

REVIEW ARTICLE

MEDICAL PROGRESS

Multiple Sclerosis — The Plaque
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N Engl J Med 2006;354:942-55.
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SUBSTANTIAL ADVANCES HAVE OCCURRED IN THE UNDERSTANDING OF some of the central mechanisms underlying the inflammation, demyelination, and neurodegeneration that occur in multiple sclerosis since the topic was last reviewed in the *Journal*.¹ Accordingly, the available clinical strategies for the management of the disease have widened (Table 1).² However, the treatment options for the disease are most effective during the relapsing–remitting phase (relapsing–remitting multiple sclerosis), which is characterized by clinical exacerbations, inflammation, and evidence of plaques within the brain and spinal cord on magnetic resonance imaging (MRI). Less understood are factors that promote the transition from relapsing–remitting multiple sclerosis to treatment-resistant secondary progressive multiple sclerosis. Evidence now suggests that neurodegenerative mechanisms within the disease plaques constitute the pathologic substrate for the latter disabling phase.^{3–5} Effector mechanisms that underlie the relapsing inflammatory and the progressive neurodegenerative phases of multiple sclerosis appear to be distinctly different.

This review focuses on the current knowledge of the pathogenesis of the inflammatory and neurodegenerative elements of the multiple sclerosis plaque.

EVOLUTION OF THE MULTIPLE SCLEROSIS PLAQUE

A central mission in multiple sclerosis research has been to determine the sequence of events underlying the development of the inflammatory plaque. It is generally held that this histopathological hallmark originates from a breach in the integrity of the blood–brain barrier in a person who is genetically predisposed to the disease. One hypothesis suggests that some forms of systemic infection may cause the up-regulation of adhesion molecules on the endothelium of the brain and spinal cord, allowing leukocytes to home to and traverse vessel walls to enter the normally immunologically privileged central nervous system. If lymphocytes programmed to recognize myelin antigen exist within the cell infiltrate, they may trigger a cascade of events resulting in the formation of an acute inflammatory, demyelinating lesion.⁶ These lesions typically develop in white matter, where the primary targets are the myelin sheath and the myelinating cell, the oligodendrocyte (Fig. 1). However, gray-matter lesions, in which the primary target is also myelin, are known to occur.⁷

CELLS INVOLVED IN THE PATHOGENESIS OF THE MULTIPLE
SCLEROSIS PLAQUE

T CELLS

Studies of animal models demonstrating that autoreactive T cells (CD4+ or CD8+) can result in inflammatory demyelination of the central nervous system support the

Table 1. Treatment Options for Multiple Sclerosis.*

Status	Treatment	Suggested Mechanism of Action	Uses and Range of Effects	Forms of Multiple Sclerosis Affected
Approved by the Food and Drug Administration	Interferon beta	Inhibits adhesion Inhibits synthesis and transport of MMPs Blocks antigen presentation	Treatment of relapses Slows progression Reduces lesions seen on MRI and brain atrophy Potential cognitive benefit	Relapsing
	Glatiramer acetate	Increases regulatory T cells Suppresses inflammatory cytokines Blocks antigen presentation	Treatment of relapses Reduces lesions seen on MRI	Relapsing–remitting
	Mitoxantrone	Reduces Th1 cytokines Eliminates lymphocytes	Treatment of relapses Reduces lesions seen on MRI Slows progression	Relapsing–remitting Secondary progressive Progressive relapsing
Possible adjunctive therapy	Corticosteroids (intravenous or oral formulations)	Inhibit synthesis and transport of MMPs Alter cytokine profile Reduce CNS edema	Treatment and prevention of relapses	Relapsing
	Azathioprine	Inhibits purine synthesis, affecting B cells, T cells, and macrophages	Treatment of relapses Slows progression	Relapsing–remitting Secondary progressive
	Methotrexate	Acts as folate antagonist, affecting DNA synthesis in immune cells	Slows progression	Secondary progressive
	Plasma exchange	Removes deleterious antibodies	Treatment of relapse	Relapsing
	Intravenous immune globulin	Has antiidiotypic effects Blocks Fc receptors Alters cytokine profile	Treatment and prevention of relapses	Relapsing

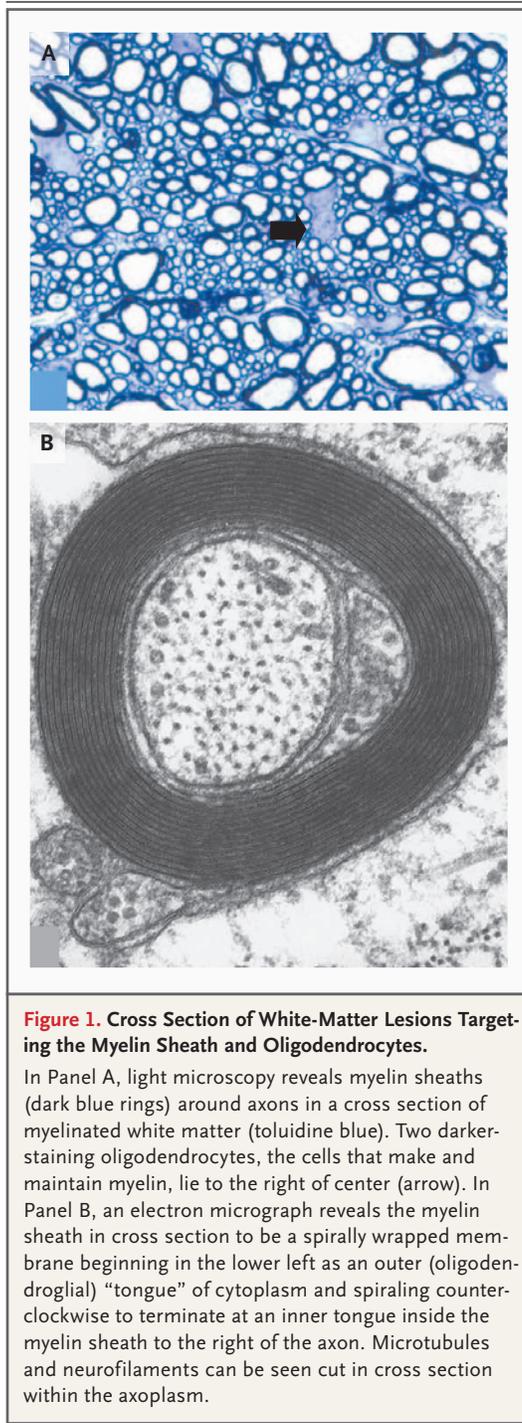
* This table is adapted from Goodin et al.² MMPs denotes matrix metalloproteinases, MRI magnetic resonance imaging, Th1 type 1 helper T cells, and CNS central nervous system. Natalizumab had been approved by the FDA for treatment of multiple sclerosis but was withdrawn from the market in February 2005, to allow assessment of the risk of progressive multifocal leukoencephalopathy.

