. At first the spinal column seemed unaffected but on closer examination Cruveilhier discovered that the nervous tissue had succumbed to a grayish degeneration. On the white matter of the spinal cord, these areas of degeneration took the form of patches. They were superficial but reached some depth in the gray matter. They were more dense than the spinal cord itself, and they replaced the spinal matter, precisely filling in any gaps without forming a line (Cruveilhier, 1841). This first autopsy seemed to be a monumental leap in terms of conceptualizing disseminated sclerosis.

Charcot: First Accurate and Comprehensive Clinicopathological Description of MS

Although Cruveilhier was one of the first individuals to implement the clinicopathological approach, Jean-Martin Charcot (1825–1893), often referred to as the father of clinical neurology, was the first individual to provide a more comprehensive description of disseminated sclerosis based on this new methodology (see Table 2 for a comparison of Charcot's description of MS and the current information). That is, when attempting to understand a disease process, he felt it was equally important to collect both detailed clinical information and detailed pathological information. In 1868, he presented *The Lectures on the Diseases of the Nervous System* to medical students at La Salpetriere in Paris. At the beginning of the *Lectures*,

Charcot recognizes M. Vulpian as being a vital contributor to the *Lectures* because he and Charcot worked side by side for many years at La Salpetriere where many of the cases were identified. Some of the clinicopathological work was conducted by M. Vulpian predominantly, some by Charcot, predominantly, and some of the work was shared more equally by both physicians.

MB read the 1877 *Lectures* in both the French and English versions while at the New York Academy of Medicine. The presentation of the *Lectures* included visuals of sections of autopsied brains that were properly stained to enhance certain neuronal features, and in parallel with this pathology, Charcot would supply the students with an abundance of clinical information from those same individuals. The *Lectures* covered every aspect of MS, i.e., pathology, etiology, course, symptomatology, prognosis, and treatment. Of interest is that so much of what Charcot asserted is still supported today. This is particularly apparent regarding pathology, course and symptomatology of MS. The sections on prognosis and treatment are much more reflective of the Zeitgeist present in the mid-1800s.

Historical Note

In a Historical Note at the beginning of *Lecture VI-Pathological Anatomy*, Charcot gives credit to Cruveilhier for being the first individual to describe disseminated sclerosis.

> Disseminated sclerosis is found mentioned, for the first time, in Cruveilhier's *Atlas d'Anatomie Pathologique,* 1835–1842, an admirable work, which ought to be more frequently consulted by all who desire to avoid the disappointment of making second hand discoveries in morbid anatomy . . . You will observe representations of the lesions found in disseminated sclerosis, and side by side, you can read the clinical observations which relate to them. Previous to this epoch, so far as I am aware, there is no trace of disseminated sclerosis to be discovered anywhere. (Charcot, Lecture VI, 1868/1877, p. 158)

Charcot recognized that Carswell also depicted lesions that pertain to disseminated sclerosis in his 1838 *Atlas*. However, Carswell does not relate any clinical case in connection with this subject and for Charcot this omission clearly places Cruveilhier's work above Carswell's in terms of its clinical utility.

Macroscopic Anatomy

In the *Lectures*, Charcot presented the macroscopic anatomy, the microscopic anatomy and the clinical observations from case studies (see Fig. 1 for an example of macroscopic section). Regarding the macroscopic anatomy and the external examination, he said that this information could only give an imperfect understanding of the lesion because the randomly situated spots or patches in the central nervous system that Charcot had observed penetrated the substance of the tissues. So he would always follow up with microscopic examinations (Charcot, Lecture VI, 1868/1877).

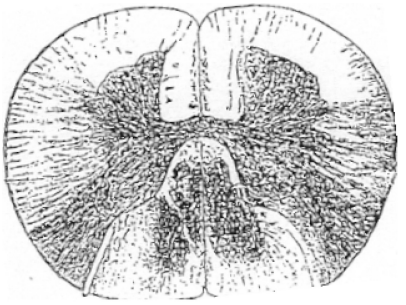

Fig. 1. Macroscopic Anatomy: Representation of lesions observed on a section taken from the uppermost portion of lumbar region. The posterior columns are invaded throughout their breadth and the lesions predominate in their middle region (from Charcot, J. M., *Lectures on the diseases of the nervous system, Lecture VIII*, 1868/1877, p. 215).

Macroscopically, Charcot observed that the lesions could be salient and swollen and at other times they would be flush with adjacent parts. In addition, older lesions tend to be more concave. The lesions observed were similar in color to gray matter, but when they made contact with the atmosphere, they had a rosy appearance and were vascularized. Their consistency was firm and when sectioned on a clean surface, they released a transparent fluid (Charcot, Lecture VI, 1868/1877).

Regarding the "encephalon," or cerebrum, Charcot stated that in general the cerebrum had not undergone "modification of form or color" because the patches were not frequently found on the "gray substance of the convolutions." He continues on to say that the story is quite different regarding the central portions of the cerebrum. Centrally, the patches were found on the "walls of the ventricles, in the white substance of the centrum ovale, the septum lucidum, the corpus callosum and in certain regions of the gray matter such as the optic thalami (Charcot, Lecture VI, 1868/1877).

The cerebellum was described as having only internal patches that primarily affected the corpus rhomboideum, the bulbus rachidicus, the pons Varolii, and various parts of the isthmus. Although, Charcot knew that disseminated sclerosis could present as either, cephalic, spinal or cerebrospinal, Charcot favored studying the spinal cord above all other regions including the brain, because he felt more comfortable due to its simplicity. Consequently, most of his lesion analyses were derived from samples from

diseased spinal cord (Charcot, Lecture VI, 1868/1877). However, he also said that the cerebrospinal form was the most interesting and one that the medical students would mostly see in practice (Charcot, Lecture VII, 1868/1877).

Upon macroscopic examination of the cord, he said that often through the pia mater, one can observe grey spots that sometimes assume a rosy tint or salmon color on contact with the atmosphere. If the pia is extracted, they are more readily observed.

In addition to the spinal cord and other above mentioned structures, the three cranial nerves that are the most often affected are the optic, olfactory and trigeminal nerves (Charcot, Lecture VI, 1868/1877).

