

# Counseling Points™

Enhancing Patient Communication for the MS Nurse

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## Pathophysiology of MS: What We Know, What We Think We Know, and What We Don't Know *A Roundtable Discussion*

One of the most common questions asked by patients with multiple sclerosis (MS) is “what causes this disease?” Although researchers over the past two decades have been drawing closer to an answer to this question, a definitive reply remains elusive. Still, we now have a better understanding of the complex circumstances that may predispose a person to developing MS, as well as the underlying pathophysiological processes.

When discussing the pathophysiology of MS with patients, it is important to underscore that the advances in our understanding have led to the intro-



duction of the current array of Food and Drug Administration-approved disease-modifying agents, as well as set the stage for the development of a new generation of therapies that prom-

ise to even further decrease the burden of this disease. Understanding the immune mechanisms and pathophysiology of MS and uncovering potential therapeutic targets are essential for the

*Continued on page 3*

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# Welcome to MS Counseling Points™

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Dear Colleague,

An understanding of the disease processes underlying multiple sclerosis (MS) is a critical factor in the identification of therapeutic targets and the optimization of available and emerging therapies. Unfortunately, explaining these processes to patients is no simple matter. Apart from the fact that the extent of our knowledge is constantly expanding, making it difficult for the average clinician to keep up with the latest developments, the subject matter is not particularly easy for a layperson to grasp. If we aren't careful, it's easy to overwhelm, and even scare, our patients with descriptions of complex immune reactions and by using terms such as "atrophy" and "neurodegeneration."

In this issue of *Counseling Points™* we've tried to distill the essentials of the progress that is being made in our understanding of MS into language and concepts that should be understandable to patients. As with any information you share with your patients, it is up to you to gauge the ability and/or need for individual patients to understand it.



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design of new and combination treatments. Having said that, it is up to you to decide the level of detail you want to go into when explaining why some people develop MS and describing the processes that underlie relapses and ongoing progression of disability.

## Why Me?

“Why me?” is the \$64,000 question in MS. Over the last 150 years, multiple theories have been advanced, but none has turned out to be the answer. It is accepted that the cause of MS is multifactorial—that is, it is the result of a combination of genetic susceptibility, environmental factors, some viral exposure, and possibly hormonal interplay. Each day, new research uncovers more of the answers to this and other important questions. MS nurses must have a current understanding of the theorized etiology of MS and the pathological changes that are characteristic of MS so that they are better able to address the concerns of and provide explanations to patients and their families.

## Proposed Etiologies for MS

### The Usual Viral Suspects

Several studies suggest that MS and its accompanying exacerbations are associated with viral or microbial infections.<sup>1,2</sup> It has been noted that following the onset of a viral infection, such as an upper respiratory tract infection, a relapse may be triggered.<sup>3</sup> In fact, some researchers suggest that recurrent viral infections are associated with the progression of disability.<sup>4,5</sup> The list of suspect viral triggers gets longer every year and includes paramyxovirus, coronavirus, Epstein-Barr virus, herpes zoster, herpes simplex virus, human herpesvirus, and rubella.<sup>6</sup> A few researchers believe that a single infectious agent causes the condition. However, no active or latent virus has consistently been demonstrated in cultures of the cerebral spinal fluid (CSF) of patients with MS. Therefore, it is generally accepted that there is still no convincing evidence that viruses are related to MS etiology.<sup>7</sup>

### Is It in the Genes?

The first real indication that genetics may play a role in MS

came in the 1970s when an association between certain human leukocyte antigen (HLA) alleles and MS was reported.<sup>8-10</sup> HLA is the designation for a cluster of genes that code for the Major Histocompatibility Complex (MHC), a component of the immune system involved in MS. Since then, it has been confirmed that the HLA-DR2 allele is associated with the development of MS.<sup>11-13</sup> More recent evidence has uncovered additional non-HLA genes that seem to play a role in MS susceptibility. Research conducted by the International Multiple Sclerosis Genetics Consortium, for instance, identified variations outside of the MHC region—specifically, the IL-2 receptor gene (IL2RA) and the IL-7 receptor gene (IL7RA)—as being associated with an increased risk for the development of MS.<sup>14</sup>

