Multiple Sclerosis: The History of a Disease

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ry were continued into the 20th century. Although most doctors did not feel the therapies altered the course of the disease, they provided some relief or hope to patients. There was always a desire to offer something to those who suffer.

It is interesting how the illness of many of these early cases lasted 20–40 years, while many later medical writers felt the illness lasts about 8–12 years. This probably indicates that the most serious, advanced, and progressive cases were the experience of the consultants in clinics and hospitals. Those doing well, or with mild disease mostly cared for themselves. Margaret Davies was hardly a mild case, but her condition still lasted two decades, despite disability and pressure sores.

The cases just outlined are examples of disorders of the nervous system that resemble only MS. That only a few are known over a number of centuries should not suggest the disease was rare, or any less common than today. Patients with the disease were regarded differently in different eras and with different nosologies. The concept of disease, particularly of the nervous system, caused patients with many forms of neurological disease to be viewed as having nervous disorders, brain disease, palsy, paralysis, infirmities, or creeping paralysis.

That we can recognize cases before doctors became interested in the disabling disease characterized by scattered lesions throughout the central nervous system just emphasizes that the disease was there. Was it less common in the 15th or 17th century? We cannot tell; MS patients would have been mixed in with those suffering from other disorders. It is hard to find definitive data that the number of cases of MS have increased much in the century and a half since it was recognized. Even correcting for our refined clinical classification, recognition of milder and benign cases, and newer diagnostic tools such as spinal fluid examination, evoked potential tests, and MRI, the apparent stability of the disease suggests it has probably been part of the social fabric for a very long time. As Compston said, it has been more an epidemic of recognition, rather than a epidemic of increasing cases.⁵⁵

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the right and then on the left, and with little change in the hands. She began to improve after two months in the hospital and was eventually able to walk well.

ROBERT CARSWELL (1793–1857)

Carswell presented the first pathologic demonstration of MS in an atlas of pathologic conditions published in 1838.¹¹ In the English tradition of Hunter and Thompson, Carswell incorporated the approaches and discoveries of the French school in his observations and illustrations of pathology.^{12,13} He also used the visual approach of Hooper, who had produced the first handcolored atlas of neuropathology in 1828.¹⁴

Robert Carswell was born on February 3, 1793 in Thornliebank, Scotland, and his artistic talent was noted when he was attending Paisley Academy. James Jeffray, professor of Anatomy and Physiology at Glasgow, asked him to illustrate one of his inventions, a machine to propel boats on the Clyde. Jeffray later had Carswell draw anatomical teaching models and encouraged the young man to consider medicine as a career. Carswell's atlas was dedicated to his teacher.*

After his initial medical studies at Glasgow, Edinburgh, Paris, and Lyon, Carswell was commissioned by Dr. John Thompson of Edinburgh to make a collection of drawings of pathology. Thompson was a prominent figure in pathology and surgery in Edinburgh who encouraged his two sons, as well as Carswell, a family friend, to study further in Paris. Thompson wanted the pathological drawings for his teaching. Jacna makes it clear that Carswell had a focused interest in his hospital and dead-house studies, concentrating on the pathology of the cases rather than their clinical background.¹⁵ Jean Cruveilhier, creating his atlas of pathology at the same time, demonstrated an interest in correlating the

^{*}Jeffray was a multifaceted dramatic individual involved in body-snatching for his contract or cal experiments, and who carried out public dissections on murderers. One of his contract or matic and distasteful displays was to stimulate the body electrically so that it sature. This contract a flourish, he would cut the neck and the body would fall down. Some observers to the it is not surprising to learn that he was the last to perform such public dissection.

of the poor. He returned a number of times to London, and on one of these trips was knighted by Queen Victoria for his services in caring for Louis Philippe of France while he was in exile. Carswell died in 1857. Neither the *British Medical Journal* nor *The Lancet* saw fit to recognize his passing with an obituary, but his atlas is a fitting memorial.²⁷

William Osler, who owned a copy of Carswell's atlas, said, "These illustrations have, for artistic merit and for fidelity, never been surpassed, while the matter represents the highest point which the science of morbid anatomy had reached before the introduction of the microscope."²⁸

JEAN CRUVEILHIER (1791-1874)

An advertisement in 1828 asked for subscribers to a planned anatomical atlas by Jean Cruveilhier, with lithographs, to begin appearing in 1829.²⁹ Cruveilhier worked in Paris at the same time as Carswell, and sometimes in the same hospital autopsy rooms, although there is no record of their meeting.* Credit for the first illustration of MS has been given to Carswell, but these were soon followed by similar illustrations by Cruveilhier (1835–1842), who reported four patients in his atlas under the heading "Diseases of the Spinal Cord," all of whom had autopsy findings of grey degeneration in patches though the nervous system. These were well described by Compston.³⁰

Jean Cruveilhier was born in Limoges in 1791 and had decided to enter the priesthood, but with his mother's encouragement, he transferred from the College of Limoges to the University of Paris to study medicine under Guillaume Dupuytren, graduating in 1811.³¹ His work on anatomical pathology, privately printed during his internship, gave an inkling of things to come. Initially, he wished only for the quiet life of a practicing community physician; he married and returned to Limoges. Things did not go well and he was unsuccessful in two applications to be a surgeon at

^{*}Compston notes that there is a striking similarity in the lesions in the pons illustrated by Carswell and Cruveilhier, but Josephine Paget, described by Cruveilhier, was still alive when Carswell's atlas was published, so it could not have been the same case.



Figure 6.3 A sketch made in 1875 by Brissaud showing Charcot examining a brain for pathological changes, in his apron and top hat. (Courtesy of the National Library of Medicine.)

making the condition known. In the history of medicine and science, the credit usually (and perhaps appropriately) goes to the person who makes a discovery known rather than to the person who may actually have made the discovery first.

According to D.M. Bourneville and I. Guerard, students of Charcot and the authors of the first monograph on MS, Charcot first became aware of the disease in 1855 when he asked a woman who had some motor problems to serve as his housemaid. He thought she had neurosyphilis. She broke many dishes as her condition slowly worsened. Charcot was able to follow the course of disseminated sclerosis by watching her symptoms over the years. When she became too ill to function on her own, he arranged for her to be admitted to the Salpêtrière and when she died, he examined her brain and spinal cord. Although he expected to see the changes of syphilis, he saw instead scattered plaques throughout the nervous system.¹⁰

On May 9, 1866, Vulpian and Charcot gave a report on the clinical features and autopsy findings of three cases of *sclérose en plaque disseminée* to the Societé Médicale des Hôpitaux. Vulpian described one case and

Charcot presented two. Vulpian managed most of the discussion of these cases. When the presentation was published, Vulpian was listed as the sole author, but indicated that Charcot had presented to the society previously (March 8, 1865)¹¹ on sclerosis of the lateral columns.¹²

In 1868, Charcot gave a lecture before the Societé de Biologie on the characteristics of disseminated sclerosis; he indicated that it was not usually recognized clinically, but had distinct neurologic and pathologic features. He differentiated the picture from that of Parkinson's disease. He published this lecture and another report on the histology of MS the same year, clearly defining the features of this disorder.¹³ Naturally, the patients he described all had advanced signs of the disease, but over the next few years, Charcot was able to study cases earlier in the course of the disease.^{14–16}

Although he began pursuing the differentiation of the tremor of this disorder from that of paralysis agitans (Parkinson's disease),*¹⁷ Charcot soon initiated additional studies of the disease, its clinical features, variations, and pathologic features, making his own drawings of the changes he saw under the microscope. He recognized the nature of transient symptoms in the disease and the possibility of remissions. He was able to

Hôpital de Salpêtrière

"This great asylum (of human misery) holds a population of 5,000 persons, among whom are a large number who have been admitted for life as incurables; patients of all ages, affected by chronic diseases of all kinds, but particularly by diseases of the nervous system. There are numerous examples of the clinical types available for study, which enables us to study a specific disease during its entire course, so to speak, since the vacancies that occur in any specific disease are quickly filled in the course of time. We are, in other words, in possession of a sort of museum of living pathology of great resources." Jean-Martin Charcot

^{*}It was Charcot who began to call this disease after James Parkinson, for he objected to the word "paralysis," which he did not think characteristic of the condition. It was only in the 20th century, with the encouragement of a visiting American physician, that the English commonly used the eponym that recognized the contribution of their countryman.