theory that multiple sclerosis is an immune-mediated disorder involving one or more antigens located in the myelin of the central nervous system.⁸⁻¹⁰ Patients with multiple sclerosis and healthy persons appear to have similar numbers of T cells in peripheral blood that react to myelin. Nevertheless, these two groups have substantial qualitative differences in responses mediated by circulating mononuclear-cell populations (B cells, T cells, and macrophages). Myelin-reactive T cells from patients with multiple sclerosis exhibit a memory or activated phenotype, whereas these same antigen-specific cells in healthy persons appear to have a naive phenotype.^{11,12} Marked differences in the cytokines secreted and the specific chemokine receptors expressed suggest that myelin-reactive T cells from patients with multiple sclerosis are relatively more inflammatory.^{13,14} Further, myelin-specific CD8+ T cells appear to be more abundant in patients with relapsing multiple sclerosis than in healthy persons or in those with secondary progressive disease.^{13,15}

Perhaps the most convincing evidence that myelin-reactive T cells lead to inflammatory de-

myelination came from a clinical trial in which an altered peptide ligand was used as a putative disease-modifying treatment in patients with multiple sclerosis.¹⁶ In this study, either clinical exacerbations or an increase in disease activity, as measured by MRI, unexpectedly developed in several patients treated with the ligand (a peptide developed to stimulate autoreactive T cells and render them inactive). These changes coincided with marked increases in T cells responding to a specific component of myelin basic protein (signifying immune-cell activation rather than inactivation). In contrast, in another study, a lower dose of this peptide ligand actually reduced evidence of disease activity on MRI.¹⁷ This treatment strategy is currently being studied in a phase 2 clinical trial.

The cytokine-producing phenotype of myelin-specific T cells determines the ability of these cells to cause inflammation in the central nervous system.¹³ Organ-specific autoimmune diseases such as multiple sclerosis are thought to be mediated by type 1 helper T cells (Th1) that produce interferon- γ .⁹ Abundant data also sug-



gest that inflammatory immune responses or delayed hypersensitivity responses are primarily mediated by inflammatory Th1 cells, which produce lymphotoxin and interferon- γ , but little interleukin-4.¹⁸ Alternatively, CD4+ type 2 helper T cells (Th2) represent an antiinflammatory population of lymphocytes that produce large amounts

of immunoregulatory cytokines (e.g., interleukin-4 and interleukin-5). Myelin-reactive T cells from patients with multiple sclerosis produce cytokines more consistent with a Th1-mediated response, whereas myelin-reactive T cells from healthy persons are more likely to produce cytokines that characterize a Th2-mediated response.¹³ Cytokines such as interleukin-12 and type 1 interferons such as interferon- β can activate the transcription factor Stat-4 in human T cells, thus causing the cells to differentiate into pathogenic Th1 lymphocytes.¹⁹ Interferon beta, which has been used to treat patients with multiple sclerosis (Table 1), was thought to cause a shift from a Th1-mediated to a Th2-mediated response.²⁰ However, microarray studies indicated that a number of genes in patients with multiple sclerosis that are up-regulated by this cytokine are associated with differentiation into Th1 rather than Th2 lymphocytes, suggesting that such a shift may not be the mechanism of action of interferon beta.²¹

Certain members of the interleukin-12 family of proteins probably have a role in the regulation of T-cell responses that have potential relevance to multiple sclerosis.²² In experimental models of inflammatory demyelination, such as experimental autoimmune encephalomyelitis in mice, the likelihood of disease development depends on which interleukins are functional. For example, experimental autoimmune encephalomyelitis did not develop in mice deficient in both interleukin-12 and interleukin-23, but severe disease developed in animals with a deficiency of interleukin-12 alone. Other studies indicate that interleukin-23 probably has an essential role in brain inflammation.²³ For instance, interleukin-23-deficient mice are resistant to experimental autoimmune encephalomyelitis but have a normal Th1 response.²⁴ Such studies in mice may be directly relevant to patients with multiple sclerosis. Interleukin-23 causes T cells to produce interleukin-17, which some investigators believe is the chief determinant of brain inflammation, rather than interferon- γ . Recent microarray studies of lesions of multiple sclerosis from patients demonstrated increased expression of interleukin-17, suggesting that it may be an important factor in the development of inflammatory demyelination.²⁵ Studies of experimental autoimmune encephalomyelitis in mice have recently shown that the T-bet and Stat-4 (necessary for Th1 differentiation) transcription factors are important in the differentiation of autoimmune T cells.²⁶⁻²⁸ Studies in

humans are now needed to determine whether similar transcriptional programs determine the mechanism underlying the pathogenic potential of myelin-reactive T cells in multiple sclerosis.

B CELLS

It has long been recognized that intrathecal synthesis of immunoglobulins is increased in patients with multiple sclerosis, as evidenced by the presence of oligoclonal bands on agarose-gel electrophoresis and an increased IgG index or synthesis rate. Many studies have suggested that these antibodies recognize myelin antigens, but only recently has it become possible to characterize the antibody response on a molecular level in the cerebrospinal fluid of patients with multiple sclerosis. Perhaps not surprisingly, the demonstration in the cerebrospinal fluid of B-cell proliferation and increased mutations in B-cell receptors, a process called somatic hypermutation, suggest that a B-cell response to a specific antigen is occurring in the central nervous system, whereas corresponding clones are absent from the peripheral circulation.^{29,30} Examination of these B-cell clones also indicated that some B cells had undergone a process called receptor revision, or editing, in which these cells recognize the body's misguided capability to manufacture autoantibodies and sub-

sequently remove this capacity.³¹ Investigations are now under way to determine which specific central nervous system antigens are recognized by the autoantibodies generated by clonally expanded B cells in patients with multiple sclerosis. The observed overexpression of immunoglobulin genes and Fc receptors in lesions of this disease suggests that targeting the B-cell component of the immune response (e.g., with rituximab) may represent an attractive therapeutic strategy (Table 2).