In conclusion, using these macroscopic techniques, Charcot documented the appearance and location of the lesions of disseminated sclerosis and was aware that these lesions could occupy different neurological regions in different individuals. He also insightfully surmised that this variation of position should be represented by very different functional disorders (Charcot, Lecture VI, 1868/1877). For example, if the damage occurs in the cerebral hemispheres, it would be predicted that cognitive deficits could follow. In fact in *Lecture VII, Symptomatology*, Charcot calls disseminated sclerosis "an eminently polymorphic affection." This is a confirmed reality today. MS presents in different individuals differently because of the variation in regions of the nervous system affected, and MS can present differently in one individual at different points in time for the same reason (O'Connor, 1999).

Microscopic Anatomy

As stated above any macroscopic examination was incomplete, according to Charcot, without a follow up microscopic examination of the tissues (see Fig. 2 for an example of microscopic section). While at the Malloch Rare Book Room in the New York Academy of Medicine, MB also happened upon an early copy of an 1868 French newspaper clipping in which Charcot describes the methods required to microscopically examine lesions at autopsy. It is clear from Charcot's writings and biographical commentaries that he was a dedicated, gifted physician and a charismatic teacher. In this article, Charcot summarized that the microscopic examination required viewing thin transparent sections of affected tissue under a low power microscope. This tissue was taken either transversely or longitudinally from the spinal cord and fixed in dilute chromic acid and stained with carmine to enhance certain features (Charcot, 1868/1877).

As an example of the limitations of macroscopic examinations, the lesions mistakenly appear abruptly divided from the healthy tissue. There seems to be a very distinct line of demarcation between the damaged and healthy tissue. Upon microscopic examination, it is clear that what appears to be the preserved region, is a region that also displays more subtle alteration (Charcot, 1868/1877). Charcot consistently went the distance for accuracy.

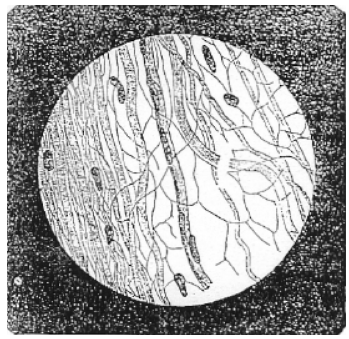

Fig. 2. Microscopic Anatomy: Represents a fresh preparation, taken from the center of a patch of sclerosis, colored with carmine, and dilacerated. In the center is seen a capillary vessel, supporting several nuclei. To the right and left of this are axis-cylinders, some voluminous, others of very small diameter, and all deprived of their medullary sheaths. The capillary vessel and the axis-cylinders are vividly colored (not shown) by the carmine; the axis-cylinders present perfectly smooth borders, without ramification. Between them are seen slender fibrillae of recent formation, which form on the left and in the center a sort of network resulting from the entanglement or anastomosis of the fibrils. These are distinguished from the axis-cylinders, primarily by their diameter, which is much smaller; secondarily by the ramifications, which they present in their course; third, by taking no coloration from carmine. Nuclei are seen scattered about; some of them appear to be in connection with the connective fibrils; others have assumed and irregular form, owing to the action of the ammoniacal solution of carmine (from Charcot, J. M., *Lectures on the diseases of the nervous system, Lecture VI*, 1868/1877, p. 173).

Charcot noted that as one moves from the circumference of a lesion to the center, it becomes apparent that there are several concentric zones. In the *peripheral zone*, there are many preliminary changes, but the one of greatest interest is that the nerve tubes (axon with surrounding myelin) appear to be farther apart from each other than in healthy tissue, but in reality this is a reflection of their atrophy. Importantly, this includes the degeneration of the medullary (myelin) sheath. In addition, the axis cylinder (axon without the sheath) often maintains its normal diameter or it may even be hypertrophied (Charcot, 1868/1877).

Charcot denoted the middle portion of a lesion the *transition zone.* Charcot observed that this zone was characterized by the nerve tubes that are more slender than they were in the peripheral zone. Many of these nerve tubes seem to have disappeared, but in reality, it is the medullary sheath that is gone. All that is left is the axis

cylinder (axon) and these can even acquire colossal dimensions (Charcot, 1868/1877).

The *central zone* represents the most advanced portion of the lesion. At this point, all of the medullary (myelin) sheath is gone and a certain number of axis cylinders remain but for the most part they do not retain the large volume that was observed in the earlier stages of disease (Charcot, 1868/1877). In summary, Charcot capitalized on the methods that were at his disposal to meticulously describe and depict these lesions as he began to illuminate the details of this disease process.

Symptomatology

In *Lecture VII*, Charcot precedes his discussion of symptomatology by addressing the practice of diagnosing disseminated sclerosis. He firmly stated,

> It is singular that a morbid state which possesses so distinct and so striking an anatomical substratum, and which, in short, is not a rare disease, should have escaped clinical analysis for such a length of time. Yet nothing is simpler, as I trust to show you, than to diagnose the affection in question, by the bedside of the patient, at least when it has reached a typical period of perfect development. (Charcot, Lecture VII, 1868/1877, p. 182)

Physicians today might be surprised to know that Charcot found this disease fairly routine to diagnose since the diagnosis of multiple sclerosis in the 21st century is often cumbersome to diagnose. A confirmed diagnosis can often take several years so as to document repeated attacks to different portions of the nervous system (O'Connor, 1999). It is possible too that there were less known diseases with which to perform a differential diagnosis compared with today and in this way it might have appeared simpler to Charcot. We do not know how many false positives Charcot might have diagnosed. The disease that Charcot predominantly differentially diagnosed from disseminated sclerosis was paralysis agitans, commonly known as Parkinson's Disease today. To accomplish this, Charcot focused on the type of tremor that the patient was experiencing. With disseminated sclerosis the patient had intention tremor and with paralysis agitans, the tremor occurred at rest. Charcot spent much time on these issues of tremor and diagnostics; however, he was not asserting that intention tremor was a pathognomonic sign for disseminated sclerosis (Charcot, Lecture VII, 1868/1877).

