Multiple sclerosis
A clinical and theoretical review

AUGUSTUS S. ROSE, M.D.
Department of Neurology, University of California, Los Angeles, California

The author presents a review of multiple sclerosis, and summarizes the present knowledge of the disease in relation to cause, pathogenesis, pathophysiology, and treatment. He stresses the inconsistency between the central nervous system pathology and the occurrence of signs and symptoms.

KEY WORDS · multiple sclerosis · epidemiology · immunology

MULTIPLE sclerosis (MS), a nonsurgical condition of the nervous system, is of clinical interest to both surgical and nonsurgical neurologists. The symptoms may simulate surgically treatable conditions yet, because a full neurological work-up that includes injection of contrast media may be hazardous to MS patients, a review of this disease and its present status should be of prime interest to neurosurgeons. Furthermore, the increasing attention given to MS in the scientific and public press, reflecting expansion of research, justifies a status report.

Historically, the present era of widespread interest in multiple sclerosis might be considered to have begun in the early 1930's when Tracy Putnam, then a neurological surgeon in Boston, first described demyelinating lesions in dogs after partial obstruction of the superior sagittal sinus. The concept of venous thrombosis as a pathogenic factor in demyelinating lesions was developed. This led to active clinical and basic investigations and provided theoretical reasons for a possible therapy. Although the observations and the hypothesis have not been substantiated, public and scientific interest were stimulated and much benefit resulted.

More recently, another neurological surgeon, Albert W. Cook of Brooklyn, has made an interesting and potentially significant observation that may lead to a better understanding of the pathophysiology of MS symptoms. After the installation of a dorsal column stimulator for the purpose of pain relief in an MS patient, Cook and Weinstein observed that during stimulation, a number of neurological abnormalities in addition to pain were ameliorated. Comparable results were obtained in a number of additional patients. These intriguing observations could lead to a broadened understanding of symptom formation in MS and provide symptomatic benefit for some severely affected patients.

Clinically, MS is well known to all who care for neurological patients, but there are few physicians in practice who have the inclination or who take the time to think through the many puzzling features of this disease. The pathology of disseminated demyelinating central nervous system (CNS) lesions located primarily in the white matter with relative preservation of axons, was well
established many years ago. The dissemination of symptoms and signs in time and location has become accepted as the basis for making this diagnosis. But it is not commonly recognized that numerous CNS lesions are often found at autopsy, that were not productive of symptoms or signs, and in patients without either history or neurological evidence of CNS disturbance during life.\textsuperscript{12,13,15} Similarly, it is striking that, at autopsy, disseminated pathology is sometimes found in the CNS of patients whose symptoms and signs prior to death consisted of only slow steady progression of spasticity of the legs. In addition to these clinicopathological peculiarities, it is common knowledge that "precipitating factors," such as fever, fatigue, and emotional stress, are frequently part of the clinical picture of MS but no completely satisfactory explanations have been proposed. It has recently become commonplace to apply external heat to a patient to assist in diagnosis, since it has been repeatedly observed that this simple procedure will either exaggerate or precipitate abnormal neurological signs in those with demyelinating pathology. Still another clinical puzzle is that a host of widely different types of "treatments" are reported to give excellent results. Miraculous "cures" are sometimes observed and reported, but to date no evidence has been established that significant remyelination occurs after the lesions develop.

These and many other perplexing features of MS have existed for as long as patients have been observed, but the development of basic research techniques in immunology and virology and the advent of the "slow-virus era" stimulated and expanded the general interest in this fascinating and distressing disease complex.

Present Concepts Regarding Multiple Sclerosis

General

Multiple sclerosis is a primary CNS disorder, acquired in youth by susceptible individuals after contact with an external factor or factors. Many demyelinating lesions develop and are present in the CNS for variable periods before the first symptoms or signs.\textsuperscript{15} Lesion formation and lesion extension are thought to be due, at least in part, to an immunological process. Many consider that one or more viruses that are common to the community are involved in the induction of the original, and possibly also in the ongoing pathological process.