OTHER IMMUNE CELLS

It is likely that still other types of cells play a role in the pathogenesis of multiple sclerosis. For example, regulatory cells, such as CD4+/CD25+ and CD8+ regulatory T cells, appear to be deficient in patients with this disease.^{32,33} Glatiramer acetate, a treatment for multiple sclerosis that may increase the numbers of these regulatory cells, may provide a means of reconstituting tolerance to self-antigens (Table 1).

DISEASE INITIATION AND PATHOGENESIS

There is substantial evidence to support the hypothesis that genetics has an important role in a person's susceptibility to multiple sclerosis, prob-

Table 2. Neuroprotective and Restorative Strategies for Multiple Sclerosis.*

Strategy	Rationale or Mechanism	Preliminary Observations
Combinations of approved agents	Targets multiple injury mechanisms	Evidence of reduced activity on MRI Reduced relapses
Rituximab	Depletes B cells	Clinical trials under way
Chemokine-receptor antagonists	Reduce entry of lymphocytes into CNS	Clinical trials under way
Riluzole	Blocks N-methyl-D-aspartate and sodium channels	Reduced spinal-cord atrophy Reduced number of hypointense lesions on T ₁ -weighted MRI
Phenytoin and flecainide	Block sodium channels	Neuroprotective in animals Clinical trials under way
Blockers of neurite outgrowth inhibitor	Promote axonal sprouting	Studies in animals under way
Blockers of NG2, LINGO-1, Notch, and Jagged	Promote oligodendrocyte differentiation	Studies in animals under way
Activation of oligodendrocyte transcription factor 1	Promotes oligodendrocyte differentiation	Under development
Stem cells	Initiate myelin repair	Established efficacy in animal models Early trials in humans under way
Growth factors	Promote neuronal survival	Under development
Antiapoptosis factors	Promote survival of neurons and oligodendrocytes	Studies in animals under way

* CNS denotes central nervous system, NG2 neuron-glia antigen 2, and LINGO-1 leucine-rich-repeat and immunoglobulin-domain-containing neurite outgrowth inhibitor receptor-interacting protein 1.

ably in conjunction with environmental factors. Although some investigators argue for a direct causal link between various infectious agents and this disorder, such agents may merely provide the appropriate milieu for the development of an autoreactive immune response directed against central nervous system myelin. Recent work in experimental autoimmune encephalomyelitis has focused on pathogens that can stimulate toll-like receptors, highly conserved receptors that recognize pathogen-associated molecular patterns. These patterns are important for the initiation of disease and the production of interleukins, specifically interleukin-12 and interleukin-23, which lead to the differentiation of T cells into autoreactive effectors.^{34,35} Infectious agents may also have a role in the central mechanism that culminates in the interaction between T cells and the cerebrovascular endothelium by up-regulating adhesion molecules important for immune-cell recruitment into the central nervous system.³⁶

Studies of experimental autoimmune encephalomyelitis in mice demonstrated the importance of T-cell expression of a family of cell-surface receptors (the integrins) that promote adhesion and transport mechanisms. Such studies led to the development of a therapeutic antagonist of integrin, natalizumab, a monoclonal antibody specifically against α_4 integrin.³⁷ This agent significantly reduced both clinical relapses and the formation of gadolinium-enhancing lesions in patients with multiple sclerosis.³⁸ Despite its early promise, the development of progressive multifocal leukoencephalopathy in a few patients receiving natalizumab in combination with interferon, or with azathioprine and infliximab, resulted in its withdrawal from the market and a halting of all clinical trials in February 2005; whether it will return to the market is unknown as of January 2006.³⁹⁻⁴¹ These observations underscore the principle that strategies interfering with the recruitment of leukocytes in the pathogenesis of multiple sclerosis may also interfere with routine immunosurveillance functions of the central nervous system.

Several additional targets for potential study and therapeutic intervention have been identified with the use of microarray techniques. For instance, this approach led to the discovery that osteopontin was overexpressed in multiple sclerosis lesions and subsequently to the finding that it has an important role in the progression of experimental autoimmune encephalomyelitis.⁴²

PATHOGENESIS OF MULTIPLE SCLEROSIS LESIONS REVISITED

In the light of the current consensus that the pathogenesis of the lesions of multiple sclerosis is heterogeneous, it is not surprising that no single predominant mechanism for this disease has emerged. Indeed, with a condition that includes fulminant as well as chronic forms with such a wide-ranging phenotype, multiple pathogenetic mechanisms have been proposed.⁴³ In fact, the pattern of the lesions appears to be totally unpredictable; both acute and chronic cases have old as well as new lesions, illustrating the dynamic nature of the disease process. Regardless of this innate variability, the end-point chronic silent lesion (without active inflammation) is a constant and pathognomonic feature of multiple sclerosis.

NEUROPATHOLOGY

The histologic features of lesions of acute multiple sclerosis (Fig. 2A, 2B, and 2C) include an indistinct margin, hypercellularity, intense perivascular infiltration by small lymphocytes (Fig. 2D and 2E), parenchymal edema, loss of myelin and oligodendrocytes, widespread axonal damage (Fig. 2F and 2G), plasma cells, myelin-laden macrophages, hypertrophic astrocytes, and little or no astroglial scarring. Demyelination in acute lesions may be due to an antimyelin antibody-mediated phenomenon in which normal lamellar myelin is transformed into vesicular networks (Fig. 2H and 2I), coated with antimyelin oligodendrocyte glycoprotein or antimyelin basic protein immunoglobulin, and phagocytosed in the presence of complement by local macrophages.⁴⁴ Remyelination is occasionally seen.