In *Lecture VII*, Charcot presented the case of his patient, Mlle. V. whom he diagnosed with the classic cerebrospinal pattern of disseminated sclerosis. Mlle. V. was a 31-year-old woman, a former patient of Dr. M. Vulpian, who had been suffering from this condition for about eight years. She was admitted to La Salpetriere about three years before Charcot's examination. When she walked into a room, one was struck by the "violently agitated, rhythmical tremor" of her head and limbs. As soon as the patient sat down, the tremor almost completely disappeared. The tremor would return immediately if she were asked to raise a glass of water, or a spoon, to her mouth. Charcot often collected handwriting samples to study the characteristics of tremor (see Fig. 3 for handwriting comparison of active vs. inactive disease). Also in his effort to communicate information to aid differential diagnoses, Charcot spends some time delving into the symptoms and tremor associated with paralysis agitans, chorea, locomotor ataxia and others (Charcot, Lecture VII, 1868/1877).

In addition to tremor, Charcot also noted other important symptoms. The first set he groups as cephalic and they included disorders of vision, speech and intellect. Visual disorders include diplopia, amblyopia and nystagmus. Diplopia often presents early in the course of the disease and Charcot believed is worth noting. He also asserted that amblyopia, a loss in the sharpness of one's vision, strongly supported the notion that medullary sheaths were being destroyed, but much of the axis-cylinder (axon) was spared which resulted in this partial impairment of vision. Mlle. V. suffered from amblyopia in both eyes, which was preceded by flashes of light and sparks. Nystagmus was considered very important in diagnosis because it is present in about half of afflicted individuals. Nystagmus was also advanced and persistent in Mlle. V; it is most evident when the patient is asked to focus intensely on a single object (Charcot, Lecture VII, 1868/1877).

A symptom that is even more common than nystagmus is difficulty with enunciation and these difficulties were also clearly evident in Mlle. V.

> The affected person speaks in a slow, drawling manner, and sometimes almost unintelligibly. It seems as if the tongue had become too thick and the delivery recalls that of an individual suffering from incipient intoxication . . . words are measured or scanned; there is a pause after every syllable, and the syllables are pronounced slowly. (Charcot, Lecture VII, 1868/1877, p. 192)

Similarly, Mlle. V. experienced slowness in the movements of the tongue and tremor was sometimes observed when the tongue was protruded. Charcot believed that these enunciation problems become progressively worse during the course of the disease, progressing until the speech is mostly incomprehensible. He also noted that sometimes these symptoms do subside for a time only to return again later (Charcot, Lecture VII, 1868/1877). In advanced stages of the disease, the person might experience progressive bulbar paralysis evidenced by

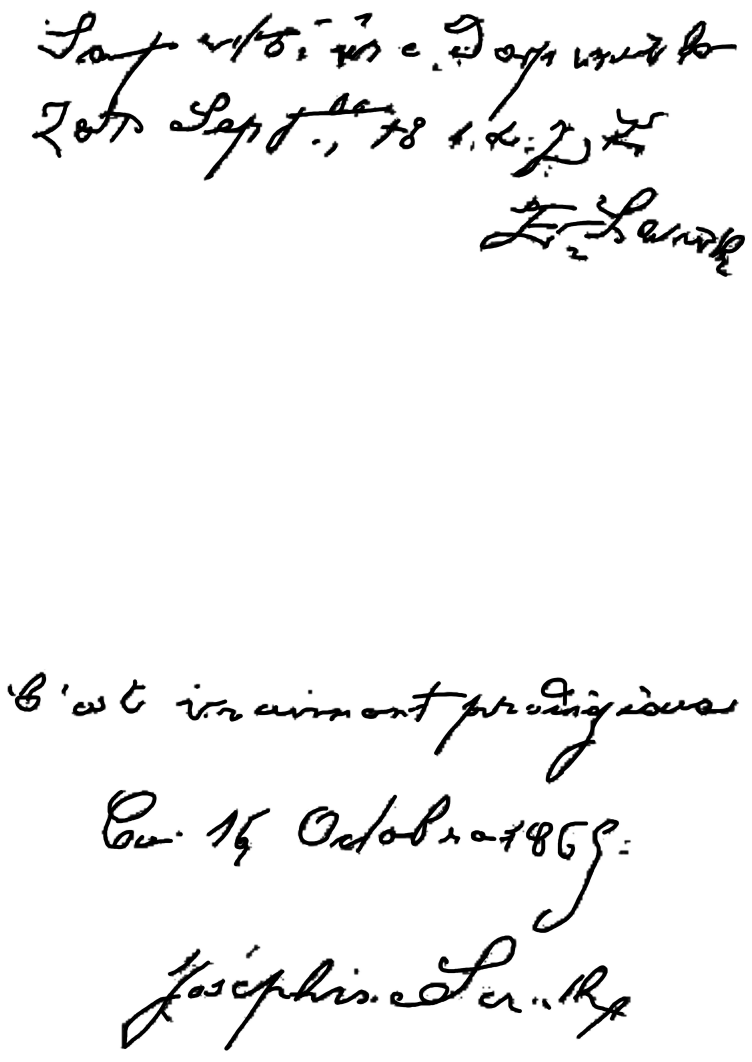

Fig. 3. Symptomatology: Charcot used handwriting samples to evaluate tremor, particularly when differentially diagnosing disseminated sclerosis from paralysis agitans (Parkinson's disease). The first writing sample above was taken in May 1865 without treatment and the second was after administration of nitrate of silver in June 1865. Charcot attributed the improvement to the nitrate of silver, but there could have been other intervening variables such as remission (from Charcot, J. M., *Lectures on the diseases of the nervous system, Lecture VII*, 1868/1877, p. 187).

problems in deglutition (swallowing), circulation, and respiration. If present, these should cause some concern because they can have fatal consequences (Charcot, Lecture VII, 1868/1877).

Vertigo occurs in about three fourths of cases. The vertigo is described as gyratory with all objects seeming to rapidly spin about the individual and the individual also feels like he is spinning on his own axis. This "giddiness" is usually short lived, but in some cases can be of longer duration. This symptom is often quite useful for differential diagnosis (Charcot, Lecture VII, 1868/1877).

