thoughtful psychopharmacological intervention, can be extremely helpful, although they do not guarantee prevention of an actual suicide. Suicidal thinking shared with others is a cry for help. It is probably safe to assume that the patient in the clinical vignette presented by Zametkin et al experienced long-standing suicidal thinking accompanied by subtle signs of depression before her leap to her death.

There are several important practical implications for the generalist physician or nonpsychiatrist specialist who is faced with a suicidal patient, particularly an adolescent or young adult. Zametkin et al suggest referral to a psychiatrist unless the physician has training or special expertise with evaluating depressed or suicidal patients; however, the authors also provide many practical suggestions for the practitioner, such as engaging the family and suicidal adolescent to discuss the situation, urging that firearms and potentially lethal medications such as acetaminophen be removed from the home, and increasing vigilance on the part of caretakers. Assuming the patient is not becoming psychotic or manic, immediately starting a selective serotonin reuptake inhibitor antidepressant is a safe course of action, particularly since such drugs generally cannot be used for a lethal overdose.

Hospitalizing an agitated, intoxicated, unmanageable, suicidal adolescent is often indicated, although it has become increasingly difficult because many adolescent psychiatric units around the country have closed. Zametkin et al point out that there is no evidence that hospitalization per se prevents an actual suicide. Nonetheless, probably because of fear of malpractice suits, there is still pressure to hospitalize suicidal adolescents even if it means sending the patient to a distant community. Risk management places youth and young adult suicide high on the vulnerabilities list as shocked and often guilty family members ask, "How could this have happened? Why didn't somebody do something about it?" Thus, clinicians dealing with suicidal patients, particularly an adolescent, constantly wonder whether they will be blamed if a patient leaves their office and commits suicide or what they can or should do to prevent it. The research reported by Dube et al and the article by Zametkin et al provide useful evidence-based context for facing that difficult clinical situation.

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EDITORIAL

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Viruses and Multiple Sclerosis

Donald H. Gilden, MD

MULTIPLE SCLEROSIS (MS) IS THE MOST COMMON demyelinating disease of humans. In the United States alone, the prevalence is 250 000 to 350 000 cases.[1] Based on data accumulated in 1994, the annual cost was estimated at more than $34 000 per person, translating into a conservative estimate of a national annual cost of $6.8 billion and a total lifetime cost per case of $2.2 million.[2] Most MS patients are young. Disease usually begins between ages 15 and 45 years and has a relapsing-remitting course, although a substantial proportion of patients develop chronic progressive disease.

The pathologic hallmark of MS is the plaque, an area of white matter demyelination often accompanied by inflammation. The inflammatory infiltrates are composed of T lymphocytes, some B cells and plasma cells, and activated macrophages or microglial cells.[3] Although it is generally believed that inflammation is an obligatory and possibly primary feature of demyelination in MS, myelin destruction also may proceed despite a nearly complete lack of lymphocytic in-

See also p 3083.

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filtration, suggesting a role for endogenous glia, such as microglia or astrocytes, as a source of injury mediators.[3] Immunoglobulin G and complement are localized primarily at the periphery of plaques.[4]

Although the cause of MS is unknown, 2 leading theories are that the disease is infectious, probably viral, or that it is produced by a host-immune response to an infectious agent or autoantigen.[5] Results from 3 different areas of investigation argue for a viral cause of MS. First, epidemiologic analysis of all cases of MS in the Faroe Islands in 1920-1977 indicated a point-source epidemic of MS, probably introduced by British groups or their baggage; thus, MS in the Faroes appeared to be a transmissible, most likely infectious disease.[6] Second, studies of identical twins in which one has MS have shown that only 30% of the other twins develop disease, suggesting that more than a putative susceptible genotype determines disease.[7] Third, although the protein of normal human cerebrospinal fluid (CSF) contains up to 13% IgG, the CSF of MS patients contains 15% to 30% IgG and sometimes more, as well as oligoclonal bands (OGBs).[8] The latter are found almost exclusively in central nervous system (CNS) disorders of infectious origins, such as neurosyphilis, tuberculous and fungal meningitis, some acute viral CNS infections, and subacute sclerosing panencephalitis (SSPE), a chronic encephalitis caused by measles virus.

Furthermore, for the 2 instances in which the specificity of CSF OGBs was studied, they represented antibody directed against the agent that causes disease. For example, the OGBs in the CSF of patients with SSPE are antibody directed against measles virus.[9] Similarly, the OGBs in cryptococcal meningitis were shown to be completely removed by absorption with cryptococcal antigen but not by absorption with *Candida* antigen, ruling out the possibility that cryptococci nonspecifically absorb the IgGs.[10] Other examples of the specificity of OGBs in CNS infectious disorders include the fact that the oligoclonal IgG in human T-lymphotrophic virus 1 (HTLV-1) myelopathy is directed against HTLV-1 virus[11]; that the oligoclonal IgG in the CSF of patients with mumps meningitis is directed against mumps virus[12]; and that the oligoclonal IgG in the CSF of neurosyphilis patients is directed against *Treponema pallidum*, the cause of syphilis.[13] In addition, progressive multifocal leukoencephalopathy is an exclusively human demyelinating disease that has been proven to be caused by a virus.[14]