Figure 6.6 Charcot giving one of his famous Tuesday clinical demonstrations, as painted by Louis Brouillet's "A Clinical Lession at the Salpêtrière," displayed at the Paris Salon in 1887. It shows him discussing the hysteric Blance Wittman who is swooning, held by Joseph Babinski. Among the physicians, politicians, medical administrators, writers, and hospital staff are Pierre Marie, Gilles de la Tourette, Charcot's son Jean, D.M. Bournville, H. Perinaud, and A. Goumbault. Many interested members of the public and artistic community, as well as local and visiting physicians would attend these dramatic and carefully planned demonstrations. Other visitors included Guy de Maupassant and Sarah Barnhart. Freud was often said to be in the picture, perhaps because of his resemblance to many of the bearded men. Although he often attended these demonstrations, he is not in the painting. (Erich Lessing/Art Resource, NY.)

This would explain the absence of secondary degeneration, either of an ascending or descending nature in the cortico-spinal tracts. This observation of axonal change became a major focus of attention in the closing years of the 20th century.

In lesson 8, Charcot discussed the possibility of sudden, acute, "apoplectiform" attacks of MS, many in the presence of infection. These were seen in a fifth of the cases in his experience. Although the "fit" might be temporary, there was usually some persistent aggravation of the condition afterwards. He personally observed this in three cases, not assomated with fever, which had been seen by Vulpian, Zenker, and Léo. Many physicians believed this to be due to *partial sanguine congestion*, but Charcott, in his usual direct approach to observation, said he followed these cases to autopsy and could find no evidence of vascular congestion

Charcot then detailed the case history of Josephine Vauthier, a patient of Vulpian's (Mme. V), the subject of the preceding lecture, who succumbed in this fashion. Then he discussed one of his cases, Pauline Bezot, a children's nurse. His lecture contains drawings of the pathology of these cases, showing loss of myelin, diminished numbers of axons in the plaques, and thickening and obstruction of the small blood vessels.

Charcot noted that abortive forms (*forme frustes*) are common in MS, so that there might be only cerebral symptoms, but more commonly, there might be spinal symptoms of the disease, as if the process of advancing sclerosis were fixed in one area. The most common picture encountered in practice, however, was the cerebro-spinal form, with signs of a widespread involvement.

Charcot confined himself to summary points on pathophysiology, etiology, prognosis, and treatment, indicating that knowledge on these subjects was scanty and imperfect. The cause of the disease is unknown, he said, and the suggestion by Rindfleisch that it is due to inflammation in the blood vessels seen in the center of the sclerotic patches only sets the question of cause a little further back. If the cause was in the blood vesssels, then what was the cause of the abnormality in the blood vessels? Indeed, from his observations Charcot was unsure of the vascular abnormality. He felt it might be possible to relate the location of the patches to the symptoms in the patient, and gave a suggested locale for various symptoms. He speculated on how the disruption of the medullary sheathing of the axis cylinders (the axons) could still allow conduction along the nerves to continue, even if it did so irregularly, "in a broken or jerky manner," to produce the irregular tremor.

Now that there is so much interest in the role of axonal damage in the progression of MS, many reflect on the fact that Charcot was interested in this question. He realized that the axon had great resistance to the inflammatory damage breaking down the myelin, but also felt that if the axons were finally damaged, the disease would permanently progress:

"Generally one of the lower limbs is first and solely affected. The other limb is seized, sooner or later, in its turn; the paresis advances with extreme slowness ... but at last the day comes when ... they may be confined to bed.... This resistance of the axis cylinders... may account for the slowness with which the paretic symptoms advance in disseminated sclerosis and for the long space of time which relapses before they give place to complete paralysis and permanent contracture."

Charcot related the sclerotic lesions in the nervous system to the symptoms experienced, and demonstrated that the features were also distinctive enough to separate sclérose en plaque from paralysis agitans, syphylitic disease of the nervous system, Friedreich's ataxia, locomotor ataxia, and chorea. The tremor was different in paralysis agitans. The vertigo present in three-fourths of his sclerosis patients was not usual in paralysis agitans or locomotor ataxia. Sclerotic patients did not have the involuntary jerky sudden movements at rest seen in chorea. Charcot also felt that patients with MS had a particular facial appearance and attitude, with a vague uncertain look, drooping lips, a lethargic look, and emotional lability. Intermittent episodes of symptoms with improvement was a feature of MS. Then there would be progression, spasticity, and spasms with contractures in the terminal stages. Charcot considered the disease a primary form of inflammation affecting the neuroglia, a separate and distinct disease with cerebrospinal, cerebral, and spinal forms, based on the anatomical level most involved in the symptomatology of the patient.

In later writings and lectures, Charcot acknowledged that little was known about the cause of the MS, but that it was most common in females. He said that combining his 18 cases (published in the monograph of Bourneville and Guérard),³⁴ with 16 new cases, there was a ratio of 25 females to nine males. Multiple sclerosis might develop by age 14, but is most common between 25 and 30 years.* Patients seldom live beyond 40, he thought. As to heredity, he knew of only one suggestive case, an example communicated by Duchenne. Certain infections (typhoid, cholera, smallpox), moist cold, and trauma were related to onset in certain cases.

^{*}In a footnote, Charcot referred to a case report in German literature by Leubé (1870) of a girl with onset of multiple sclerosis at age 7, who died at age 14; autopsy confirmed the disease. Childhood reports are common in the early literature of MS due to inclusion of other diseases in the case series.

Even though Charcot confessed that he did not know the cause of the disease, patients often referred to issues related to "moral order," such as grief, anger, illicit pregnancy, and the stresses of a false social position. For some reason, he suggested this was especially so in female teachers. In males, MS might relate to loss of caste, having been thrown out of the general social current, and the experience of not being able to cope with the problems of life.

As to outcome, Charcot briefly and somberly concluded: "The prognosis has hitherto been of the gloomiest."

He was no more cheerful on the issue of treatment:

"After what preceded, 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 I have tried, the results of which, unfortunately, have not been very encouraging."

Charcot stated that little could be done to alter the disease, but therapies were still being applied. In his experience, chloride of gold and phosphate of zinc seemed to aggravate the disease. Strychnine and nitrate of silver had only a transient effect on tremor, and the silver nitrate was contraindicated in advanced spinal involvement, which it might worsen. He noted that hydropathy gave transient benefit in one case, and worsened another. Arsenic, belladonna, ergot of rye, and bromide of potassium, as well as faradic and galvanic stimulation had no effect, although Charcot said it might be necessary to wait for further experience with continuous current before making a firm conclusion on that technique. Although he did not comment on it in his section on therapy, his "suspension apparatus" used at the Salpêtrière, adapted from the inventor Dr. Motchoukowski of Odessa, was later used in cases of ataxia, including MS. Patients thought to have "hysterical signs" were treated with ovarian compression belts.³⁵

In lecture 15 on spasmodic tabes dorsalis, Charcot indicated the clinical similarity between spasmodic tabes dorsalis and disseminated sclerosis. He pointed out that MS in its typical widespread form is not difficult to identify, but that "imperfect forms or abortive forms" were a different

Chapter

Medical Reports After Charcot

It is interesting to follow the stages in the recognition of a new disease. Very rarely does it happen that at all points the description is so complete as at once to gain universal acceptance ... First a case here and there is reported as something unusual; in a year or two someone collects them and emphasizes the clinical features and perhaps names the disease. Then in rapid succession new cases are reported and we are surprised to find that it is by no means uncommon.

William Osler, 1908¹

A lthough Charcot did not publish a lot on multiple sclerosis (MS), perhaps only 34 cases,² his description of the disease was acknowledged by all who later published on the disease. Ebers³ pointed out that Charcot probably had additional thoughts and views on the disease, which were expressed through the writings of his pupils Bourneville and Guérard,⁴ and in the first monograph on MS by another student,

^{*}Désiré Magloire Bourneville (1840–1909) was a Paris neurologist and a student of Charcot's who coauthored the monograph on multiple sclerosis with Guérard that contained many of the views of Charcot on multiple sclerosis. Bourneville also described adenoma sebaceum coupled with seizures and mental deficiency (1880), which became known as Bourneville's disease, now called tuberous sclerosis. He founded the Progrès Médical in 1873 and established the first school in France for medically defective children.

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chapter 10

Experimentation, Meetings, Reviews, and Symposia, 1920–1960

A lthough there was not a great amount of activity in multiple sclerosis (MS) research between the World Wars, there were two landmark events, one a meeting and one a review. They changed the directions in the study of MS by focusing on the current understanding of the distast. In an age that had many therapeutic approaches, most physicians included that none of them was better than using no therapy at all.

