Multiple Sclerosis: Genetic Link, Viruses Suspected

Multiple sclerosis (MS) is one of the most common neurological diseases in North America and Europe, affecting as many as 500,000 individuals in the United States alone. The disease was first described scientifically more than 129 years ago by the Parisian Jean M. Charcot, but, surprisingly, little more can be done for an MS patient now than at that time. That situation may soon change. New developments in MS research have been occurring at an increasingly rapid pace during the past few years, and there is the promise of many more developments during the next few years. The new findings in several different fields provide the first comprehensive view of the causes and nature of MS. These findings suggest that, within the next 10 years, it may be possible to prevent the initiation of MS although the development of a cure will probably take quite a bit longer.

MS is a disease in which myelin, the fatty substance that sheathes components of the central nervous system, is attacked and destroyed. Patches of destroyed myelin are replaced by scar tissue that interrupts and distorts the flow of nerve impulses in much the same way that breaks in the insulation on telephone cables, for example, can interfere with the flow of information. The resultant symptoms include, among other things, paralysis, numbness, loss of coordination, hand tremors, loss of balance, and speech difficulties.

The disease usually affects people between the ages of 20 and 40, with the peak incidence occurring at age 30. Spontaneous periods of remission are common, but MS is generally progressive and is marked by a series of unpredictable, increasingly severe attacks, each of which causes further disability. There is no known cure for MS, and virtually no therapy that can be used against it.

A series of new discoveries during the past few years strongly suggests that MS is the result of a viral infection that precipitates an autoimmune disease in which the body's own immune defenses attack the myelin sheathing. Some of the genetic evidence about MS and the epidemiological evidence implicating viruses are discussed in this article. A second article will discuss biochemical evidence that viruses are implicated in the disease. A third article will examine evidence that the immune system is involved.

The initial suggestion that viruses are involved in MS came from epidemiological investigations. A fascinating series of observations by Milton Alter of the Temple University School of Medicine, John F. Kurtzke of the Georgetown University School of Medicine, and Geoffrey Dean of the Medico-Social Research Board of Ireland, indicate that the incidence of MS follows closely the classical pattern associated with a viral infection whose effects are delayed until some time after the initial infection. The pattern is most closely related to that of poliomyelitis, which suggests that, like paralytic polio, MS is a disease closely associated with geography, affluence, and a high standard of living.

Increases with Latitude

The prevalence of MS increases with increasing latitude both north and south of the equator. Among the first to observe this correlation was Leonard T. Kurland of the Mayo Clinic, who in 1953 found that the prevalence of MS was three times as high in Halifax, Nova Scotia, as in New Orleans. Similar increases with latitude have subsequently been demonstrated throughout North America and Europe. Alter has shown, for example, that the prevalence is 37 times as high in Minnesota as in Mexico City. But there are a few exceptions. MS is uncommon in both the northernmost and southernmost islands of Japan, for instance, and is rare in certain sections of northern Europe, such as the Faeroe Islands and the coast of Norway.

Studies of immigrant populations suggest that the risk of developing MS is determined by some event in adolescence or preadolescence. Studies conducted by Alter in Israel and by Dean in South Africa show that adults who move to a new environment retain the risk of MS associated with their original environment, whereas those who move at or before the age of 15 acquire the MS risk associated with their new environment. It seems reasonable, Alter says, that those who migrate as youngsters would show the pattern of childhood illnesses characteristic of the new rather than the old environment. Children of Afro-Asian immigrants to Israel, for example, have the high rate of MS of European immigrants rather than the low rate of their Afro-Asian forebears.

A similar effect has been demonstrated within the United States by Roger Detels and his associates at the University of California School of Medicine in Los Angeles. All these results, Detels says, suggest that long-lasting "immunity" to MS is conferred by residence in an area of low prevalence during early life. But it is still unclear, Alter says, at what age one can leave an area of low risk and still retain "immunity." The results also indicate, Detels concludes, that the risk of developing MS may be modified by migrating to an area of low prevalence.

These results suggest that MS might be caused by a virus; the prevalence would then be mediated by those factors that affect the spread of a virus, such as climate and hygiene. The most likely candidate for a causative agent, many investigators believe, is the measles (rubeola) virus. Climate and hygiene regulate the age at which children are infected by the measles virus or, perhaps, by a similar virus. Age at infection, it seems, then governs the type of secondary illness associated with the infection.

Measles infections tend to occur early in life in tropical and subtropical areas, where MS is rare, and somewhat later in life in temperate areas, where MS is more common. In Nigeria and Guatemala, for example, investigators have shown that nearly all individuals of the population have antibodies to the measles virus by the age of 5. In the northern United States and England, in contrast, a similar high degree of immunity among the population occurs only by the age of 13 to 15. Furthermore, retrospective studies by Alter and by Martin Panelius and his associates at the University of Turku in Finland suggest that MS victims have generally had measles later in life than their peers.

The classic case where age at the time of infection governs the severity of the illness is poliomyelitis. It is now generally well accepted that infection by the poliomyelitis virus during infancy produces a lifelong immunity to the virus and only rarely produces a severe illness, infantile paralysis. Infection in adolescence when there has been no prior exposure to the virus, however, frequently produces paralytic polio. Paralytic polio did not become common until early in this century, and then only in economically advanced countries where improvements in hygiene delayed exposure to the virus until adolescence. Alter

and others argue that a similar situation may exist with measles and MS.