Lesions of chronic active multiple sclerosis display a sharp edge; along the edge are perivascular cuffs of infiltrating cells, lipid-laden and myelin-laden macrophages, hypertrophic astrocytes, and some degenerating axons, and demyelination is occurring (Fig. 3A). In contrast to acute lesions, demyelination in chronic active lesions is associated with the deposition of immunoglobulin and the dissolution of myelin into droplets, which undergo phagocytosis once they become attached to macrophages.^{45,46} An increase in the number of oligodendrocytes and some remyelination are not uncommon in chronic lesions. The centers of such lesions are hypocellular and contain naked axons embedded in a matrix of scarring (fibrous) astrocytes, lipid-laden macrophages,

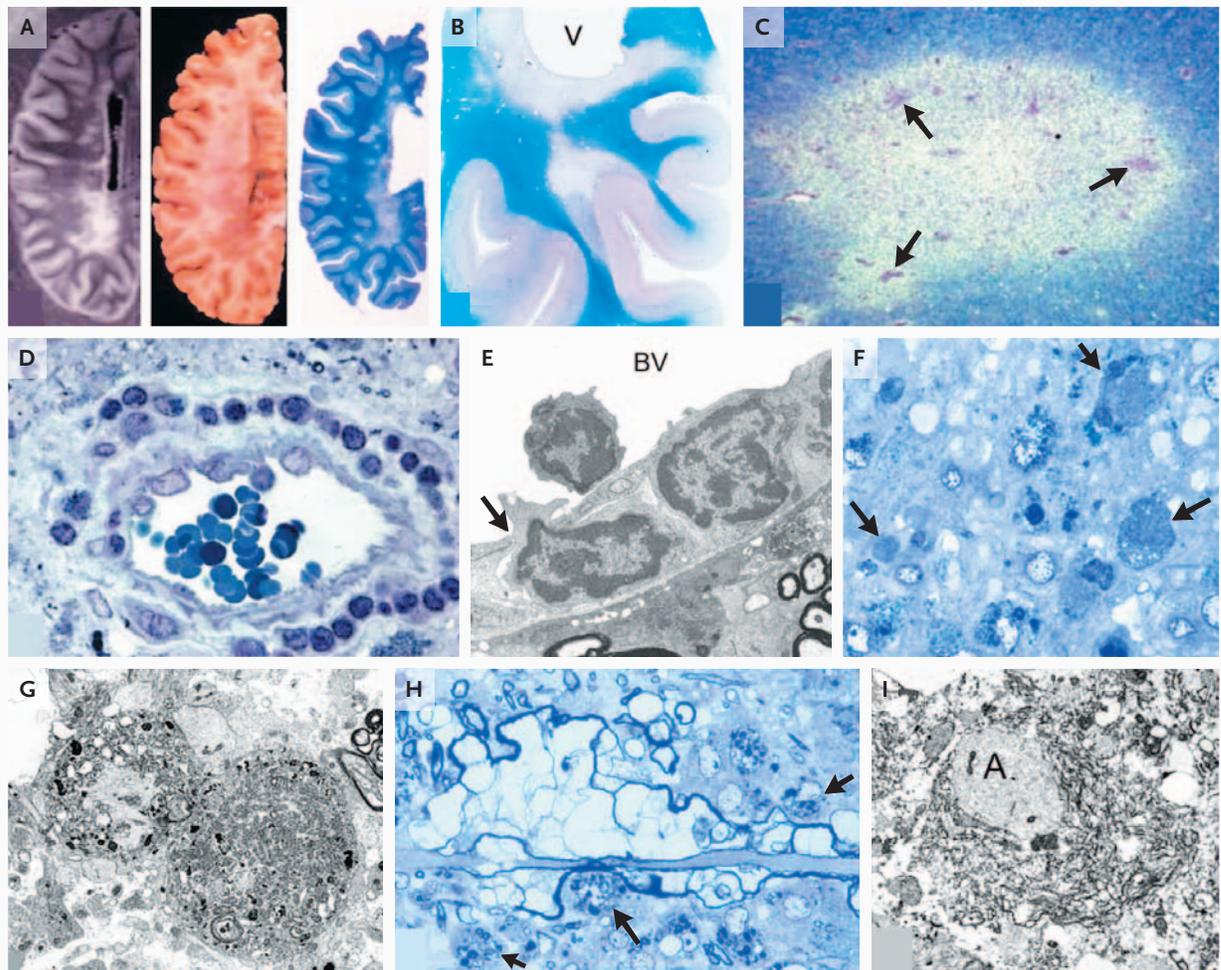


Figure 2. The Active Lesion of Multiple Sclerosis in Human Tissue (Panels A, B, C, D, F, G, H, and I) and Mouse Tissue (Panel E).

In Panel A, lesions are present in the cerebral hemisphere in the frontal (upper) and parieto-occipital (lower) periventricular white matter. The image on the left shows a proton-density image obtained by MRI, the center image shows a gross specimen from the same level, and the image on the right shows a section from the same level stained with Luxol fast blue to reveal myelin and the demyelinated lesions. The margins of the lesions are rather irregular and indistinct, suggestive of ongoing activity, and some demyelinated areas are pale blue, consistent with the presence of remyelination. In Panel B, a section of temporal lobe stained with Luxol fast blue for myelin reveals a periventricular plaque extending to a cup-shaped zone of demyelination beneath the sulcus to the lower right. Some areas around the margins of the lesion stain pale blue (e.g., adjacent to the affected sulcus), probably indicative of remyelination. V denotes ventricle. In Panel C (Luxol fast blue), a section of an acute lesion has an indistinct margin and numerous perivascular infiltrates (arrows). In Panel D (toluidine blue), a blood vessel, with red cells in the lumen of an acute lesion, is ringed by small lymphocytes — probably T cells; the surrounding parenchyma of the central nervous system has undergone demyelination. In Panel E, an electron micrograph from an actively demyelinating lesion in the spinal cord of a mouse with acute experimental autoimmune encephalitis, an animal model of multiple sclerosis, shows a small lymphocyte, possibly a T cell, within the blood-vessel lumen (BV), adherent to the vascular endothelium, and another cell has almost traversed the endothelium through a gap (arrow), to enter the Virchow–Robin space, and another to the right is within the perivascular space. The perivascular cuff of cells is separated from the central nervous system parenchyma below (myelinated nerve fibers are seen) by a layer of astroglial cells known as the glia limitans. In Panel F (toluidine blue stain), an area within an acute plaque is completely demyelinated and contains numerous transected, damaged axons (arrows) that form spheroids. In Panel G, an electron micrograph shows axonal spheroids; each is filled with accumulations of mitochondria, dense bodies, and neurofilaments. In Panel H (toluidine blue stain), a longitudinal section of the myelin sheath surrounding an axon at the margin of an acute lesion displays vacuolation and vesiculation; macrophages are present next to the degenerating myelin (arrows) and are filled with droplets of myelin. In Panel I, an electron micrograph shows an axon (A) within an acute lesion surrounded by a myelin sheath that has been transformed into a vesicular network, the result of interactions with antimyelin antibodies.³