Most advances in medicine are recorded by the date of publication of the discovery and remembered in association with the discoverer. We normally do not recognize that a field or discipline can be advanced by a positial meeting, by an intelligent review of the state of the art, by the gublication of a book, or by the formation of an organization. The understanding of MS was advanced significantly by the 1921 and 1948 meetings of the Association for Research in Nervous and Mental Disease (AENMID ¹¹² and by reviews by Russell Brain in 1930³ and Schumacher (a 1955). Tand by the monograph by McAlpine, Compston, and Lumsden (a 1955). Another landmark that continues to influence the direction of MS state and research was the formation of the National MS Society by Sylvia Lawry in 1946.

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ARNMD held its annual meeting in New York City on December 27–28, 1921 and took as its theme that year the current knowledge and research on multiple sclerosis. The papers from that meeting were published in 1922, with the discussion following each presentation.⁶ The papers covered current understanding of pathology, epidemiology, etiology, and clinical features of the disease. This landmark meeting clarified an increasingly confused field; although it produced a few erroneous conclusions, it clarified many more. The meeting's influence was the result of overviews by leaders in the field of MS and was due to the attendance of many leaders in neurology, particularly American neurology, medical professors writing papers and textbooks on neurology, and teaching the next generation of neurologists.

Walter Timme, founder of the ARNMD, began the meeting with a general history of the disease to that date. There was a review of the geographical distribution of MS by Charles Davenport, as well as studies on World War I troops (by Percival Baillie), psychological effects (by Sanger Brown and Thomas Davis), a discussion of the psychopathology by Smith Ely Jelliffe, and a review of the pathology by George Hassin.

The conclusions of the meeting tried to capture a consensus of quite varied opinions and were in keeping with the understanding and state of medical research of the time. In writing the conclusions, the commissioners emphasized that MS was among the most common organic diseases affecting the nervous system. They de-emphasized the importance of the Charcot triad, but continued to emphasize the importance of the abdominal reflexes (lost in 83.7 percent of cases), and the value of temporal pallor of the optic disc as a sign. They concluded that there was no particular psychic disorder characteristic of the disease, that euphoria was not very characteristic, and mental deterioration often absent. They could not support Jelliffe's belief that MS was "schizophrenia of the spinal axis" with plaques induced by repressed tensions.⁷ Impressed by the inability to reproduce studies by many investigators that suggested the disease was due to a transmissible virus, spirochete, bacterium, or other agent, they concluded there was no solid evidence for a bacteriological cause, but expected further experiments on this in the future.

Hassin concluded that MS was a degenerative disease due to some unknown toxin, probably an endotoxin. William Spiller disagreed с С and argued that MS was an inflammatory disease. In answer to the question posed throughout the meeting—whether MS was an inflammatory or a degenerative disease—the commission took the middle road and concluded that it might be initially inflammatory and later degenerative.

Conclusions of the ARNMD Commission, 1921

- 1. MS occurs chiefly in the age group 20-40, but can occasionally be seen as early as age 10 and as late as 60.
- 2. Males are attacked more often with a male: female ratio of 3:2.
- 3. MS makes up 1-2 percent of organic diseases of the nervous system, including those due to syphilis.
- 4. The duration may vary from one to 30 years.
- 5. It occurs more in skilled manual workers than in laborers or in brain workers.
- 6. In the United States, it occurs more around the Great Lakes, while in Europe it is more frequent in the Northern parts than in Italy or the Mediterranean area.
- 7. It is not familial or inherited, with rare exceptions, but in the ancestry, there is often evidence of neuropathic stock.
- 8. Acute infections may precede the disease in 10–12 percent of cases, and it occurs no more frequently in those who have or have not had the usual childhood diseases.
- 9. It is not caused by syphilis.
- 10. In a few cases it might be "excited" by trauma, but trauma itself cannot cause it, though it may "awaken" the disease which is already there.

At this juncture, there was some clarity about the way MS could manifest as signs and symptoms; more uncertain were the male/female ratio, the prognosis of the disease, the role of heredity, and the underlying factors that could explain the cause of the disease.

Gender

Over the previous 150 years, there had been controversy about whether the occurrence of MS was more common in men, more common in women, or equal in both sexes. Although it seems as though in the first century after Charcot's description it was found more often in men, that Charcot found it two and a half times more often in women was dismissed as a reflection of the predominance of women at the Salpêtrière. Some clinicians recorded MS as more common in women, others more often in men, and still others equally in the sexes. Wechsler told the ARNMD that the ratio was 3 men to 2 women in his survey of 1,970 records. The ARNMD Commission accepted this as the correct figure. Two decades later, Limberg thought it equal in the sexes⁸ as did the fledgling NMSS in the late 1940s, and Schumacher found it slightly more in women by 1960.9 Today investigators seem to agree that it is at least twice as common in women as men. Why the great variation? Partly this was due to the differing patterns of patient referrals to some clinics. There was also a tendency to give men with neurological disease an organic diagnosis, while women were often diagnosed with hysterical or functional labels, like Mrs. Gatty. The situation was also complicated by the fact that many of the multiple sclerosis cases were diagnosed as other conditions, such as

All agreed that the diagnosis was difficult; textbooks and papers emphasized the differential diagnosis and how to separate multiple sclerosis cases from other disease, particularly hysteria (hysterical patients were unlikely to have spasticity with Babinski signs, optic atrophy, nystagmus, and bladder involvement). There are many cases in the early literature of MS in which the case presented was diagnosed in life as "paresis" (syphilis) or hysteria, only to exhibit characteristic changes of MS at autopsy.¹⁰ One sees what one looks for, and often clinicians assessing a patient with complex and multiple neurological symptoms considered neurosyphilis, hysteria, or some other neurological disorder first. In

neurosyphilis and hysteria; this continued well into the 20th century.

Brain noted there were many reports of greater frequency of MS among those of Scandinavian, Finnish, Scottish, French, Slavic, German, English, and Irish descent compared to those of other populations. He felt the reports of greater rural frequency could not be justified from the inadequate studies. He also could not accept reports that disease incidence was higher in certain occupations: woodworkers, ironworkers, and sailors. Brain reviewed the pathology of the disease and examined the concept that it is primarily a diffuse glial hypertrophy, possibly a reaction to an external agent. He commented that if there were such an agent, it must be able to produce mainly perivascular lesions attended by infiltration of plasma cells and lymphocytes. Such an agent could be a toxin or a virus. Making the same point that Dawson made in 1914, he argued against a toxic cause because toxins are characterized by diffuseness, symmetry in distribution, and timing of their neurological effects, rather than the focal, asymmetrical, and episodic changes as seen in MS. On the other hand, various forms of encephalitis could produce a pathological picture similar to that of MS. Although he respectfully acknowledged the "weighty support" for the toxin theory by Oppenheim, Dawson, and others, Brain thought that infection was a more likely suspect in the cause of MS.



Runn 1930

Figure 10.2 Russell Brain (1895–1966), later Lord Brain, contributed substantially to the understanding of MS by his extensive review of the disease in 1930 and his overview of the disease in his textbook editions over the next four decades. He kept careful statistical records on the disease.

Brain looked at the question of which central nervous system tissue is first affected by the disease. Was it the glia, the blood vessels, the nerve, or the myelin? Noting that each had its supporters, he concluded that the myelin seemed to be the constant factor, and the glial reactions were probably a response to the external agent and the breakdown products.

Brain felt Pierre Marie had overemphasized the causal relationship to infection; although he allowed that it could be an aggravating factor (not a cause), a distinct relationship was seen in less than a third of the cases. He gave a list of possible explanations for the apparent relationship of trauma and MS, but felt there was little reason to consider trama a cause of MS. The same applied to cold, heat, and electric shock.

Brain reviewed in detail the numerous reports of transmission and isolation of various infective agents, and the even more numerous reports that failed to reproduce these findings. He concluded that there was no satisfactory evidence that the disease had been transmitted to animals. The recent dramatic story of a virus isolated by Miss Chevassut was still unfolding, and he suggested this work should await confirmation.

He noted that the "classical" picture of MS with the Charcot triad was present in only 10 percent of cases now that milder and partial forms and variations of MS were being recognized. Monosymptomatic, "oligosymptomatic," intermittent, and progressive cases were recognized. He said that verified childhood cases did occur, but were rare; most of the early reports were probably in error, and disease onset was between ages 20 and 40 in 68 percent of cases. The course was variable. Patients might die in months or be working after 26 years.