Charcot stated that his patients often exhibited "a truly peculiar facies" (facial appearance). These patients presented with a vague and uncertain expression with hanging or half-open lips, appearing almost as if they were in a stupor with an expressionless countenance. In addition, Charcot was clearly one of the first prominent individuals in the medical community to observe and document cognitive deficits associated with MS. He noted that this facial expression is almost always accompanied by a corresponding mental state, which is characterized by memory deficits, slow formation of ideas, and the total blunting of intellectual and emotional faculties. "The dominant feeling in the patients appears to be a stupid indifference to all things" (Charcot, Lecture VII, 1868/1877). These unusual facial expressions as described here are not

as common as Charcot believed but the cognitive deficits, although perhaps not as severe as Charcot proposes, do present a growing concern and area of emphasis within neuropsychological management of MS patients today. Rao has been reported that 45%–65% of individuals with diagnosed MS have some degree of cognitive impairment (as cited in Chelune, 2002). These cognitive deficits can be mild to moderate, and are often undetectable to anyone except the patient, his/her family, co-workers, and close friends. They present when sclerotic plaques invade the cerebral cortex resulting in the impairment of higher mental functions such as memory, attention, executive functions, language, speed of processing and mood. Since not all individuals with MS have these cortical effects, there are individuals that never present with cognitive symptoms (O'Connor, 1999).

Charcot also makes reference to the occurrence of pathological laughing and weeping and the comorbidity that can occur with psychiatric illness, such as bipolar disorder. In fact, Mlle. V. experienced a period of lypemania (serious depression) accompanied by visual and auditory hallucinations. She saw frightening apparitions and heard voices threatening her with a guillotine. (If that does not reflect the context of the times, I do not know what does.) In addition, her paranoia caused her to suspect Charcot of trying to poison her. As a result, she ceased eating and had to be fed by a stomach pump. These occurrences subsided, but she continued to express convulsive, uncontrollable laughter which was often followed by a shower of tears (Charcot, Lecture VII, 1868/1877). Although emotional dysregulation along with pathological laughing and weeping has been reported in MS patients today, there are no known reliable prevalence rates at this time (Feinstein, Feinstein, Gray, and O'Connor, 1997).

Charcot also observed that individuals with disseminated sclerosis frequently experience paresis of the limbs, often accompanied by contracture. For example, Mlle. V., in the advanced stage of disease, could not stand from sitting, could not stand erect, or walk unless she had assistance. According to Charcot, this paresis often begins early in the disease process. In general, one of the lower limbs is affected first, feeling heavy and difficult to move. The foot turns while walking or the whole leg suddenly gives way, offering no support. After a while, the other limb becomes affected as well. This paresis is gradual often permitting the individual to manage well for many years. Some may get progressively worse and then become confined to bed toward the end. The upper extremities are also affected, but usually much later in the disease process. Frequently, early in the disease, "there are remissions; thus it is not rare to see the enfeebled lower limbs resume, for a time, their original energy. Such remissions may even occasionally take place two or three times." In this passage, you can hear Charcot using the same language that is used today regarding the symptom profile and disease course. He also said that these remissions were very characteristic of disseminated sclerosis, other diseases of the spinal cord did not follow this course (Charcot, Lecture VII, 1868/1877).

Charcot believed that "disorders of sensibility" were not as pronounced as the other symptoms cited above. (The terms currently employed to refer to these capacities would be disorders of perception, sensation or paresthesias.) However, the patients did sometimes complain of "formications" (sensation of ants crawling on skin), or numbness in the affected limb. So although Charcot believed that these symptoms were less common than some of the other symptoms that people experienced, he did document them when necessary in his patients. For example, he noted that Mlle. V. had clearly diminished tactile sensibility and, when her eyes were closed, she could not tell which position her legs were in, a deficit in what we call proprioception today (Charcot, Lecture VII, 1868/1877).

Lastly, Charcot noted that toward the end of the disease process, patients often have permanent contracture of the limbs. He believed that this was a habitual symptom of the advanced stages of the disease. In these instances, the lower extremities are stiffened in extension while simultaneously becoming drawn together. When the symptoms first present, they last for hours or days, but over time it becomes imminent that they are permanent. Although uncommon, contracture can also occur in the upper body in conjunction with the lower limb contracture (Charcot, Lecture VII, 1868/1877).

In summary, Charcot outlined the symptoms of cerebrospinal disseminated sclerosis as: intention tremor, vision disturbances, articulation deficits, vertigo, peculiar facies, impaired intellect, pathological laughing, weeping, depression, mania, paresis of limbs, mild disturbances of sensibility (sensation), and permanent contracture of limbs. He was also well aware of the relapsing-remitting nature of this disease's course. Clearly, Charcot was a man before his time.

Natural History of Disseminated Sclerosis

In *Lecture VIII*, Charcot described the natural history of the disease in three periods. The *first period* begins with the appearance of the first symptoms and concludes when the patient presents with muscle spasms and rigidity, which severely restrict his/her movements. During the *second period*, which is often the period of

greatest duration, the patient may be completely confined to bed or limited to being able to walk just a few steps at a time, yet the organic functions are spared. Finally, the *third period* occurs when all the symptoms of the disease are activated simultaneously and the patient suffers nutritional challenges (Charcot, Lecture VIII, 1868/1877). If Charcot were able to examine more patients, it is likely that he might have revised this conceptulization of the natural history. It seems inconsistent with his understanding that there are three main types of disseminated sclerosis: cerebral, spinal and mixed because an understanding of these three types would acknowledge that different individuals would present with different symptoms and certain individuals would not even experience the motor symptoms that are present in the above natural history.

The symptoms that indicate the initiation of the first period of disseminated sclerosis are usually spinal phenomena, although other scenarios may also occur and are further discussed in *Lecture VIII* (1868/1877). Charcot states that for months or even years, these spinal symptoms are the only symptoms of the disease. They are characterized by paresis of the lower extremities, which may gradually progress to the upper extremities. In each case, the symptoms become gradually more pronounced over time, bladder and rectal difficulties are rare and it is still problematic to diagnose unless cephalic symptoms or intention tremor present.