Clinically, the disease varies remarkably, from an acute, rapidly progressive, devastating illness leading to diffuse paralysis and early death, to a benign, clinically unrecognizable entity.\textsuperscript{12} The symptoms of MS seldom appear for the first time before 8 to 10 years of age, or after the age of 50. The most common type is manifested by exacerbations and remissions of symptoms of varying severity and duration which often lead, after several years, to a final progressive phase. Other cases, usually those of late onset, are slowly progressive from the outset and may be confined to increasing spasticity. Those cases that after a period of intermittent symptoms turn out to be relatively benign or stationary have no statistically significant clues that predict the clinical course. No satisfactory treatment has been discovered.

Epidemiological Concepts

In the early 1950's, the first of a series of epidemiological studies, stimulated by the high frequency of the disease in the north of the British Isles and in Europe, revealed a significantly greater incidence of MS in the northern portions of the United States and in southern Canada than in the southern part of the United States.\textsuperscript{10} In this study there were problems pertaining to accuracy of diagnosis, death certificate data, and other factors, yet the findings have stood the test of time and have been confirmed by repeated investigations.\textsuperscript{9}

Before and after World War II, the heavy migration of large populations to Israel from the high incidence areas in Europe and the low incidence areas in northern Africa, combined with the excellence of medical facilities in Israel, provided the opportunity for the accumulation of significant data relative to the occurrence of the disease among these people.\textsuperscript{3,5,8,11,16} Those who migrated to Israel after the approximate age of 15 carried the same incidence, either high or low, as that of the community or country from which they came. Follow-up studies have shown that second generation migrants to Israel, like those who migrated before the age of 15, have
Multiple sclerosis

developed the disease with an incidence comparable to that of native Israelis.11 Studies from South America, Russia, and China are incomplete or unpublished, but those from South Africa, New Zealand, and Australia tend to confirm a higher incidence in the cooler regions.19 Studies in Japan, a country that spreads across the temperate zone similarly to the United States, confirmed the long-accepted fact of low incidence of MS in that country.19

In England, Europe, Northern Ireland, and the United States, the familial occurrence of the disease is approximately 5% and therefore considerably greater than would be expected to occur by chance. Conjugal MS is rare. These investigations have led to additional extensive population studies in all parts of the world, designed to determine whether racial or environmental factors are the primary factors at work.5,8 Reports are presently incomplete. In spite of the different interpretations of the data derived from the epidemiological investigations, it is considered reasonable by most investigators to conclude that MS usually is contracted early in life and that moving to a different location after about the age of 15 does not affect its occurrence.4,13 It is theorized that in the southern United States and in Japan, where the incidence is relatively low, the population develops a “controlling” factor that is not acquired in the more northern areas, yet with differences in susceptibility among families. Some investigators consider that an external agent that is prevalent in all communities creates “immunity” for a larger proportion of the population in certain geographical areas than in other areas, and, based on the similarity to poliomyelitis,17 suggest that the North-South difference may be related more to factors of sanitation than to climate or to meteorological circumstances.

Immunological Concepts

Great hope and expectation of early success in the understanding of MS was developed in the 1940’s following the first reports on the animal disease, experimental allergic encephalitis (EAE). The lesions in this experimental condition being much like those of acute MS and almost identical to those that occur in post-vaccinal encephalomyelitis, led to the concept that the lesions of MS are immunologically produced. However, since the animal disease and the post-vaccinal human disease are almost always a one-shot non-recurring disorder, and since investigations have failed to reveal important comparable immunological findings in MS patients, it is now generally concluded that in spite of similarities, EAE is not a precise model for MS. Nevertheless, studies on in vitro measures of cellular hypersensitivity, the findings of myelinotoxic factors related to lymphocytes, the high frequency of elevated gamma globulin in the CSF of MS patients, the demonstration of IGG concentrated in plaque margins, and the moderate temporary clinical improvement obtained by immunosuppression and by corticosteroids, have maintained the continuing concept that demyelinating pathology, at least in part, is an immunological process. But this area of research, like all others, has many complexities yet to be worked out.