Brain began his overview of therapy of MS with this perceptive statement:

"It is notoriously difficult to assess the value of therapeutic measures in disseminated sclerosis, and most advocates of some particular line of treatment qualify their optimism by alluding to the natural tendency of the disease to spontaneous remissions. That such a qualification is necessary seems to indicate that no mode of treatment is successful enough to achieve, at the most, a greater improvement than might have occurred spontaneously." helped did not stop physicians from offering something. In clinics there was a second conflict—physicians who were anxious to be able to offer their patients something, anything, were also the ones who were supposed to be the objective, scientifically minded leaders. They were expected to calmly assess the evidence for what would be a better therapy, something that might help more than the many nostrums passed out to calm the anxious and distressed MS patient. But the experts were just as anxious to be able to offer their patients something; when they felt something might help, they had the influence and reputation to make the therapy widely accepted. This can be seen in the wide use of anticoagulants by Putnam, the histamine therapy of Horton at the Mayo Clinic and Hinton Jonez at the Tacoma Clinic, and the blood transfusions and lowfat diet of Swank at the MNI and later Oregon.

One of the most influential neurologists was Tracy Putnam. Tally recorded 126 therapies that he employed in his MS cases.⁵¹ In medicine, the personal experience of the physician has always had great cachet. No matter what the evidence and the experiment showed, the conclusion following the statement by the physician, "In my experience ...," carried greater weight. In the postwar period, great and prominent men, and they were almost always men, held sway by their opinions and their practice.

It was a period when personal experience provided the direction in MS care. However, as physicians judged their clinical experience with long-standing treatments with quinine, arsenic, strychnine, antimony, potassium iodide, and mercury, and found these useless, they also harshly judged newer therapies such as blood transfusion, anticoagulation, antibiotics, and sympathectomies. Just when they hoped to offer their patients something in an age that indicated that new therapies were just around the corner, they saw the therapeutic armamentarium getting dismally short. It was a frustrating time for patients and for neurologists. By the end of the 1970s there was a feeling, also noted in the previous century, that no therapy was of help in the disease, although some medications might modify some of the symptoms. Steroids were being used more, but the growing experience with what we would now judge very low doses was unconvincing, and of minimal benefit at best, with no change in the eventual outcome. The time was then ripe for the promise of the immunosuppressant, which dominated the MS research field for the next few decades, and the development of the randomized clinical trial to assess more objectively whether a treatment really worked in a disease that was variable and, in the short-term, unpredictable.

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chapter 16

Multiple Sclerosis and the Public: Societies, Narratives, and the Media

THE MULTIPLE SCLEROSIS SOCIETY

"It is possible that the cause of the disease lies buried somewhere in these lengthy protocols waiting to be found by anyone ingenious enough to unearth it."

Dr. Henry Miller, 1972

An important impetus for change and encouragement of research in MS in the last 50 years has been the formation of the MS societies in several countries. Although there was some organization of activities around MS and support for research in the 1920s, it was on an institutional level, such as the Commonwealth Fund, which supported MS research at New York Neurological Institute. The Commonwealth Fund recognized that neurology was relatively poorly supported by foundations, and the NYNI decided to concentrate efforts on MS and epilepsy.¹ There was a rapid increase in the number of articles related to MS in the medical literature in the 1930s and 1940s, and after World War II, research dollars going to MS projects increased substantially. Despite this,

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Chapter 11

Searching for a Cause of MS

And so we must add not wings but weights and leads to the intellect so as to hinder all leaping and flying.

Sir Francis Bacon, 1620¹

"It is easy to welcome new facts which submit themselves to a favourite hypothesis; but if we resist this first temptation and pursue our own observations with industry and caution, we are presently made aware that the new facts are far more difficult of study than we had supposed. They turn out to be far less simple and uniform than at first they seemed, and they begin to refuse the shelter of the favourite hypothesis which appeared so convenient for them."

> Sir T. Clifford Allbutt (Discussing optic neuritis with spinal myelitis, later called Devic's disease, 1870)²

"... a child one year old who was thrown into a convulsion by having a goose thrown at her, and after the convulsion, the disease (MS) developed."

Landon Carter Gray, 1893³

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"Spritka saw a case develop from fright in a cigarmaker." Landon Carter Gray, 1893⁴

"The most difficult things to explain are those which are not true." A.S. Wiener, 1956⁵

"The amount of time and money which has been expended to determine the causal factors in multiple sclerosis is beyond computing ... the result has been nil."

William Boyd, 1958⁶

"It is possible that the cause of the disease lies buried somewhere in these lengthy protocols waiting to be found by someone ingenious enough to unearth it."

Henry Miller, 1960⁷

"It therefore seems that we should view the aetiology and pathogenesis of multiple sclerosis on a multifactorial basis, like the celebrated 'Chinese Dinner' where a judicious assortment of individual items combine to give a phenomenon whose entirety transends the mere sum of its individual parts."

D.C. Dumonde, 1979⁸

"Lack of understanding about the cause of MS has generated a remarkable variety of hypotheses over the last century. Few mechanisms have not been proposed to explain the bewildering phenomena associated with this disease."

George Ebers, 1998⁹

The Oxford English Dictionary defines etiology as a medical term meaning the cause or a set of causes of a disease or condition; also the investigation or attribution of the cause or reason for something (Etiology—from the Greek, aitiologia—aitia—a cause; logia—knowledge). Over the last century, Sir William Gowers, Russell Brain, S.A. campaign to vaccinate for hepatitis B, and in October 1998, the French government suspended the school program for hepatitis B vaccination because of concern about MS, even though two preliminary studies, one French and one American, showed an insignificant increase in MS in those vaccinated. Despite the negative studies and a report from the World Health Organization that said there was no causal link between vaccines and MS, the concern prevailed and the program ceased.

The first large group to be assessed for this risk was studied during the swine flu scare in the 1970s, and no convincing relationship to MS or of aggravation of MS was noted. Recently, Christian Confavreaux and the Vaccines in Multiple Sclerosis Study Group reviewed 19 publications (1962–1997) that indicated a possible link, and these discussed mostly single cases.³⁸⁰ Their study of 643 patients from the European Database for Multiple Sclerosis who had relapses of MS showed no increased risk of relapse because of vaccination. This applied to influenza, hepatitis B, and tetanus vaccines.

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lack of substantial evidence, is still a theory because the idea fits the features of the disease so well.

An important question was raised in 1863 by Rindfleisch, who noted in his microscopic examinations that a blood vessel was often prominent in the center of the MS plaque; he postulated that the disorder was due to an abnormality in the vasculature.¹¹ In 1863, Leyden summarized the state of knowledge of this condition in 34 cases five years before Charcot's lesson on multiple sclerosis. He showed that acute myelitis and the general neurological condition we know as multiple sclerosis are the same.¹² He noted that one of his cases was hereditary, but thought the cause in the others could be exposure to cold and dampness, concussion to the body, and psychic effects such as prolonged worry and sudden fright.

Other questions about which tissue has the primary defect (glia, myelin, blood vessels, or immune cells) continue to occupy investigators. Charcot felt the disorder was one of glial hypertrophy and destruction of nerve tissues, with the "wreck and detritus resulting from disintegration of nerve fibers" being removed by lipid-laden cells.

In 1875, after a very clear outline of the clinical features and pathological findings of MS, Moxon wondered what other conditions might aid in understanding the patchiness of the change in the nervous system.¹³ He regarded the pathology as "eruptive" in nature, similar to dermatological diseases, and similar to the process that occurs in smallpox, leprosy, and syphilis. Such patchiness occurs in leprosy of the skin or in the cystoid eruption of bones. Looking for further analogies, he mused that the patchiness called to mind the lichen on a stone wall, or the round puffs of algaceous ferment plant in a changing chemical solution, "pointing clearly to some entirely foreign agency springing into action at the affected spots." He noted that subacute arteritis, of a type occurring in middle age that he called inflammatory mollities could affect the vessels to the brain and cause softening and round blotches. However, he confessed that such analogies helped little when there was little knowledge of what caused the vascular change. Moxon concluded that the disease remained of unknown origin.