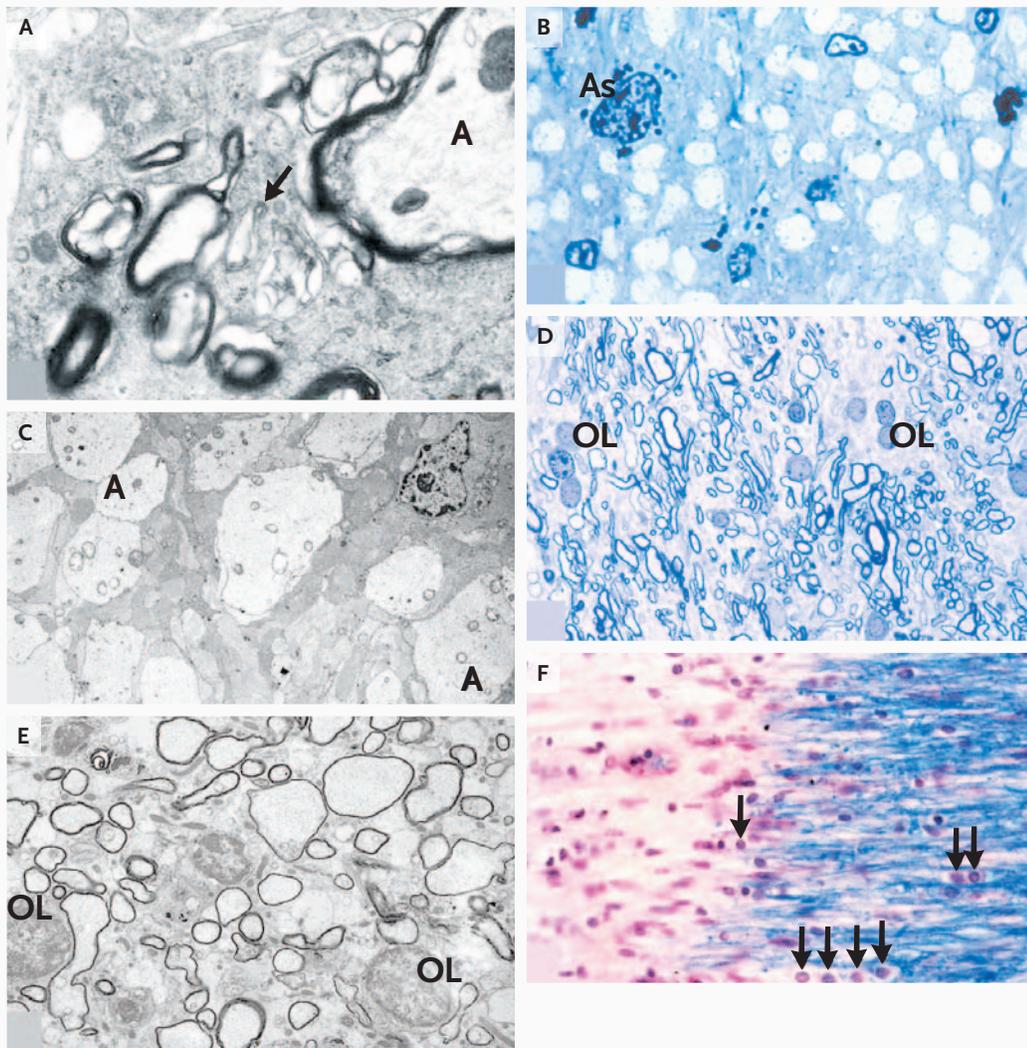


Figure 3. The Chronic Lesion of Multiple Sclerosis in Humans.

In Panel A, an electron micrograph of a chronic active lesion shows a myelinated fiber undergoing demyelination. The arrow shows myelin droplets on the macrophage surface being internalized by the cell. The fiber is invested by a microglial cell, which is engaged in the phagocytosis of myelin droplets as they are divested from the myelin sheath. The end product of this process is shown in Panel B (toluidine blue stain). An area from a chronic silent gliotic lesion is made up of astroglial scar tissue, in which intact demyelinated axons (light profiles) are embedded; mitochondria can be seen within the axons; the smaller nuclei belong to microglial cells, but no oligodendrocytes are present. In Panel C, an electron micrograph with a field similar to that in Panel B shows large-diameter demyelinated axons (A) within the glial scar; an astroglial-cell body is at the upper right. In Panel D (toluidine blue stain), a biopsy specimen from a patient with secondary progressive multiple sclerosis shows an area of remyelination (shadow plaque) in which the myelin sheaths of many axons are disproportionately thin and oligodendrocytes (OL) are overabundant. These cells are probably oligodendroglial precursor cells recently recruited into the lesion. In Panel E, an electron micrograph shows remyelination; the myelin sheaths are thin in comparison to the diameters of the axons, and two oligodendrocytes are evident (OL). In Panel F (Luxol fast blue and periodic acid-Schiff), there is an abrupt transition at the edge of the chronic multiple sclerosis lesion. The myelin internodes (blue) terminate sharply at the demyelinated plaque. Oligodendrocytes are present (arrows) up to the edge of the lesion, but not within the lesion. Rod cells (microglia) are lined up along the boundary. A denotes axon, and As astrocyte.

a few infiltrating leukocytes, and virtually no oligodendrocytes. Lesions of chronic silent disease display sharp edges, astroglial scar tissue (Fig. 3B and 3C), a reduced number of demyelinated axons, macrophages, and vessels with thickened (hyalinized) walls around which occasional leukocytes are seen; these lesions contain few or no oligodendrocytes.⁴³

CLASSIFICATION OF LESIONS —
STAGES OR TYPES?