In addition, Charcot was well aware that the disease is characterized by remissions and aggravations. He cites some cases in which paralyzed patients had such complete remissions that they were able to resume their occupations. In one of M. Vulpian's cases, there were a series of ameliorations and aggravations. He writes:

> When the disease was still recent, there supervened, after an attack of small pox, a quasi-complete recovery. This improvement lasted for three years. At the end of that time, the menses were suppressed; new but slight, symptoms showed themselves, which disappeared on restoration of the catemenia. Two years after, the patient had an attack of jaundic followed by new symptoms. These improved, but on bronchitis supervening, the paresis of limbs reappeared in a more marked form, and after, successive remissions and recrudescences, became permanent. Sometimes the remission is incomplete and only affects certain symptoms, particularly incontinenece of urine and feces. (Charcot, Lecture VIII, 1868/1877, p. 211)

During the second period, all symptoms become exacerbated and intensified. In addition, there are spasmodic contractions of the limbs, which leave the person quite powerless and definitely confined to their rooms or beds.

The third period is marked by

> ...progressive enfeeblement of the organic functions along with inappetency, diarrhea and general emaciation. There is a further aggravation of all symptoms, the obnubilation of the intellect progresses to dementia, the difficulty of enunciation continued to the extreme and the patient can only utter unintelligible grunting. The sphincters become paralyzed. It is not rare to find the mucous coat of the bladder affected with ulcerous inflammation. Then from continuous pressure on sacral region and all points on lower limbs, eschars appear which occasionally assume enormous dimensions and consecutively comes the whole series of accidents which depend on this complication, purulent, burrowing sores. Death follows without delay. (Charcot, Lecture VIII, 1868/1877, p. 213)

The prognosis for individuals living with MS in 2002 is not as grim as Charcot's description and it is rare to encounter individuals with good medical care to experience the eschars mentioned above. MS is not classified as a fatal ailment. In fact, most people live out the normal course of their lives with a life expectancy rate of only slightly less than that of the national average. In very severe cases, it is possible that complications caused by symptoms can eventually lead to death; but, in general, this is rare. MS is a disease that people can live with (Chelune, 2002; O'Connor, 1999). In addition, it is important to reiterate the variability that characterizes every aspect of this disease including prognosis.

Clinical Cases

Two cases follow which help to illustrate Charcot's use of the clinicopathological method, symptomatology, treatments of the day and autopsy results. The variability of the presentation of the disease is apparent by conducting comparisons across cases.

Case of Josephine C. Vauth:

> ...patient was admitted March 21st, 1867 to M. Vulpian's wards, and died January 7th, 1871 at age 32 in M. Charcot's charge. From fourteen to twenty-one years of age, she suffered from vertigo followed by vomiting. Pregnancy, at age twenty-one, put an end to vomiting. Disseminated sclerosis showed itself at the age of twenty-three years and six months: weakness of the lumbar region, very great fatigue of the lower limbs, lancinating pain in the right leg, enfeeblement of sight, diplopia. At twenty-five years, feebleness of the arms, which are occasionally affected by pains.
>
> 1867—Nystagmus, diplopia. Integrity of the muscular masses, loss of idea of position as regards lower limbs. Paresis and tremor of the upper extremities. Tactual sensibility largely lost everywhere. Momentary improvement under nitrate of silver.

1868—The patient can no longer stand erect; the symptoms are more marked on the right side than on the left; the tremor in the upper extremities has augmented. Frequent fulgurant pains, especially in the left half of the face. Fits of giddiness (vertigo) coming on at close intervals. Nystagmus more marked. In May, M. Vulpian administered two pills of .025 gram of extract of Calabar Bean. Soon after, a fit of weakness, tremor exaggerated, cold sweats, pallor of the face (these phenomena are perhaps due to the Calabar Bean). From July, three pills of .03 gram (or nearly 1/2 grain) of extract of belladonna. The incontinence of urine, after presenting some transient improvements, ceased altogether in the course of December.

1870 (January)—Psychic disorders. In the course of this year, the symptoms noted augmented in severity; and besides symptoms of bulbar paralysis made their appearance. These became rapidly worse, and the patient died, as it were asphyxiated, Feb. 7, 1871.

Autopsy—Numerous sclerosed patches found to exist in the brain and spinal cord. On account of the ataxic symptoms presented by the patient, the lesions of the spinal axis deserve mention. There were sclerosed patches throughout the whole length of the lateral columns. As to the posterior columns, they are affected nearly throughout, but, principally, from the lower extremity of the dorsal region upwards. (In a section taken from the upper part of the lumber region) At this level the posterior columns are completely invaded but especially affected in the mid-region. The lateral columns are comparatively less injured. (Charcot, Lecture VIII, 1868/1877, p. 214)

Case of Pauline Bez:

Pauline Bez, aged thirty-five, child's nurse, admitted Feb. 17th, into M. Charcot's wards. To the ordinary symptoms of disseminated sclerosis were added, about the month of May, dyspnea and dysphagia. The difficulty of deglutition (swallowing) compelled the patient to eat very slowly. Return of food, through the nasal orifices, was not observed until near the end. The patient died of asphyxia, June 12, without any rales having been noticed in the lungs.

Autopsy—Sclerosed patch on the chiasma of the optic nerves, invading the tractus opticus. Sclerosed patch in the ventricles and in the centrum ovale. In a section made a centimeter above the inferior border of the protuberantia annularis, on a level with the apparent origin of the trifacial nerve, a large and irregular patch of sclerosis is found. Another transverse section, corresponding to the middle part of the corpora olivaria, reveals another patch of sclerosis apparently involving the pneumogastric. Microscopic examination of the nerves showed the existence of numerous degenerated fat tubes in the hypoglossal, and traces of irritation in Schwann's sheath in the pneumogastric nerve. As to the other organs, and particularly the pharynx, the larynx and the lungs, they were all healthy. (Charcot, Lecture VIII, 1868/1877, pp. 215–216)

Etiology, Prognosis, and Treatment

Charcot was both a meticulous scientist and gifted clinician as was apparent in his utilization of the clinicopathological approach and the information about disseminated sclerosis that was gleaned from this method. However, he was clearly a man at least partially defined by the times in which he lived when it came to matters of etiology, prognosis and treatment.