In 1878, Hamilton said little was known about etiology, but noted that moist cold, emotional excitement, and venereal excesses were susKrafft-Ebing said in 1894 that 40 out of 100 cases of MS had a history of heat injury.²⁰ In 1940, S.A. Kinnier Wilson said heat, like infection, could aggravate MS, but was not a cause; cold might be more important.²¹ Landon Carter Gray was sure that when MS occurred in children, it usually came on after a convulsion.²² Oppenheim believed that all MS begins in infancy and only manifested later in life, probably due to some external toxin.²³

Charles Beevor felt that certain occupations were vulnerable, a concern often expressed in the German literature.²⁴ This idea was never emphasized, nor was there much evidence to support it, but the idea would return whenever clusters of MS cases were observed, especially in the workplace. Occupations that were suspected included woodworking, ironworking, farming, working with lead, phosphorus, copper, or aniline dyes; occupations that gave workers constant water exposure; and more recently, working with animals that suffered from swayback disease. Charles Dana believed that MS occurred more often in persons doing skilled manual work than in ordinary laborers or in "brain workers."²⁵ None of these suggestions about occupational risk have surfaced as relevant in large surveys of MS in recent times.

The idea of a neuropathic constitution coupled with the propensity to many nervous and mental diseases, poverty, and crime was widely discussed early in the 20th century when eugenic theory and practices were in vogue. It persists today under the more respectable mantle of a genetic predisposition to MS. Dana believed many factors could act on a "neuropathic constitution" that existed in some families. These factors included acute infections such as typhoid, diphtheria, smallpox, measles, erysipelas, malaria, myelitis, and encephalitis. MS had been seen in a case of hemoglobinuria, as well as after trauma and concussions.

The idea of causal infection was fading in the 1920s (it was revived in the 1930s), and the concept of some toxin or lytic substance affecting myelin became more prominent, as Marburg suggested in 1906 and 1911. He felt the myelinolytic toxin caused breakdown of the lecithin fraction of myelin.²⁶ A myelinotoxic substance was also considered by Mott (1913) and Dawson (1916) and was clearly argued by George B. Hassin at the 1921 ARNMD meeting, where he stated that MS was a myelin degener-



Figure 11.2 Lewellys Barker was a Canadian physician who succeeded Sir William Osler at Johns Hopkins and made many contributions to neurology, discussing the various causes of MS at the 1921 ARNMD meeting in New York. He was said to have produced the first major neuroanatomical text in the United States.

ative disorder, not an infection.²⁷ What this lytic factor might be was uncertain, but Brickner (1931) announced that he had found a lipolytic enzyme in the plasma of MS patients.²⁸

Lewellys F. Barker discussed the exogenous causes of multiple sclerosis at the 1921 ARNMD meeting and indicated it was accepted clinically that infections could produce an exacerbation of MS. A specific infection was unlikely as a cause, but there was also no longer much support for <u>Oppenheim's belief in an environmental toxin.*^{29,30}</u> Differentiating a causative agent from an aggravating one, Barker noted that thermic injury occurred in 40 percent of cases, but was likely an aggravating factor, not a cause. He was skeptical about the role of trauma and noted that patients easily incriminate trauma, and "neurologists, who

^{*}Barker was a Canadian, who succeeded William Osler when Osler accepted the position of Regius Professor at Oxford. He contributed to the understanding of chronic diseases, geriatrics, liver and kidney physiology, endocarditis, TB, gout, and rheumatic diseases, but his book *The Nervous System and its Constituent Neurons* (1899) was said by Courville to be "the first major anatomic treatment of the nervous system to originate in the United States." His book *Time and the Physician* is an interesting view of medicine in his era.

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Figure 11.15 Leonard Kurland and Donald Mulder on a neurological epidemiological study in Guam, 1955. In their studies there, they found only one case of MS and it was in a man who had spent six years in the northern United States. (Courtesy of Dr. Leonard Kurland.)

Prevalence was double that reported elsewhere, and median survival was 35 years, compared to earlier reports of eight, 10, and 12 years in studies in hospitals. Limberg in 1950, and Goldberg and Kurland in 1962, reviewing the prevalence of MS in 33 countries around the world, confirmed a striking geographical pattern for MS.

Kurland believed that up to 1948 there had not yet been valid evidence of a variation in the geographic distribution of the disease. In that year, Limberg found that deaths from MS were more common farther away from the equator. The growing evidence from North America was particularly convincing; it covered such a huge geographical area, and the language, medical practice, medical certification at the time of death, and the coding of death were similar throughout. Death rates from MS were higher in Canada and in the northern United States than in the southern United States in the initial studies by Kurland, who looked at New Orleans, Boston, and Winnipeg.

Registries began to be developed in the 1950s because of the growing interest in determining the prevalence and distribution of MS. Most floundered because of inadequate methodology, but for the next few decades, and even now, areas studied will claim they have more MS than other areas because their study shows more than the outdated and incom1996, which provided evidence for linkage of MS to HLA, and identified six new chromosomal regions, which may contain susceptibility genes for multiple sclerosis.

A major genetic study of MS patients has been undertaken in Canada by Dessa Sadovnick, George Ebers, and The Canadian Genetic Collaborative Group surveying 20,000 Canadians coast to coast, and now entering its fourth phase. This is the largest genetic study on MS and has already provided important information on the risk in relatives of MS cases, in identical and nonidentical twins, and in the families of MS patients who were adopted.²⁶⁵

THE VASCULAR THEORY

For a number of reasons, a vascular basis for MS has been considered from the earliest days, when the pathology was being examined under the microscope. In the early 19th century, lenses for microscopes were of poor quality, one of the reasons many French clinicians paid little attention to microscopy. But even with a crude microscope, Eduard Rindfleisch (1836–1908) noted in 1863 the consistent location of a <u>blood vessel in the</u> center of MS plaques.²⁶⁶ He saw that there were changes in blood vessels and nerve elements secondary to inflammation combined with hyperemia in the plaque. In addition, he recognized perivascular cell infiltrations and fatty changes in the neuroglia. He suggested that the search for a primary cause of MS should address alteration of individual blood vessels and their ramifications.

"If one looks carefully at freshly altered parts of the white matter ... one perceives already with the naked eye a red point or line in the middle of each individual focus ... the lumen of a small vessel engorged with blood. ... All this leads us to search for the primary cause of the disease in an alteration of individual vessels and their ramifications; all vessels running inside the foci, but also those which transverse the immediately surrounding but still intact parenchyma are in a state characteristic of chronic inflammation."

Eduard Rindfleisch, 1863

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Putnam (1935–1947), Marburg (1942), and others who saw a relationship of the plaque to a blood vessel. Courville discussed a case from the English pathologist William McMenemey of Maida Vale Hospital, London, who provided him some blocks of wet pathological material. The patient was a woman with multiple sclerosis and in the small areas of early demyelination, there were vessels whose lumens contained small fat globules. Courville thought the fat globules in this one case resembled those seen in traumatic fat embolism, and although he admitted one swallow did not make a summer (and he did not find such fat globules in the several other cases he had studied), he was impressed enough to build a case for a vascular fat embolic cause for MS on the basis of this patient. His many earlier publications focused on the vascular relationship, but he was now writing when the interest and belief in a vascular cause had waned, as attention had shifted to the burgeoning sciences related to immunology, epidemiology, and viral diseases as a way to explain MS.

THE IMMUNOLOGICAL THEORY

"Certainly one of the most lengthy and unfinished chapters in the history of MS research has been the search for the postulated 'immune defect' believed to cause MS."

George C. Ebers, 1998²⁸³

The theories of etiology of MS that arose in the 19th century posited a degenerative, vascular, infective, environmental, or toxic cause. Early in the 20th century, the genetic concept slowly grew, and only in the last half of this century was there a strong sense that an immunological mechanism might underlie the basis of the disease, though the seeds of this idea had been laid much earlier. Waksman said that the paradigm shifts from vascular to infection and later to immune mechanisms occurred slowly, as the understanding of what was occurring in the MS plaque developed, with studies by Adam and Kubik in the 1950s and by McDonald and Prineas in the 1970s.*²⁸⁴⁻²⁸⁹

^{*}Reviews of the pathology of the plaque can be found in Dawson 1916 and 1917–1918; Lumsden 1970; Prineas 1985; Raine 1993, and Prineas and McDonald 1997.

The recent studies of Rabins³⁶⁸ and Franklin et al.³⁶⁹ provide marginal, if any, evidence for any association of stress and MS. Grant,³⁷⁰ however, found severe threatening events in 62 percent of his MS patients, but only in 15 percent of controls. In 1991, Warren noted that 56.8 percent of patients with an exacerbation of MS had had an intense emotional event in the six months prior to the event, compared to 28.4 percent of patients in remission.^{371,372}

One of the more interesting studies is that of Nisipeanu and Korczyn, who reported in 1993 on the experience of attacks of MS in relation to the Persian Gulf War.³⁷³ There appeared to be a lower rate of attacks immediately after the war than before, suggesting that acute severe stress might actually reduce attacks of MS. However, the results of the study are not strong evidence as the numbers are small and the period of study is short, and because it is well-documented that attacks decrease over time.