Viral Concepts

The concept that a virus, which is common to the community, might be of importance in the cause of MS was given impetus 10 years ago, when it was first shown that significant levels of measles antibody were present in the sera of MS patients in greater frequency than in the population as a whole.1,2 And, when later, through special techniques, subacute panencephalitis was demonstrated to be due to measles, the observation of a high titer of measles antibody seemed very hopeful. However, even though the high measles serum antibody titer has been repeatedly confirmed, its significance has not yet been clarified. Many patients with classical MS have low measles antibody titer in the serum and the CSF does not always have a high titer even in those cases with elevated serum antibody.6

The development of the electron microscope and techniques which facilitated study of tissue not necessarily obtained in the most ideal manner, directed much effort toward a search for viral particles in MS material obtained at autopsy. With certain exceptions, these efforts have thus far failed. It was encouraging, however, when viral particles of the papova type were demonstrated by several investigators in the lesions of multifocal leucoencephalopathy.20 These obser-
rations, although they did not prove a viral cause of that disease, gave impetus to the concept that a primary demyelinating disease process can be associated with a virus. However, the many clinical and pathological features of that disorder, which are different from those in MS, temper the enthusiasm.

The magnificent studies by the group at NINDS and elsewhere have shown that the New Guinea disease, kuru, is characterized by a transmissible but undefined replicating agent. After a very long incubation period, this agent was demonstrated in the brains of primates inoculated with brain tissue of kuru victims. Later when comparable investigations in Creutzfeldt-Jakob disease were similarly effective, stimulus was provided to search for an agent of the same type in MS. These investigations together with animal studies in scrapie, mink encephalopathy, and others ushered in the "slow virus era," which still holds the imagination and hope of many who are working in the field of MS research.

The search for a viral agent responsible for initiating the pathological CNS events in MS are still inconclusive. Yet, in 1972, a group from West Germany and the Wistar Institute in Philadelphia combined cultured MS brain cells with indicator cells to demonstrate nucleocapsids and virions in the brain tissue of two MS patients; from this tissue a parainfluenza virus was isolated. The presence of this agent was confirmed by electron microscopy and hemadsorption antibody tests. Later in the same year, a report from Australia demonstrated nuclear and cytoplasmic particles resembling paramyxovirus nucleocapsids in formalin-fixed material from a case of relapsing MS. These particles were found in mononuclear cells related to the central vein and infiltration zones of active demyelination. Also, a virus with the cultural and morphological characteristics of a paramyxovirus was isolated by a laboratory in England from a biopsy specimen obtained from an MS patient. Another case in which virus-like particles were found in tissue from the spinal cord of a patient dying with subacute demyelinating disease was reported from California.

These investigations are encouraging and it can be anticipated that further experience by competent virologists using the new techniques will surely provide more information. Most investigators advise caution in the interpretation of these findings since the possibilities of contamination or secondary involvement are great. However, the studies raise the distressing question of whether the syndrome of demyelinating disease might be induced by more than one virus.

No one has yet been able to induce disease by inoculation of MS brain tissue into primates; nor is there any evidence that the several types of viral agents or virus-like particles demonstrated in MS brain tissue are actually related to the cause of the disease. But in this connection it must be recognized that routine inoculation of brain tissue from patients with subacute panencephalitis does not induce that disease in primates; possibly the techniques employed to date are less than adequate.

Variation and Fluctuation of Symptoms

As mentioned earlier, one of the most puzzling clinical features of MS is the inconsistency between the CNS pathology and the occurrence of symptoms and signs. Furthermore, the tendency for remission is unexplained since significant remyelination does not occur. Briefly stated, the pathophysiology is not well understood. It can be assumed that the loss of myelin interferes with normal axonal function especially if the process is extensive. Yet, after the acute demyelinating process subsides or is contained, axonal conduction may be reestablished. It is presumed that the axonal membrane having lost the myelin covering becomes vulnerable to local biochemical environmental changes which under some circumstances induce interruption of function.