Charcot concludes *Lecture VIII* with his general impressions of the disease. He stated that the disease is far more common in females than in males. This comment is based on Charcot's cases but also the multitude of cases examined by others. Using these same statistics, it was also concluded that this was a disease of youth, or the first half of adult age, occurring most often in individuals between twenty-five and thirty years. Charcot and others had only seen one case that seemed to involve hereditary predisposition and there did not seem to be any clear pathological antecedents that people had in common. Regarding etiology, there is not one resounding pattern that presents itself in many afflicted individuals. However, "the prolonged action of moist cold" is cited fairly often and there is at least one case in which the first symptoms seem to have appeared after an infection, not unlike Lidwine of Schiedam. There is a case of Herr Baerwinkel's in which symptoms were said to have appeared after the patient fell into water and allowed his clothes to dry upon him. Etiological factors cited even more frequently than the above are of "the moral order."

These might include

> ...long continued grief or vexation, such, for instance, as might arise from illicit pregnancy, or the disagreeable annoyances and carking cares which a more or less false social position entails. This is often the case as regards certain female teachers. Having said so much with respect to women, the question of the male sufferer arises. These are, for the most part, persons who have lost caste, and who, thrown out of the general current, and too impressionable, are ill-provided with the means of maintaining what, in Darwin's theory, is called the "struggle for life." (Charcot, Lecture VIII, 1868/1877, p. 220)

Dr. Moxon also cited the case of an individual who began to present with symptoms after the patient experienced a "violent moral emotion on seeing her husband in bed with another female" (Moxon, 1873).

The context of the times can have a profound effect on the interpretation of illness. In 1825, Jean Itard, chief physician at l'Institution Royale des Sourds-muets in Paris, recorded the ticcing and cursing behavior of the twenty-six year old Marquise de Dampierre. In 1885, Tourette later used this case as a primary example of

"maladie des tics," now known as Tourette syndrome. Not unlike Charcot, Itard thought that his female patients were victims of domestic unhappiness, which caused brain irritations that weakened their will. Itard was convinced that symptoms were exacerbated or alleviated by modifications in their social roles as women, wives, and mothers (Kushner, 1999).

As stated above, Charcot was not optimistic regarding prognosis. He stated, "the prognosis has hitherto been of the gloomiest." He hoped that when the disease became better known, physicians would learn how to take advantage of the spontaneous remissions that characterize the disease (Charcot, Lecture VIII, 1868/1877). And now, 134 years after Charcot, we can appreciate his foresight into a possible solution for the problem. The reason we can appreciate his vision now is that many treatments today *are* focused on pharmacotherapy, which capitalizes on the tendency of the disease to remiss. Current medications prescribed for individuals with relapsing-remitting multiple sclerosis aim to increase time between exacerbations, hence increasing the remitting period. Some examples are the interferons, glatiramer acetate, and mitoxantrone (Chelune, 2002).

However, in Charcot's time, the treatment options for disseminated sclerosis were painfully lacking. Regarding treatment, Charcot writes, "The time has not yet come when such a subject can be seriously considered." They tried a variety of treatments experimentally, hoping they would alleviate symptoms, but most had no effect and some even aggravated symptoms. Chloride of gold and phosphate of zinc intensified symptoms while strychnine and nitrate of silver have occasionally and transiently reduced the tremor. The effects of hydrotherapy to treat muscle spasms and contracture were unpredictable. Arsenic, belladonna, ergot of rye and bromide of potassium, faradisation, and galvanism were also futile. This trial and error approach to treatment, which was not grounded in any scientific understanding, must have been very frustrating for physicians and patients alike. It is as if physicians preferred attempting a given treatment, even if it was a shot in the dark, rather than doing nothing at all. This pattern of trial and error treatment along with the specific treatments are also observed in the case of Auguste d'Este who was mentioned earlier in this paper.

Contributions by Students and Colleagues of Charcot

After the *Lectures* were published in 1868, disseminated sclerosis research proliferated. Fellow physicians and students of Charcot were also publishing papers and books that included case analyses of disseminated sclerosis. These works embodied Charcot's vision and most physicians implemented the clinicopathological approach. Compared with the *Lectures*, these follow-up works were more limited in scope, and their goal was often to share information about the most recent cases that had been identified and examined, not to provide general conceptual information about the many facets of disseminated sclerosis. The following physicians were some of the most prolific, prominent and well-respected contributors at that time, but these inclusions are not intended to be exhaustive.

Bourneville

An example of this new genre in disseminated sclerosis literature was a paper written by Bourneville, a medical colleague of Charcot's. He documented the case of Dr. Pennock, a frequently reported case by Charcot and others. In fact, Charcot referenced it in the *Lectures* even though both were officially published in the same year, 1868. Within this account, Bourneville credits both Vulpian and Charcot for the first description of the disorder; neither Carswell nor Cruveilhier are given mention. Most writers, even in the 1800s do not credit Vulpian, except for Bourneville and Charcot himself. It would seem then, as a result, Vulpian has not enjoyed the eminent reputation that Charcot has coveted for approximately 150 years. MB read the original case analysis of Dr. Pennock in French at the Malloch Rare Book Room. In this document, it is apparent that Bourneville was well aware of the cognitive deficits which could present in disseminated sclerosis; however, he also understood that there was often a disconnect between cognitive and spinal symptoms. For example, Bourneville writes that although Pennock suffered from chronic paralysis, his intelligence was unaffected (Bourneville, 1868). This disconnect is often a characteristic of the disorder as it is observed today; the presence of spinal symptoms does not predict the propensity for cognitive symptoms and vice versa (Chelune, 2002; O'Connor, 1999).