In 1997, Sibley reported the final results of the study mentioned above under the discussion of trauma,³⁷⁴ concluding there was no association of MS with stress, but the AAN committee noted marginal evidence for an association of MS with job and marital stress.³⁷⁵ The AAN committee concluded that there was Class 2 evidence both for and against an association of stress and MS, but there were reasons to regard the possible association as weak. There is a recent observation that new lesions on MRI may be more frequent two months after major stress, but this is again circumstantial, weak evidence.³⁷⁶

What is the conclusion of all the evidence over the last 150 years? Assessment of the evidence suggests no association of MS onset with physical trauma, and the data are so limited that no convincing association of MS with psychological stress can be established "with reasonable medical certainty."

Environmental Factors

An early proponent of an environmental cause for MS was Hermann, Oppenheim.^{377,378} The favorite assistant to Westphal at the University of Berlin, he was interested in environmental toxins early in his career. His initial publications included observations on lead intoxication and alcohol. His monograph on traumatic neurosis, in which he suggested that

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psychic disturbances had an organic basis, initiated an acrimonious debate; one of his major critics was Charcot.* Reviewing possible exogenous toxins in 1922, Lewellys Barker did not accept the suggestion of Oppenheim of lead, arsenic, and tin, and of von Jaksch of manganese as causes of MS; he said that any neurological disorders they caused were unlike MS.³⁷⁹ Using the same logic as Risien Russell had some 30 years before, Barker argued that if metal poisoning were the culprit, then MS would be a disease of men, as they were commonly exposed to such agents; but he thought MS occurrence was about equal in the sexes, as many researchers did. Also, the disease often occurred early in life before men could have much chance for occupational exposure. Finally, it would hardly be credible that repeated attacks were repeated bouts of poisoning. In his series of 44 cases from the records of Johns Hopkins Hospital and his own practice, there were no cases of metal poisoning. Barker also rejected Jelliffe's suggestion that alcohol might be a factor in MS, based on his finding that eight percent of his MS cases were inebriates. 'Barker argued that MS was not common in alcoholics. He also dispensed with the implication of carbon monoxide as a cause, even though scientists recognized that it could cause damage to the nervous system. He then outlined reasons why trauma, thermal injury, and electrical injury were also not reasonable suspects. Barker concluded:

"If multiple sclerosis is a disease entity due to a single cause that acts early in life, it may be due to some specific infection, but the evidence available is strongly against it being caused by any of our well-known infections, by any ordinary intoxication (organic or inorganic), or by electrical, thermal or traumatic influences. If the exogenous factors mentioned play any role at all in the etiology of the disease, they must act either as predisposing influences for the true cause, or as aggravators of a disease already started by the true cause."

^{*}Hermann Oppenheim (1858–1919) seemed always at the center of controversy, but he did not accept criticism well. When he was not confirmed as Westphal's successor, he started his own successful neurological clinic that gained an international reputation from its many publications. It was Oppenheim's diagnosis that enabled Koehler to carry out the first brain tumor removal. He wrote a monograph on brain tumors and coined the term dystonia musculorum deformans, which for a time was named Oppenheim's disease, and his description of amyotonia congenita is still called by that eponym.

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Figure 7.20 A girl with multiple sclerosis walking with her nurse in the Blockley Hospital for the Poor. Photogravure after Eadweard Muybridge, 1887. This was one of the 781 photogravures on animal locomotion by Muybridge carried out at the University of Pennsylvania. (Courtesy of the Wellcome Library, London.)

Marie felt there were three major forms of MS: spastic, purely cerebellar, and cerebello-spastic. He classified the course of the disease into the chronic progressive course: intermittent attacks, chronic remitting course, and patients with increasing improvement or apparent cure. He showed the diagram by Gilles de la Tourette of the foot pattern of a patient with multiple sclerosis trying to walk along a line. The pattern shows the gait (foot pattern) of the patient with spastic *and* cerebellar forms of MS.

Marie said that many of the causes of multiple sclerosis were wellknown—overwork, exposure to cold, injury, and excess of every kind. Although these are common precipitants, he said he knew of another cause even more common—infection—"or rather infections." He listed the most common infections he had seen that precipitated MS: typhoid, malaria, smallpox, diphtheria, erysipelas, pneumonia, measles, scarlatina, whooping cough, dysentery, cholera, and other fevers.

Marie confessed that the evidence was not yet conclusive for infection as a cause for MS, and prudent reserve was reasonable from a purely scientific point of view. Although this seems open-minded, in a

chapter 13

The Nature of the MS Plaque

One of the recognizable characteristic features of multiple sclerosis, evident to the first observers in Germany, France, and Austria was the scattered lesions throughout the white matter of the central nervous system. Charcot called them plaques, and even though Greenfield indicated later that this word refers to something that is flat, rather than ovoid, spherical, or the many other shapes that these lesions take, the term has held.¹

Virchow described neuroglia of the nervous system and named myelin in 1858. He suggested neuroglia provided mechanical support and repair functions. In 1883, Golgi suggested the neuroglial cells also provide nutritional support and in 1897, Bevan and Lewis noted the cells' role in removal of debris. Early users of microscopes noted a marked loss of myelin in the plaques of MS, with relative sparing of axons. The oligodendrocyte was first described by Robertson in 1899. It was further defined in 1921 by Rio Hortega, who named, characterized, and typed these cells. In 1932, Penfield suggested the cells were involved in the production and maintenance of myelin. Classic descriptions of the pathology of the plaques have been given by Bielschowsky (1903, 1904); Marinesco and Minea (1909); Siemerling and Raecke (1911); Dawson (1916); Jacob

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Figure 13.1 Rudolph Ludwig Carl Virchow (1821–1902) changed the concept of disease by his book Die Cellularpathologie (1858). His cellular concepts of disease, along with his many publications on the brain and neurological disease influenced those who studied MS, including Vulpian and Charcot. Although capable of visionary reductionist science of the cells in disease, he was also capable of a broad community vision and was throughout his career a left wing activist and politician, believing that politics was just medicine on a grand scale. (From the collection of Dr. Hans Schlumberger.)

(1929); and Steiner (1931). Important reviews of the field have been presented by Brain (1930); Ferraro (1937 and 1944); Schaltenbrand (1943); and Hurst (1952).

The earliest writers speculated little on the nature of the grey softening they saw and felt as they ran their fingers over spinal cords at the autopsies of their MS patients. However, in 1863, Rindfleisch indicated that the basis might be in an inflammatory process in the small veins seen in the center of the grey lesions.² Charcot felt that an overgrowth of glia was the specific abnormality, damaging the myelin sheaths and sometimes the axons. The local vascular changes would be secondary to glial overgrowth and the breakdown of nerve tissue that was followed by macrophage removal of the lipid products of myelin, a process Charcot observed under his microscope and illustrated in his careful drawings. His student Joseph Babinski^{3,4} also felt the changes were a demyelinating process, even though Compston⁵ had pointed out that one of the illustrations to his thesis showed the appearance of remyelination, with thin layers of myelin surrounding the axon and fat granule cells removing the myelin debris. Strümpell⁶ and Müller⁷ agreed with Charcot that the defect was an inborn disease of neuroglia. Another Charcot student, Pierre Marie, argued strongly (and he did argue the point with his detractors) that these changes were the result of an infection.⁸ This was later supported by the observation that viral infections could cause scattered areas of perivascular demyelination, also seen in postvaccinal encephalomyelitis, and postinfectious encephalitis.

The lesions in MS are scattered, some small and some large, and some coalescing into other lesions to form even larger areas of demyelination. They can be anywhere in the white matter, and even extend into the grey matter in some instances.⁹ They tend to be in characteristic areas, especially in the periventricular region.*^{10,11} Cruvielhier^{12–16} showed lesions in the corpus callosum,[†] and Gowers felt the lesions were more numerous posteriorly.¹⁷

Charcot and other early writers noted the relative preservation of the axons in the MS plaques. Charcot felt that repair could occur after myelin breakdown. His student Babinski agreed, but described a process of nerve regeneration rather than remyelination, even though some of the fibers in the illustrations of his 1885 thesis on multiple sclerosis showed thin myelin around some axons, which is now recognized as remyelination.¹⁸ In 1903, Bielschowsky was impressed that the axons were preserved within the plaques, but also noted some axonal shrinkage, and he suggested that the picture may convey a false impression of normality. Greenfield and King¹⁹ used Bielschowsky's method on frozen sections to examine 125 cerebral plaques; they noted that only 10 percent had severe loss of axons, retaining only 15-20 percent, but of the remaining 90 percent, half the plaques had moderate loss, and the rest had little change. They concluded that axons do not pass intact through a plaque. They and others found some evidence of sprouting and some "retraction bulbs," but cautioned that this should not be interpreted as attempts at regeneration.