The current classification schemes for the lesions of multiple sclerosis are under study, principally stimulated by a series of insightful categorizations by Lucchinetti and colleagues.⁴⁷⁻⁴⁹ The most quoted categorization from these investigators grouped active lesions into four types, I through IV, on the basis of the pathogenesis of the lesions.⁴⁷ All four types of lesions are characterized by T-cell and macrophage-dominated inflammation. Type I is characterized by demyelination and macrophage-related products (e.g., tumor necrosis factor α). Type II is characterized by the presence of immunoglobulin and complement. Type III lacks immunoglobulin and complement, yet it shows early loss of myelin-associated glycoprotein and no remyelination; the demyelination in type III has been attributed to oligodendrocyte dysfunction. Type IV is distinguished by apoptosis of oligodendrocytes through DNA fragmentation. Although this approach has merit, concern has been expressed regarding the details of the cases on which it is based and whether the central nervous system-biopsy specimens examined came from patients with typical multiple sclerosis. Furthermore, Barnett and Prineas⁵⁰ have recently demonstrated that lesions from a given patient can, in fact, contain features of more than one category of lesions. This important observation underscores the fact that the development of a cogent and accurate lesion-classification scheme remains a work in progress.^{48,49}

AXONAL DYSFUNCTION
AND CHANNELOPATHY

The oligodendrocyte–myelin–axon unit represents a unique structural and functional specialization within the central nervous system. Myelin not only increases the cross-sectional diameter of the nerve axon (Fig. 1A), which increases conduction

velocity, but also contributes protectively and trophically to the health of the axon.⁵¹ Disruption of these relationships appears at the earliest stages of multiple sclerosis.³⁻⁵

Axonal injury in multiple sclerosis appears to be partly explained by demyelination and the proliferation of abnormal expression of sodium channels localized within the membrane (Fig. 4).⁵² In an attempt to reestablish normal conduction, there is an increased entry of sodium, slowing of nerve conduction, and potentially, even conduction block. These processes appear to be followed by reversal of the sodium–calcium exchanger (i.e., sodium efflux and calcium influx), which can trigger intracellular cascades of calcium-mediated injury, ultimately leading to neuronal degeneration (Fig. 4). This hypothesis has been supported by recent evidence that sodium-channel blockers such as flecainide and phenytoin preserve axons in mice with experimental autoimmune encephalomyelitis, thereby preserving physiologic function, as compared with that in untreated animals (Table 2).^{53,54}

It has been known since the time of Charcot that axonal injury is a pathological feature of the multiple sclerosis plaque. This important characteristic of the composition of the lesion has been long deemphasized, since the main pathological features appeared to be related to myelin. An analysis by Trapp et al.³ rekindled interest in the topic.⁴ Pathological changes in axons, detectable early in the process on the basis of the accumulation of amyloid-precursor protein,⁵⁵ appear to be due to inflammation and are important in the evolution of the lesion (Fig. 2F and 2G); they are most conspicuous during the acute and progressive stages. Cumulative loss of axons, as a result of inflammatory demyelination and ultimately, transection, correlates with irreversible disability. The number of axons continues to dwindle throughout the course of the disease, and some old lesions display an axonal loss of more than 80 percent.⁵⁶

Factors that have been associated with axonal damage include cytokines, nitric oxide, proteases, superoxides, CD8+ T cells, and glutamate excitotoxicity.⁵⁷ Furthermore, such damage may even extend to nerve cells, mediated by microglia through cholesterol-breakdown products.⁵⁸ In addition, MRI studies have correlated axonal loss with a reduction of N-acetyl aspartate (a substrate within axons) and hypointensity (gray

or black holes) on T₁-weighted images.^{59,60} The extent to which pathological changes in axons may be therapeutically reversible remains undefined.

EXCITATORY AMINO ACID RECEPTORS AND NEURODEGENERATION

Although glutamate-mediated entry of calcium into neurons is important for learning and memory, perpetuation or exaggeration of this process — termed “glutamate excitotoxicity” — can have deleterious consequences.⁵⁷ Three distinct classes of inotropic receptors regulate ion flow — N-methyl-d-aspartate, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, and kainate receptors. In oligodendrocytes, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors and kainate receptors can trigger calcium influx and cell death. Recently, riluzole, a glutamate antagonist and sodium-channel blocker, has been suggested to promote stabilization of cross-sectional atrophy of the spinal cord and reduce the number of hypointense lesions on T₁-weighted MRI in patients with multiple sclerosis, perhaps constituting a neuroprotective effect (Table 2).⁶¹

GROWTH FACTORS

Axonal injury, transection, and the death of neuronal cells may be modifiable with the application of particular growth factors. Similarly, neuronal survival may be improved by the use of antiapoptotic elements, such as the *BCL2* gene. In contrast, the neurite outgrowth inhibitor (Nogo) receptor mediates inhibition of axon sprouting, a process probably important during central nervous system development, when critical approximation occurs between axon terminals and the downstream dendritic trees of the receiving neuron at the synapse.⁶² A number of Nogo-receptor agonists produced by oligodendrocytes, including Nogo, oligodendrocyte-myelin glycoprotein, and myelin-associated glycoprotein, can lead to arrest of axonal growth. Alternatively, Nogo-receptor blockade may promote axonal regeneration, which perhaps will be a future therapeutic strategy for multiple sclerosis.⁶²