In connection with these variations of symptoms in MS, it is of interest to cite a case reported from Boston a few years ago. A young man with MS, who had recovered from an attack of optic neuritis and who enjoyed the recreation of watching pretty girls on the beach, found that his vision would diminish after exposure to the hot sun, interrupting his pleasure. He soon discovered, however, that by going into the cold water of Massachusetts Bay, visual acuity was promptly restored and he could return to his weekend avocation. This observation of reduced vision on exposure to heat in MS patients who have had optic neuritis has been repeatedly and
Multiple sclerosis

precisely documented many times but its explanation is still in doubt.

These imponderable circumstances of worsening of signs and symptoms of the disease in association with transient changes in the external and internal environment are, interestingly, counterbalanced by comparable and equally puzzling therapeutic phenomena. All who read the medical journals and the daily press are aware of frequent claims of success by eager therapists with some special type of treatment. Anyone who has become a source of confidence to these patients is aware of the remarkable improvement that may take place in direct association with some therapeutic effort. Coincidence plays a part in some but the observation is so general that explanation is needed. In the National ACTH Study a few years ago, patients in acute exacerbation were treated double-blind on a strict protocol. It was possible to demonstrate that ACTH has an effect somewhat greater than placebo, but a measurable improvement in 69% of those treated for 1 month by placebo seemed to some of us to be about as significant as the 72% that improved on ACTH. Indeed, the trend of change in the two groups of treated patients was approaching equity at the end of the study, suggesting that if the study had been continued for 1 more month, the results may have been the same in both groups.

The fluctuating signs of worsening and improvement in patients with MS are obviously based on clinical facts that must be related in some way to the peculiar pathological and physiological processes that are involved in demyelination. The elucidation of these phenomena could bring logical approaches to symptomatic therapy.

Cook and Weinstein's observation that there is improvement in neurological signs during dorsal column stimulation provides further evidence that disability in MS is partly due to a functional imbalance set up by demyelination, rather than to the usual concept of lesion pathology. One can only suppose that dorsal column stimulation in some manner brings about temporary suppression of abnormal reflex patterns that have resulted from incomplete interruption of some pathways. This approach may be expected to provide help for a number of patients who are partially incapacitated.

Management of Multiple Sclerosis

No clinical discussion of multiple sclerosis is complete without some comment concerning practical clinical management. In the several decades in which I have been interested in this disease, my innate conservative bias has been repeatedly reinforced. There being no treatment method that will bring the desired result of arrest or sustained improvement in the majority of cases, and there being a number of conditions which tend to exaggerate symptoms and/or signs, it has been my personal practice to listen, to explain, to examine, and re-examine, and to watch and wait. In the majority of cases there is no hurry and if the patient can establish confidence in this management, many unnecessary diagnostic procedures, most of which are uncomfortable, expensive and potentially likely to increase the manifestation of disease, can be avoided. Of course, some patients and some families demand that something be done, that some treatment be administered. But these are fewer than the number of physicians who feel inadequate unless they do something. Consequently, patients are subjected to unnecessary procedures; for instance, far too many are given steroids. Rather than subject every patient to risky procedures, it is better, in my judgment, to delay the diagnosis of some condition that may mimic the disease until the improbability of MS is determined. MS patients as a group respond to the genuine interest of the physician when he is willing to admit he doesn't know but wishes to be safe by repeated observation. Furthermore, good dietary habits, conservation of energy through intervals of rest and other cautious measures, often bring surprisingly satisfactory results.

It may be concluded, therefore, that multiple sclerosis is a complex disease process that occurs throughout the world, with heavy concentration in certain areas and that its cause, pathogenesis, pathophysiology, and treatment are all yet to be fully solved. The horizon is brighter than at any previous time but the significant breakthrough has not yet occurred. Well-organized, cooperative clinical investigations leading to better understanding of the environmental effects must be expanded while we await the finding of the specific cause or causes.
References


13. McAlpine D: The benign form of multiple sclerosis. A study based on 241 cases seen within three years of onset and followed up until the tenth year or more of the disease. *Brain* 84:186–203, 1961


This review was presented at the Annual Meeting of the American Academy of Neurological Surgery, Pasadena, California, October, 1973.

Address reprint requests to: Augustus S. Rose, M.D., Department of Neurology, University of California, Los Angeles, California 90026.