^{*} S.A. Kinnier Wilson referred to the periventricular location of lesions as the "Wetterwinkel of Steiner."

[†] In 1940, Hallervorden said they were so characteristic of MS that the diagnosis should be questioned if they were not present.



Figure 13.3 Santiago Ramon Y. Cajal made many advances in the understanding of the peripheral and central nervous system by his remarkable microscopic and staining techniques. (Courtesy of the National Library of Medicine.)

droglial cells when he was working in the Madrid lab of Pio del Rio-Hortega in 1924.²⁷ There was controversy at the time about the non-nervous cells in the brain that formed the supporting structure. There were astrocytes, often referred to as neuroglia (from the Greek, meaning "nerve glue"), and there was a "third element" made up of oligodendrocytes ("few-branching glue cells") and microglia ("small glue cells").*28 Some researchers, including the famed neurohistologist Ramón y Cajal, also in Madrid, did not agree that oligodendrocytes were part of the neuroglia, because this could not be demonstrated in his stains. Trying out tissue stains in Rio-Hortega's lab, Penfield saw an oligodendrocyte that was particularly well stained; it was not "few branching," but had many branches. He made a note of the details of his staining technique, did ink drawings of the cells he observed, and sent a paper off to the journal Brain, pointing out that the oligodendrocyte was confirmed as a cell that made up a third of the neuroglia.²⁹ The 33-year-old Penfield was not hesitant to chide the famous Cajal in the paper, indicating that the Nobel

^{*} The Germans called microglia Hortega cells. Del Rio-Hortega first described oligodendroglia and microglia.



Figure 13.4 Wilder Penfield, famous Canadian neurosurgeon, published on glial cells while studying with Rio-Hortega early in his career. (Courtesy of Little Brown and Company Publishers.)

laureate rejected the presence of oligodendrocytes because he could not find them in his stains. Penfield emphasized that it was Cajal who had previously said it was dangerous to assign value to negative results.

Penfield had brought some microscopic sections from New York that he hoped to review in Madrid and one was from a man who died of a malignant brain tumor. When looking at the neurologlial cells, he saw something that amazed him, and he suddenly understood what happens when the brain reacts to damage. Penfield had made another discovery of importance for the understanding of changes in the plaques of MS: the recognition that microglia were in one form when "at rest" in the brain, but change into "amoeba-like scavenger cells that wander through the tissue and devour the broken parts of the dead cells and their branches." Soon he was sending off his second paper. The first had been based on the observation of a few cells, and the second was based on a single slide. The view that macrophages were scavenger cells persisted until Prineas examined their function further in recent years.

In 1936, J.G. Greenfield and Lester King described the histopathology of lesions in 13 cases of MS, describing the early changes in fresh plaques with intense wall formation by gitter cells packed against the normal myelin.³⁰ In the secondary stage, they saw perivascular accumulation of gitter cells with lymphocytes, plasma cells, and pale mononuclear cells. Some cells contained fat granules and these phagocytic cells were thought to be of connective tissue origin. In the third stage, the fat disappeared and the gitter cells were fewer. They described the staining characteristics of the myelin breakdown and the products of this destruction. They stated that the persistence of the axons in MS is only relative, and there is loss in many cases. Extreme loss, however, as reported by Putnam, was not common in the 125 plaques they examined.

Greenfield and King noted that the changes seen in the axons have been ignored in the English literature, but were well-described in the French and German literature. There were nerve sprouts, nerve bulbs and loops, and *boules de retraction* interpreted as regenerative phenomena. Some of these changes, particularly the *boules de retraction*, were probably changes representing degeneration and they pointed out illustrations of this degenerative change in the works of Cajal.

They then discussed gliosis, noting that it was one of the six stages in the natural history of MS (the fourth) noted by Dawson, and that in the English literature, it was regarded as a secondary phenomenon, whereas in the Continental literature it was regarded as a primary process, even though the view of glial change as the primary cause put forward by Strümpell and Müller was not tenable. They asked if gliosis is an initial process or a reaction and concluded it was too early and intense to be just a secondary process.

The vessel changes were thought to be common by Dawson and others, but Bielschowsky and Greenfield felt that this was not a constant finding, seen mostly in small plaques, but obscured in larger ones where coalescence of many plaques occurred. The perivascular nature of the pathology was also less definite, as in postinfectious encephalomyelitis.³¹



Figure 13.5 Joseph Godwin Greenfield (1884-1958) was the dean of "neuropathology" in the early half of the 20th century, known to all neurologists by his influential and comprehensive textbook of Neuropathology published in 1958. He died prior to the publication of the second edition in 1963. When in Edinburgh, the young James Walker Dawson worked under Greenfield and produced the definitive work on the pathology in 1916. Greenfield contributed to the pathology of MS over four decades.

Greenfield described the centrifugal spread of plaques as a "wall formation" of inflammatory cellular activity at the periphery of the plaque, with more complete demyelination in the center, forming a "shadow plaque." Shadow plaques (*Markshattenherde*) have been interpreted differently by different writers. Marburg thought they were areas of demyelination. Alzheimer (1910) thought they were young plaques in the making, but Greenfield said he found them mostly in chronic cases of MS, where there was little activity. Prineas later showed they were older areas that had remyelinated fibers.

Dr. William G. Spiller initially wondered in 1904 whether the primary change was in the "noble tissues" using the French term referring to the nerve fibers, or whether it was primarily in the neuroglia, and he concluded the latter.³² He concluded that MS was probably an acute disease caused by some circulating toxin, partly inflammatory, and probably dependent on vascular supply to the area of the plaques. In 1922, Joshua H. Leiner indicated that the axis cylinder could be involved in the lesion, although it might survive.³³ Studies on the proliferative progenitor oligodendrocyte are summarized by Compston.³⁴

A



Figure 13.6 Illustration used by Joshua Leir paper to the ARNMD in 1921. The myelin I ed by glial fibres (A). The axons show irregu end bulb (B). (ARNMD, 1922.)

By 1937, Schmidt used polarize to demonstrate that the structure of layers of lipid and protein. Review extensive in the first 40 years of the to suggest in 1938 that it was unlike learned further about the process of tions are always risky and we are su tion as we enter a new century.

Putnam had done experiments i carotids of eight cats and seven dogs, resembled MS.^{35,36} He later block However, his presentation of this **w** gists, who were not impressed with his interpretation of the areas of demyelination. One other experiment of interest in the discussion of the current vogue among MS patients for subcutaneous injections of bee venom, and actual bee stings as a form of therapy, was the work of Cornil in 1939 producing demyelination with subcutaneous injections of bee venom in mice and guinea pigs. Continuing the experiments on vascular induction of demyelination, Hurst injected olive oil and egg yolk in a solution he called a "mayonnaise" into one carotid of animals and got changes of demyelination but concluded these were not related to the changes in MS; he felt they looked more like those of Binswanger's disease.³⁷

Hans Reese gave a critique of the various theories of etiology of MS at the ARNMD meeting on MS in 1948 and in a later publication.^{38,39} He indicated that various theories have come from the interpretation of the morphology of the MS plaque, the scattered nature of the plaques, the role of blood vessels, heredity, the constitution of the patient, immunization, geographic distribution, racial differences, and whether there may be both intrinsic and extrinsic causes working together. He felt that the Strümpell-Müller theory of glial dysplasia and myelin dysplactic theories were now discounted, but work on tissue changes resulted in fruitful knowledge of the process of the disease. He was unconvinced by the familial studies and the twin data and the resulting theories of neuropathic traits, which he thought led only to confusion and argument. The myelinolytic theory of Marburg (1906) and the lipolytic theory of Brickner (1930) were equally unconvincing as was Weil's theory of an abnormal esterase activity, or impaired inorganic phosphorous balance in MS. Reese was more impressed that the problems MS patients noted during menstruation, pregnancy, and the postpartum period suggested an abnormality of hormonal or lipid metabolism.