It is already established that there are at least two age-dependent responses to the measles virus in man. Several investigators have shown that the risk of encephalitis as a complication of measles increases with age at the time of infection up to adolescence and decreases thereafter. There is no evidence that this phenomenon is related to MS.

Other investigators, including Detels and Jacob A. Brody of the National Institute of Neurological Diseases and Stroke, have shown that infection by the measles virus before the age of 2 is associated with an increased risk of contracting subacute sclerosing panencephalitis (SSPE), which is a persistent and usually fatal degenerative encephalitis of children and young adults. SSPE is now generally believed to represent a delayed reaction to measles infection.

The epidemiological contrasts between MS and SSPE are interesting. SSPE, Alter points out, is more common in males, whereas MS is more common in females. SSPE occurs more often among the poor, whereas MS generally occurs among the higher socioeconomic groups. SSPE is more common in blacks, while MS is more common in whites. And in Israel, SSPE is more common among Arabs and Sephardic Jews and rare in Ashkenazi Jews, whereas the reverse is true for MS. If SSPE represents a host response to a measles infection early in life, Alter concludes, MS could represent a host response to an infection later in life.

The possibility that measles virus is involved in MS offers much hope, Alter says. Around 1965, the United States began a large-scale program to vaccinate against measles early in life. Since there is at least a 10- to 15-year lag period between a measles infection and the earliest onset of MS, the results of that program may not show up for another few years. But if, in fact, measles virus is a major factor in the development of MS, then the prevalence of MS in this country should begin to fall around 1980 and drop precipitously thereafter. Such a drop would probably be the best available proof of the role of measles.

But even if the measles virus—or some other virus—is the causative agent in MS, it is clear that not everyone infected with the virus develops the disease. In fact, the opposite is true. Most everyone who is infected does not develop MS. Much evidence now suggests that those who do develop MS have a specific gene that renders them susceptible to its development in response to a viral infection. That gene most likely either occurs in association with or is one of the immune response genes that regulates the body's defense against invading viruses.

The evidence for a genetic link comes largely from studies of histocompatibility antigens, markers on the surfaces of cells that are used to determine compatibility with tissues from other organisms. Several investigators, including Paul I. Terasaki and his associates at the University of California Medical School at Los Angeles and Casper Jersild and his associates at the Copenhagen University Hospital in Denmark, have shown that certain histocompatibility antigens coded for by genes known to be spatially close to the immune response genes occur more frequently in MS patients than among the population at large.

Twice the Risk of MS

Teraski and Jersild initially found that the antigens known as HLA-A3 and HLA-B7 occur as much as two to three times more frequently among European and American MS patients than among healthy individuals in those areas. In other words, individuals with those antigens run as much as two times the normal risk of contracting MS. But this is not necessarily true among other populations. Alter, for example, found that the two antigens actually occur less frequently in Jewish MS patients in Israel than in healthy Jews. The two antigens also occur less frequently in Japanese MS patients than in the control population, according to Yoshigoro Kuroiwa of Kyushu University.

Jersild has subsequently demonstrated that another antigen, HLA-DW2, is present in more than 70 percent of MS patients in Denmark, compared to only 16 percent of healthy individuals. Terasaki, Gerhard Opelz, and Min Sik Parks confirmed this observation in the United States. They also found that there is an even higher incidence of another antigen, known as the B lymphocyte locus or B group 4, among MS patients.

Terasaki and Max R. Mickey have analyzed the genetic data and postulate that susceptibility to MS may have arisen from a single mutation in one individual. This mutation would probably have occurred in one of the immune response genes. They have labeled the new gene the MS susceptibility or MSS gene.

Terasaki and Mickey further postulate that the original MS patient had the specific gene sequence: MSS, B group 4, HLA-DW2, HLA-B7, and HLA-A3. All MS patients today would then be descendants of that original individual. But because of genetic crossovers during mating, it would be expected that some of the genes would have been lost over the course of time; those that are most distant from MSS would be lost most often. Furthermore, if there were many people with the same genetic makeup as the original MS victim, it is logical that there would be a large number of people today with all those genes except MSS.

This theory could explain many aspects of MS. The two investigators postulate, for example, that the original MS patient lived in northern Europe, largely because the HLA antigens associated with MS occur most frequently in that population. This could partially explain why MS occurs most commonly in Europe and in America, whose population is primarily of European descent.

Since MS is almost nonexistent among African blacks, Terasaki says, it is reasonable to assume that the MSS gene was first introduced into the black population by Caucasians. This possibility is supported by the observation of Bo Dupont and his associates at Rockefeller University that HLA-DW2 occurs in some 30 percent of black MS patients, but could not be detected in healthy blacks. Investigators are now trying to determine whether B group 4 is even more common in blacks, as would be predicted. The situation in Japanese and Jewish populations is probably similar.

Selection for the MSS gene during reproduction is probably related to its proximity to the immune response genes. It may even be that the MSS gene may be responsible for producing an advantageous response to some agent, and that the pathologic response to a putative MS agent is a secondary phenomenon. It is conceivable, Terasaki says, that the high concentration of antibody to measles virus observed in many MS patients means simply that they can respond to a measles infection better than other individuals. The response to measles might simply be one of many other responses that the MS patient might make to a wide spectrum of antigenic challenges.

The most important aspect of this research, Terasaki says, is that introduction of the MSS gene together with its linked haplotypes into a population lacking the gene may occur through a limited exposure—in the case of Japan, for example, perhaps through a single person. It might thus be possible for the first time to follow the spread of a pathologic gene and its crossovers after it had arisen in a single individual.

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This article is the first in a series of three.