THE ENIGMA OF REMYELINATION

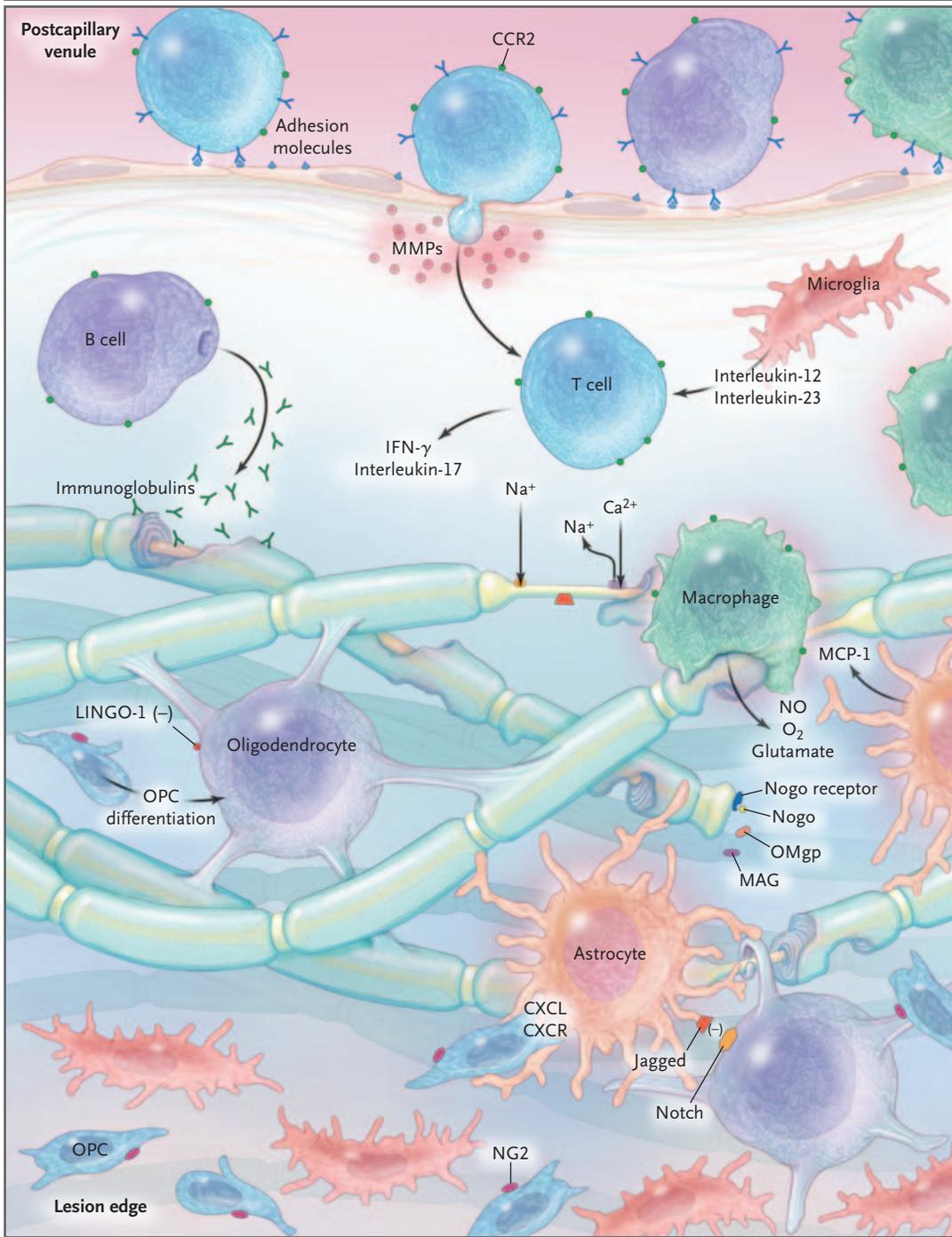
Dismissed originally as improbable, remyelination is now considered a consistent feature of the lesions of multiple sclerosis (Fig. 3D and 3E).⁴³ It is

Figure 4 (facing page). The Multiple Sclerosis Plaque.

Within a postcapillary venule, various adhesion molecules interact with mononuclear cells (T cells, B cells, and macrophages) at the endothelial surface. Matrix metalloproteinases (MMPs) digest basement-membrane type IV collagen and fibronectin, which facilitate the migration of these proteins into the central nervous system. B cells entering the area elaborate immunoglobulins. T cells are capable of releasing a series of inflammatory and antiinflammatory cytokines and chemokines. Interleukin-12 and interleukin-23 are released from microglia and can provoke T cells to release interferon- γ (IFN- γ) and interleukin-17, respectively. Macrophages engulf myelin internodes, exposing axonal surfaces and releasing injury effector agents such as nitric oxide (NO), oxygen free radicals (O₂), and glutamate. Calcium entry can provoke a series of deleterious processes, resulting in further damage to the axon and, eventually, transection and neurodegeneration. At the edge of the plaque, microglia are aligned at the perimeter. At this fine line between the multiple sclerosis plaque and the surrounding normal tissue are rows of recruited oligodendrocyte-precursor cells (OPCs) that are capable of entering the plaque zone and potentially mediating repair processes. In the lower right portion of the figure, an astrocyte with a CXC chemokine ligand (CXCL) is interacting with an OPC with a CXC chemokine receptor (CXCR). Other oligodendrocyte-precursor cells are converted into oligodendrocytes. Nogo denotes neurite outgrowth inhibitor, LINGO-1 leucine-rich-repeat and immunoglobulin-domain-containing Nogo receptor-interacting protein 4, MCP monocyte chemoattractant protein, and CCR2 chemokine receptor 2.

conspicuous in lesions that develop early in the disease process⁶³ and in satellite areas of large lesions, so-called shadow plaques. Remyelination is probably transient, since it is a minor feature in older lesions and has been attributed to recruitment of oligodendrocyte-precursor cells,^{64,65} which may reexpress developmental genes and produce new myelin in demyelinated areas. Among these genes, the gene for myelin basic protein (*MBP*) exon II, an early, transient gene expressed during myelinogenesis, has been demonstrated at the remyelinating edge.⁶⁶ In addition, studies of oligodendrocyte-lineage genes have shown that oligodendrocyte transcription factor 1 (*Olig1*) is reactivated during remyelination in patients with multiple sclerosis.⁶⁷ Shuttling of *Olig1* from the nucleus to the cytoplasm of oligodendrocytes recapitulates the developmental sequence of normal myelination, although this factor appears to function primarily in the process of myelin regeneration.

What, then, signals oligodendrocytes to travel to areas of damage? Molecules associated with



recruitment and, possibly, remyelination in this disease include CXC and CC chemokine receptors, which were recently described on oligodendrocytes in close association with hypertrophic astrocytes that express high levels of a respective ligand (e.g., chemokine ligand 1; *CXCL1*).⁶⁸ Thus, chemokine and chemokine-receptor pathways,

such as *CXCL1* and *CXCR2*, may be responsible for the accumulation of oligodendrocytes around the margins of active lesions (Fig. 4). Whereas the recruitment of oligodendrocyte-precursor cells to areas of tissue injury appears to be normal in multiple sclerosis, differentiation into adult myelin-producing oligodendrocytes is another matter.