Reese asked the central question: if there is something that affects the central nervous system and causes the plaques repeatedly, how does it get there? A clinician would immediately suggest the vascular system as route, and although this idea appealed to some, others disagreed. Reese felt there were four possible scenarios: the cause was an infection, a venular thrombosis as postulated by Putnam, a spasm of the vessels, or diffusion into the CNS by antigenic substances. He related the supporting data

for each and the contradictory e with the verdict of "not proven." should be in four directions: mye affect it, neuroallergy, a search f psychological assessment of the t

Fog reviewed the literature plaques from Rindfleisch's observ ry of Putnam (1930–1939 reports the underlying mechanism of plac Dow and Berglund (1942), Zimm work (1948, 1950), Fog conclude changes, but these are intermitter 51 plaques from two cases of ty plaques and following their shape section, showed that most (39/51 plaques, and that the plaques did



Figure 13.7 A shadow plaque. (Zimmerm

for each and the contradictory evidence for each theory, and concluded with the verdict of "not proven." However, he suggested further research should be in four directions: myelin metabolism and the things that could affect it, neuroallergy, a search for specific antigens and antibodies, and psychological assessment of the total personality of the MS patient.

Fog reviewed the literature on the relationship of the vessels to plaques from Rindfleisch's observations in 1863 to 1947. Noting the theory of Putnam (1930–1939 reports) that thrombosis of small veins may be the underlying mechanism of plaque formation, and the studies on this by Dow and Berglund (1942), Zimmermann and Netsky (1950), and his own work (1948, 1950), Fog concluded that there may be some small vessel changes, but these are intermittent and variable. His subsequent study of 51 plaques from two cases of typical MS, making thin sections of the plaques and following their shape and course with direct drawings of each section, showed that most (39/51) were prolongations of periventricular plaques, and that the plaques did follow the course of the venous system.⁴⁰



Figure 13.7 A shadow plaque. (Zimmermann, 1948.)

characteristic of slowing in demyelinated fibers. With their first three cases, they were able to confirm this.^{58,59} This finding led to the application of evoked potentials in MS; and the next year, they published the frequency of delays in cases of MS. The mechanism of slowing is probably not due to conduction in remyelinated nerves, but conduction in the persistently demyelinated axon is mediated by the increase in new sodium channels. McDonald demonstrated that the remyelinated axon had distinct morphological features.^{60,61} The diagnostic tests developed on the basis of the slowing of central nerves fibers, were visual, auditory, and sensory evoked potential studies. McDonald suggested that conduction could be restored in demyelinated nerves by conduction in the demyelinated nerve, or by remyelination. Perhaps both occur. Restoration of function might depend on increased numbers of sodium channels in demyelinated nerves, as shown by Waksman and Ritchie in 1985. The experiments of Bunge, Bunge, and Ris had indicated that the oligodendrocyte was responsible for myelination and remyelination.⁶² Others raised the possibility of strategies to enhance remyelination in MS.63,64

"The persistence of axons is such a cardinal point in the pathologic picture that many articles on the subject leave the impression that all are intact in all sclerotic plaques. This is certainly not the case, and modern pathologists who have made intensive studies of the disease (for example Dawson, Speilmyer, Jakob, Atassin and Bertrand) all agree that axons are seldom undamaged and are often completely destroyed and that secondary degeneration is common."

T.J. Putnam, 193665

Though it became understood that nerves could demyelinate in MS, but could remyelinate again, the question of why the disease progressed remained. Even if nerves had thin myelin and conducted slowly, reasonable function should continue. There must be some other factor that limits the process and causes the disease eventually and sometimes primarily, to progress. Evidence is accumulating that the key is an observation made over and over by even the earliest workers such as Charcot, that axons are often damaged even early in the process.⁶⁶ He noted globules at the end of axons in the plaque. Even if this damage were a minor part of an acute



Figure 13.10 Dr. Cedric Raine. (Courtesy of Dr. C Reine. H. Boudakian, Illustration Service, Rockefeller Institute.)

ability and a persistent reduction in the concentration of NAA.⁷² Trapp later showed elegant illustrations of the nature of that axonal loss.⁷³

The hope that drugs that modify and reduce the inflammatory response would encourage remyelination has not been borne out by studies so far, perhaps because we have poor methods to assess remyelination. However, newer strategies are being developed.⁷⁴ With the development of MRI and clear evidence of widespread plaques, as well as some evidence of a more general abnormality, there has been an effort to correlate the images with the changes seen pathologically. This work is continuing. Pathologically, the plaque shows inflammation and demyelination with some degree of axonal loss and gliosis or scarring. The plaques are classified according to the degree of activity present into acute, chronic-active, and chronic-silent lesions. The acute lesion has an area of acute inflammation with uniform hypercellularity throughout and with evidence of both demyelination and remyelination. In the chronic-active lesion, there are chronic changes in the center, but inflammatory changes at the periphery with demyelination by macrophages along the border, but also increased oligodendrocytes and remyelination. The chronic-silent plaque



Figure 13.12 John Prineas of Australia did much of his neurology training in England, but much of his career has been in the departments of pathology and neurosciences at the New Jersey Medical School. His careful studies of the demyelination, remyelination, and the immunological and pathological changes in the plaque of MS has advanced the knowledge of the process and aided later attempts to find ways to alter the changes therapeutically. (Courtesy of Dr. John Prineas.)

Cuzart, Chris Livingston, Hans Lassman, Wolfgang Brüch, plus many others.... The contributions that pathologists have made are generally not that well-known or understood by the clinicians." John Prineas, 2001 (Personal Communication)

Prineas listed seven main developments since the review by Lumsden in 1970 in the *Handbook of Neurology*, Vol. 9, on demyelinating diseases:⁸²

1. The view that the macrophages are scavenger cells that remove the myelin debris has altered so that we now see them as the main effectors of myelin breakdown by phagocytosis and by secreting toxic molecules. How they are directed to the myelin and recognize it remain open questions. Prineas made an important contribution to this understanding by his electron microscopic studies of MS and the macrophage destruction of myelin in Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculopathy.

- 2. Remyelination can occur and the oligodendrocytes may persist. Prineas showed that myelin internodes at the edge of plaques were thin, short remyelinated internodes. This was the first demonstration that nerves could remyelinate. Using specific oligodendrocyte markers, he was able to demonstrate in Marburg-type acute MS that oligodendrocytes had an abrupt and dramatic loss, but the areas were soon repopulated by large numbers of these cells and that remyelination could begin, leaving the "shadow plaques" commonly seen in acute MS.
- 3. Acute MS is not a variant of acute disseminated encephalomyelitis but is related to classic patterns of MS; Marburg's severe and acute variant is a *forme fruste* of the relapsing-remitting pattern of MS.
- 4. The disease is probably autoimmune in nature, and the autoantigen is still an unidentified component of myelin and/or oligodendrocytes.
- 5. Axonal loss might also be a very important aspect of MS according to Prineas, Barnes, and McDonald.
- 6. Despite the many variations in MS, and attempts to suggest the syndrome of MS may contain different conditions, the process is probably a singular one with an underlying process.
- 7. Promising HLA studies have not yet helped identify the antigen nor have interesting epidemiological studies shown convincing clues to the underlying cause of MS.

In recent years, there have been attempts pathologically to demonstsrate activity stages of various plaques. It had long been known that some lesions were acute, with great cellular infiltrate and inflammatory changes and perivascular reaction. There were also chronic lesions with signs of activity, usually at the periphery, and others with little sign of activity.⁸³ There were also shadow plaques in some areas. Bo and Trapp, van der Valk, Buicke and Lassmann, and The Vienna Consensus Conference all attempted to define stages of the plaque. Their definitions are similar, with the exception of the Vienna classification, which seems more complex and impractical. They essentially define the features of active, chronic-active, and chronic-inactive plaques. More important than the specific components of each classification is the definition, as each study attempts to outline similar features. Lucchinetti has proposed four p and 2 have features of immune-media ble oligodendroglial disease with a dy to have lesions of the same pattern implications for future therapy.

The clinical symptoms of MS an are likely due to conduction block relows inflammation. The inflammation oxide by macrophages prominent in t ed, dose-dependent conduction block

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Lucchinetti has proposed four patterns of MS lesions.⁸⁴ Patterns 1 and 2 have features of immune-mediated disease. Patterns 3 and 4 resemble oligodendroglial disease with a dying-back pneumonia. Patients tend to have lesions of the same pattern and these observations may have implications for future therapy.

The clinical symptoms of MS and deficits manifested by the patient are likely due to conduction block resulting from demyelination that follows inflammation. The inflammation causes local production of nitric oxide by macrophages prominent in the lesions. Nitric oxide causes graded, dose-dependent conduction block in nerve fibers.⁸⁵

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