Bourneville also published frequently with Guerard and in 1869 they published a comprehensive review of the state of disseminated sclerosis to date. A publication of this breadth was uncharacteristic of the works that followed Charcot. MB read the 1869 original French edition of Bourneville and Guerard's (1869) book at the New York Academy of Medicine. Within this venerable book, which is cited in the *Lectures,* the authors state that Cruveilhier was the first person to describe the lesions of disseminated

sclerosis in the case of Josephine Paget, not Carswell. So even though Bourneville does not mention this credit in *The Case of Dr. Pennock*, it is clear that Cruveilhier was regarded as having first identified the lesions of this disease. As mentioned earlier, credit may have been given to Cruveilhier rather than Carswell because Carswell focused on pathology nearly exclusively, while Cruveilhier's effort implemented the much revered, clinicopathological approach.

Babinski

Another prime example of post-Charcot literature was authored by Babinski. This physician and former pupil of Charcot's, is perhaps best known for his identification of the Babinski reflex in newborns. However, the thesis that Babinski prepared for his medical program was on disseminated sclerosis. MB read the French edition of Babinski's thesis, which is housed in the Malloch Rare Book Room. Within the thesis, he described the clinicopathological approach that he used which was modeled for him by Charcot. It is clear from reading this thesis that like Charcot, Babinski was well aware of the cognitive deficits that could present in disseminated sclerosis (Babinksi, 1885).

Malherbe

At the same time that Charcot was studying disseminated sclerosis and publishing the *Lectures,* Malherbe, was also using clinicopathological methods when he examined individuals with disseminated sclerosis. When Charcot discusses the duration of disseminated sclerosis in the *Lectures*, he cites Malherbe as having documented the case of a female who had cerebrospinal disseminated sclerosis of the shortest duration recorded at that time. The disease process lasted only one year from earliest symptom onset until death. Within this one-year time span, Renou, a twenty-year-old female, experienced nearly all of the most frequently reported symptoms of disseminated sclerosis. These included weakness in the extremities, violent head and vertebral pain, intention tremor, nystagmus, flat facial expression, tremulousness of the tongue, mouth and lips, vertigo, bladder and bowel difficulties, slowed reflexes, muscle spasms, impoverished movement and swallowing disturbances. In addition, the cognitive symptoms were quite pronounced. These included deficits in language, attention, and emotion and were accompanied by transient delirium and hallucinations. In sum, this was a rapidly progressing course that presented with many of the typical MS signs and symptoms (Malherbe, 1870).

Moxon

While Charcot and Vulpian were diagnosing some of the earliest definitive cases of disseminated sclerosis in France, Dr. Moxon, another eminent neurologist, was implementing the clinicopathological approach in England. The pattern of symptoms that emerged in Moxon's patients was similar to those of patients that had been identified by Charcot and others at that time. In 1872, Moxon examined a 28-year-old woman at Guy's Hospital. Some of Moxon's notes regarding etiology follow.

> Etiologically it is important to mention another statement the poor creature made when giving a more confidential account to the nurse which was that the cause of her disease was having caught her husband in bed with another woman. It was not possible to learn how far this was right, but she was neglected by her friends. Her answers, however, on other subjects within our knowledge were generally trustworthy. (Moxon, 1873, p. 236)

Charcot found the above etiological speculation reasonable enough to include in the *Lectures* when he discussed the etiological possibilities of disseminated sclerosis. Classic documents, such as those crafted by Charcot and Moxon, are undeniably revealing regarding the nature of the times in which they were written and they certainly encourage comparison between the historical and current views of disseminated sclerosis. It is clear that the language that Moxon used ("poor creature") was acceptable professionally at the time and it is equally apparent that the etiological theories that were being entertained (witnessing husband's transgressions) were also reasonable explanations of this medical condition. As mentioned earlier in this paper, etiology and treatment are the two arenas in which science has made its greatest strides in the understanding of disseminated sclerosis since the 1800s.

Adhering closely to the clinicopathological approach, Moxon documented the patient's symptoms throughout the illness if possible and then recorded his observations from the pathological examination. Other symptoms of this 28-year-old female patient included muscular weakness and intention tremor of hands, limbs, head, lips or tongue which resulted in impairments in speech, walking, and eating. She also presented with "scanning speech," a classic sign of disseminated sclerosis, according to Charcot (1877), in which every syllable was reliably followed by a pause. In addition, numbness was not uncommon although many aspects of sensation were preserved. Urinary incontinence had also

begun causing disruption to her daily routine. Like other neurologists of the day, Moxon was attuned to both cognitive and sensorimotor deficits. He wrote that the patient's intellect and emotionality were also affected. Moxon describes her intellect as "narrowed" when compared with before she became ill, which is evidenced by her ability to talk about immediate and relevant concrete events, but by her inability to go beyond this. Emotionally she was unstable, often laughing or crying inappropriately to the situation (Moxon, 1873).

Upon post-mortem examination, the brain was clearly damaged and exhibited telltale signs of disseminated sclerosis when considered in the context of the clinical profile. The brain was small, inflexible and the convolutions appeared sharply raised because the gyri were atrophied and punctuated by wide and deep sulci. Sectioning through the corpus callosum revealed many insulated gray patches, looking much like cerebral gray matter. Again another indicator of the times, Moxon writes, "The patches were of various sizes, from that of a hemp seed to that of a small nut." The smaller lesions were always spherical, dark-gray, and less firm; the larger lesions were irregular, paler in color, minutely stippled with bright white spots and firm enough to resist sectioning. There were about forty patches in the white matter of each hemisphere; however, the gray matter was noticeably preserved. In fact, none of the patches were visible on the cortical surface at all. Several lesions were observed in the corpus striatum and in the thalamus. Moxon concludes by saying that the pathological anatomy of this case resembles what has been found by physicians in France and Germany (Moxon, 1873).