A number of growth-inhibiting substances are contained within the gliotic scar of the multiple sclerosis plaque and perpetuate developmental arrest, precluding axonal outgrowth and myelin repair. A recently characterized negative modulator of oligodendrocyte myelination is leucine-rich-repeat and immunoglobulin-domain-containing Nogo receptor-interacting protein 1, which can be manipulated to promote myelin repair in animal models of inflammatory demyelination and may represent a viable treatment strategy for patients with multiple sclerosis.⁶⁹

Another central nervous system pathway implicated in remyelination is the Jagged-Notch signaling pathway. Jagged is expressed on axons and astrocytes, whereas Notch, the counterreceptor for Jagged, is expressed principally on oligodendrocytes around active lesions.⁷⁰ The interaction between these two molecules signals a block in oligodendrocyte differentiation. This pathway is, however, reversible and can be down-regulated, suggesting that therapeutic strategies focused on tissue repair may target this important regulatory circuitry.

A ROLE FOR OLIGODENDROCYTE APOPTOSIS?

Whether apoptosis is involved in the demise of oligodendrocytes in patients with multiple sclerosis remains a subject of vigorous debate. Apoptosis is triggered by signaling through members of the family of tumor necrosis factor receptors (although stimulation through ATP also occurs), which leads to the downstream activation of caspase, culminating in apoptotic DNA fragmentation, and has been implicated as a pathogenetic mechanism in multiple sclerosis.^{51,71} However, although evidence of oligodendrocyte apoptosis has been observed in lymphocytes and microglia, it has not been definitive. The discrepancies may be related to the examination of paraffin-embedded tissue long after it was obtained at autopsy, rather than the examination of fresh-frozen material soon after it was obtained during an autopsy.

THE PLAQUE EDGE — A FINE LINE

One striking feature of the lesion of chronic multiple sclerosis occurs at the margin where normal-appearing white matter meets the demyelinated plaque (Fig. 3F). This sharply defined zone, where

oligodendrocytes and intact myelinated internodes abut totally demyelinated, gliotic, and oligodendrocyte-depleted parenchyma, remains an enigma and understanding it remains a formidable challenge. Whereas a neuroscientist might wonder what is preventing inward progression of repair mechanisms, the pathologist might wonder why outward progression of lesions stopped where it did. Characterizing the regulatory balances at this physical boundary poses questions of potential therapeutic importance.

RADIOGRAPHIC MEASURES OF THE LESION'S PATHOLOGICAL CHARACTER

An important hypothesis that has been confirmed through the use of MRI has been that multiple sclerosis is primarily a subclinical process early in its course, characterized by frequent changes in the architecture of the brain and spinal-cord tissue, and punctuated by the evolution of infrequent clinical attacks. Occult disease activity, as detected by conventional MRI, is 5 to 10 times as frequent as clinical activity, as defined by clinical exacerbations. Lesions occur in both neuroanatomically eloquent sites (commonly associated with a clinical syndrome) and noneloquent sites (not necessarily associated with a corresponding clinical syndrome).

Eloquent sites are those occurring within the optic nerve, brain stem, cerebellum, or spinal cord and are frequently associated with well-recognized syndromes, such as optic neuritis, eye-movement abnormalities (e.g., diplopia, vertigo, and nystagmus), changes in balance, and sensory and motor deficits.⁷² In contrast, noneloquent sites are confined to other white-matter territories, including the cerebral periventricular zones (Fig. 2A), and often are not clinically evident. This observation has been corroborated by evidence of disseminated lesions consistent with the presence of preexisting multiple sclerosis within the central nervous system, which have been found in up to 80 percent of patients at presentation.⁷³

Advanced MRI techniques such as magnetic resonance spectroscopy, measurements of brain and spinal-cord atrophy, magnetization transfer, and diffusion tensor imaging have been used to reveal more fully damage to myelin, axons, and other elements of tissue architecture within the central nervous system of patients with multiple sclerosis. Normal-appearing areas of the brain,

as assessed by conventional MRI, demonstrate highly discrete abnormalities when these newer analytical techniques are applied.⁷⁴ Longitudinal studies confirm that the disease is radiographically active even during periods of apparent clinical stability.⁷⁴

PROSPECTS FOR CHARACTERIZING
THE EVOLUTION AND PROGRESSION
OF MULTIPLE SCLEROSIS

Substantial insights have been gained with respect to the roles of inflammation, adhesion-molecule biology, ion-channel alterations, terminal-injury effector mechanisms, and the process of neurodegeneration in the evolution and progression of the multiple sclerosis plaque. Recent investigations have revealed compelling evidence supporting the potential for neuroprotective and repair processes within the central nervous system. Continued progress in these areas may allow us to

modify tissue injury in response to inflammation. Such a capability would no doubt be germane to increasing our understanding of immune-mediated diseases in general and multiple sclerosis in particular.

Supported by the National Multiple Sclerosis Society, the "Once Upon a Time," the Cain/Denius Comprehensive Center for Mobility Research, the Irene Wadel and Robert Atha Fund, the Kenney Marie Dixon Pickens Fund, the Jean Ann and Steve Brock Fund for Medical Sciences, and the Hawn Foundation (to Dr. Frohman); by grants (NS37513 and NS44250 [to Dr. Racke], NS11920 and NS08952 [to Dr. Raine]) from the Department of Health and Human Services; and by grants (RG2969-B-7 [to Dr. Racke], and RG1001-K-11 [to Dr. Raine]) from the National Multiple Sclerosis Society.

Dr. Frohman reports having received speaking honoraria from Biogen Idec and Teva Neuroscience. Dr. Racke reports having served as a consultant for Genentech and having received lecture fees from Biogen Idec and grant support from Pfizer. No other potential conflict of interest relevant to this article was reported.

We are indebted to Dr. G.R. Wayne Moore (Vancouver, B.C., Canada) for Figure 2A, to Dr. John Prineas (Sydney) for Figure 3F, to Dr. Kakuri Omari for assistance with the preparation of the figures, and to Kimberly Silverman and Gargi A. Patel, Ph.D., from the Interactive Network for Continuing Education, for assistance with Figure 4.

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