Although many investigators believe that MS is an autoimmune disorder, largely by analogy with the prototype immunopathology, experimental allergic encephalomyelitis (EAE), proof is lacking. For example, the target antigen(s) in MS is unknown, and it has never been shown that abundant brain white matter proteins, such as myelin basic protein or myelin oligodendrocyte protein, bind to or absorb out the OGBs in MS. Careful examination of MS plaques has not revealed any IgG binding to the surface of intact myelin sheets, even in the presence of IgG-positive plasma cells[15]; thus, if antimyelin antibody contributes to myelin breakdown in chronic MS lesions, the determinant does not appear to be an antigen on the surface of intact healthy myelin sheaths.

Furthermore, there is no immune-mediated animal model of MS, and the collective abundant data gathered on immunogenetic background, macrophage function, specific T-cell subpopulations, and cytokine and chemokine responses in EAE and MS patients have failed to clarify the nature of disease production. Equally discouraging is that the multiple immunosuppressive and immunomodulating agents used to treat MS have not produced the gratifying response often seen in myasthenia gravis, a proven autoimmune disease. Moreover, although EAE can be induced in syngeneic recipients by adoptive transfer of lymphocytes from animals sensitized with whole brain white matter or myelin basic protein, there is only a single report of demyelination produced by passive transfer of antibody from MS patients.[16] Although seemingly heretical, it was recently suggested that a moratorium be placed on the autoimmune hypothesis in MS to redirect funds for research on novel approaches to the problem.[17]

Various microorganisms have been associated with MS, but none has been tightly linked to disease. The most recent organism to be implicated is *Chlamydia pneumoniae*, a gram-negative bacterium. Since the original detection of *C pneumoniae* DNA and antibody in the CSF of some MS patients,[18] various laboratories around the world have attempted to confirm this potentially important finding. However, multiple studies have indicated a lack of any significant association between *C pneumoniae* and MS.[19] In the past decade, 2 human herpesviruses also have been associated with MS. One is human herpesvirus 6 (HHV-6), the cause of roseola, and the other is Epstein-Barr virus (EBV), the cause of infectious mononucleosis. The detection of fingerprints of these 2 ubiquitous viruses known to be latent in blood B-EBV or T–HHV-6 cells is intriguing, since the primary encounter with either virus usually occurs before or during puberty, the same time that epidemiologic evidence indicates exposure to the disease-causing agent of MS. However, HHV-6 is found not only in the brain and CSF of MS patients, but also in neoplastic and normal brain,[20] suggesting that the detection of virus reflects its reactivation from latency and blood T-cell trafficking through brain. Furthermore, no EBV-specific RNA was detected in 10 MS patients' brains by in situ hybridization.[21]

In this issue of THE JOURNAL, a prospective serologic study of 62 439 women by Ascherio et al[22] found significant elevations in serum anti-EBV antibody titers before onset of MS, particularly antibody to the EBV nuclear antigen 2 (EBNA-2). While the findings would suggest a role of EBV in the etiology of MS, CSF data would be helpful, since the IgG in MS patients' brain tissue and CSF is synthesized intrathecally and may more accurately reflect the immune response at the site of disease. While the neurotropism of EBV and its ability to produce serious neurologic disease at all levels of the human neuraxis have been documented,[23] if

EBV or any other virus causes MS, it should be possible to demonstrate that MS OGBs contain antibody directed against the suspected agent.

Many viruses and pathogens have been associated with MS, although none has been tightly linked to disease.[24] The potential to identify rare or low-abundance pathogens has improved, and the molecular virologic strategies and techniques available today allow studies of virus detection not possible 20 years ago. For example, the ability to prepare and characterize libraries of genes from human tissue based on a difference in their genes or gene products allowed the isolation of complementary DNA clones derived from hepatitis C virus (HCV).[25] Those cDNA clones were obtained without prior knowledge of the virus, the viral genome, or presence of circulating viral antibodies. The abundance of HCV-specific RNA from infected animals was ultimately determined to be only approximately 0.00001% or $1:10^7$. Combined cloning in expression vectors (even without subtraction hybridization) and immunologic screening led to the identification of an HCV-specific clone in approximately 10^6 recombinant phage.

Some of these strategies already have been applied to MS. Cloning of IgG genes in brain tissue (and CSF) of MS patients has revealed the presence of overrepresented heavy-chain sequences expressed at multiple plaque sites. Alignment of the heavy-chain sequences to their closest germline counterparts revealed clonal amplification and extensive somatic mutation, features of an antigen-driven response.[26] Comparison of the IgG heavy-chain sequences in MS and SSPE again revealed features of an antigen-driven response in both diseases. Since the antigen in SSPE is known to be measles virus, the parallel findings in MS suggest an antigen-driven immune response,[27] rather than a nonconventional mechanism of B-cell activation. This concept warrants further analysis of the specificity of IgG in brain tissue and CSF in MS. Although the cause of MS is not likely to be found under the EBV lamppost, the search for a viral cause of MS must continue.

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