Moxon continued to report on cases of disseminated sclerosis as they appeared in the wards of Guy's Hospital. In the case of Harriet B., muscular weakness was the primary symptom. She noticed she had difficulty wiping her boots on the doormat and since could not understand why this would happen, she sought medical attention. She also had noticeable disequilibrium when walking. If she did not keep her eyes on the ground while walking, she would tumble forward. These were her main concerns for about two years, when additional deficits added to the challenge. She noticed difficulty cutting up her food, saying that her hands were not entirely under her control. Eventually, both hands and arms began to shake unless she was able to grab onto something very tightly. Like Moxon's other case, mentioned above, she also had scanning speech. Constipation was problematic, but she suffered no loss of sensation and had no numbness or pain. She also endured severe muscle spasms, contractures, and nystagmus. Cognitive deficits were again documented when Moxon stated that she had a "bland smile, and laughed trivially." In short, Moxon believed that Harriet B. suffered from a general weakening of mental capacity (Moxon, 1873).

Interestingly, in these historical cases, the physician nearly always includes the occupations/lifestyles of the patient and his or her family as well when they write up the background of the patient. In the case of Harriet S., her daily life consisted of attending to her household affairs and occasionally assisting at table. Her husband was a steady coachman in good employment, so she was not in need or want (Moxon, 1875). Is the implication being made that there might be a correlation between lifestyle and occurrence of the disease or is this just basic information that readers in the 1800s would find valuable?

Another case Moxon addresses is that of Edward M., a single man, age thirty-two, who had been in service as a footman. His health history was unremarkable in the years predating his symptoms of disseminated sclerosis. The patient first noticed that there was a problem when his knees gave way as he was carrying a tray down stairs and he was unable to use his legs for more than an hour. Since that point, he never regained the strength in his legs and instead of walking would amble about on his knees. A year before admission, his eyes failed and his head shook regularly. Edward M. also suffered from occasional bouts of intense pain and disturbances in sensation. At one time, he suffered a great amount of pain across the spine and also lost his vision for fourteen days. His vision never completely recovered, leaving him unable to read (Moxon, 1875).

Alluding to the presence of cognitive deficits and emotional disequilibrium, Moxon described Edward's facial expression as "silly" and says that he laughed heartily at trivial things. The patient also presented with language deficits which were characterized by articulation which was impeded by misplaced accents, an example of the again "scanning speech" mentioned earlier. The movements of the patient's head and legs were distinctly robotic in nature. In addition, intention tremor and nystagmus were frequently present. Paresthesias were not uncommon as evidenced by the sensation of numbness in both legs, extending from his knees to the soles of his feet ("stocking numbness"). Edward also had the characteristic symptoms of muscle spasms and rigidity in the legs. Moxon concluded that this was predominantly a case of cerebral disseminated sclerosis due to the presence of speech deficits, nystagmus, and "imbecility" (Moxon, 1875).

Bouchaud

In 1900, Bouchaud, another proponent of the clinicopathological approach and colleague of Charcot's, detailed the case of J.B. This is yet another example of an

individual who had an unremarkable medical history until the disseminated sclerosis took hold symptomatically. Initially, in 1897, J.B. presented with a staggering gait, disequilibrium, and vertigo, which made him appear as if he was intoxicated. Interestingly, this is not an uncommon analogy even today. J.B.'s symptoms progressed to include left hemiparesis and then eventually this transitioned into left hemiparalysis. Intention tremor was also present, which compounded these motor difficulties. His case was also marred by visual disturbances, some of which were transient and some more permanent. These included diplopia, amblyopia, and nystagmus. Sensation and general intellect were intact unlike cases that have been cited earlier in this paper. However, J.B.'s speech pattern was labored and scanning in nature. Bouchaud's post-mortem examination autopsy of J.B. was characteristic of disseminated sclerosis, characterized by discrete and dispersed areas of demyelination, with pronounced damage to the 6th and 7th cranial nerves, which would explain much of the facial paralysis and paralysis of the left eye muscles (Bouchaud, 1900).

Charcot's findings about MS and the value of the clinicopathological approach were strengthened by these pioneering neurologists. Along with Charcot, their work significantly advanced the medical community's conceptualization of this debilitating disease.

CONCLUSIONS

An accurate understanding of MS is necessary to offer individuals informed options for treatment and planning. To assist in this effort, this historical analysis examined how MS has been conceived from the 14th century through the early 20th century. After this review of many of the original source documents, it is apparent that there is a striking similarity between how MS symptoms have presented throughout history compared with the 21st century. This shared symptom profile includes the undisputed sensorimotor symptoms, but in addition, it properly includes the cognitive symptoms as well. These cognitive disturbances were acknowledged in the 1800s, but disregarded in the early 1900s and were not given recognition again until the latter part of the 20th century. If a set of symptoms are not recognized as real and important, and are not included in the accepted conceptualization of MS, they will not be given due consideration for treatment and planning. Science made the mistake once of not remembering what the pioneers of MS first learned about cognitive deficits, much to the disadvantage of MS patients worldwide. Historical analyses such as this can help scientists remember where they have been so they can have a clear vision of where to proceed in the future.

Although the symptom profile of MS and the agreement that it is a demyelinating disease of the central nervous system have been consistent since the early 1800s, early notions of etiology and treatment choices differed dramatically from today. In the 21st century, the most well-supported etiological explanation of MS is that it is precipitated by an autoimmune reaction triggered by a slow virus that exists in the environment. In addition, treatment strategies abound today where there were no reliable methods in the 19th century. These include medications, such as anti-inflammatory steroid treatments which decrease the intensity and duration of exacerbations and immunosuppressant agents, which have been shown to be effective in slowing down the natural course of MS and increasing time between exacerbations. They also include cytotoxic agents for acute distress and a multitude of treatment strategies to help ease the symptoms of MS as they appear (Chelune, 2002). So just as Charcot envisioned in the 1800s, successful treatment, albeit not cure, did consist of physicians capitalizing on the characteristics of remission to diminish residual damage.

The cause and cure of MS are the subject of international research. This is evidenced by the 220 research grants and fellowships which are funded by the National MS Society each year toward these efforts (NMSS, 1999). But as the field continues to advance and new knowledge accrues, it is instructive to appreciate and be aware of where the quest began. In the case of MS, it began scientifically in the 1800s with dedicated physicians who used their minds and the tools available at the time to make great strides in the understanding of this chronic and debilitating disease of the central nervous system.

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