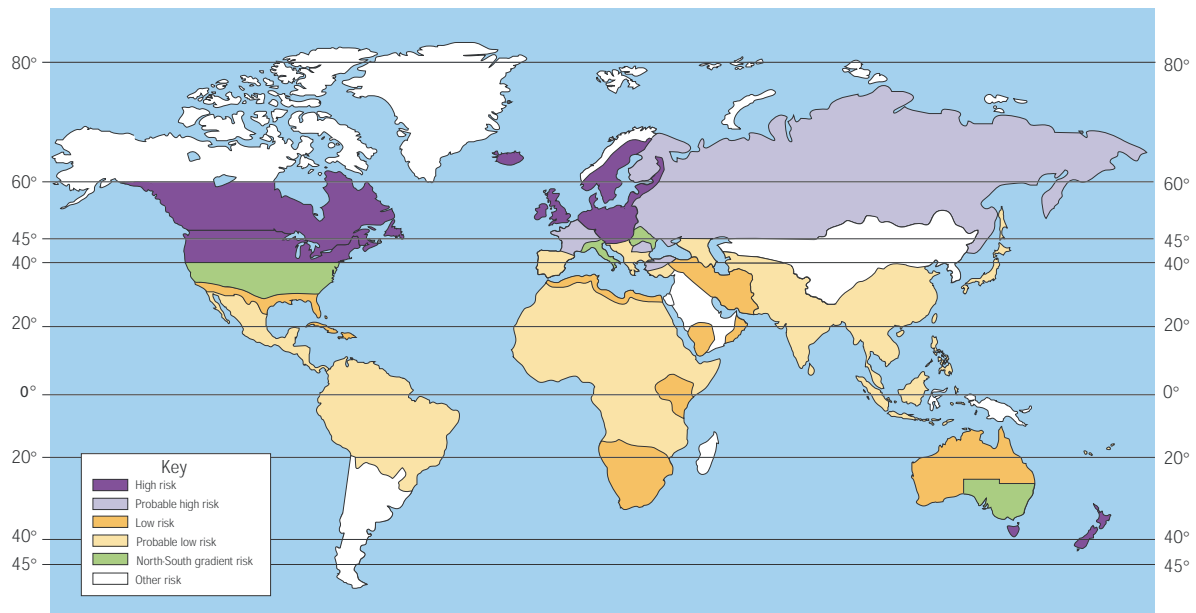
Evidence continues to reinforce a genetic susceptibility to MS; however, it is not an inherited disease. Multiple epidemiological studies describe varying risks of developing MS, but do not indicate inheritance. The risk of MS in the general population is about 0.2%. In first-degree relatives of an individual with MS, the risk is approximately 3% to 5%. The risk of developing MS in monozygotic twins is about 25%.<sup>15</sup> About one quarter of all people who have MS have a relative who also has the disease. These statistics have led researchers to conclude that up to 75% of MS cases must be due to nongenetic factors.<sup>15,16</sup>

Because there are no tests to evaluate the genetic susceptibility of people to MS, it is difficult to counsel patients who want to know their chances of passing the disease on to their children. The best we can do is evaluate the family history and be empathetic, while emphasizing that there is no way to quantify the risk at this stage.

### What About Geography?

While genetic susceptibility plays a role, epidemiological studies indicate that environmental factors also contribute to the development of MS.<sup>17</sup> It is clear that there is considerable variation in the occurrence of MS around the world (**Figure 1**). Prevalence rates increase as one moves north or south from the equa-

Figure 1. Worldwide distribution of MS.



Adapted from McAlpine D, Lumadan CE, Acheson ED. *Multiple Sclerosis: A Reappraisal*. London: Livingston Ltd;1967.

tor. Epidemics of MS have been reported in the Faroe Islands (a group of islands in Northern Europe, between the Norwegian Sea and the North Atlantic Ocean, about halfway from Iceland to Norway) and in Iceland (also in the North Atlantic).<sup>18,19</sup> No truly satisfactory explanation has been offered for these prevalence clusters. MS latitude and migration studies suggest distribution across a north-south gradient, with a significantly higher lifetime prevalence in northern latitudes.<sup>20,21</sup> Researchers have hypothesized that some of this latitude gradient is attributable to ethnicity and genetic epidemiology. Interestingly, however, in situations for which ethnicity is controlled, such as Japanese populations raised in Japan, Hawaii, and California, environmental-enhancing factors seem to be present in the United States.<sup>22</sup> In other words, people of Japanese origin living in the United States are more likely to develop MS than those living in Japan. In addition to geographic gradients, MS clusters have been reported across time, with elevated incidence rates across periods of years in certain geographic locations.<sup>23</sup> These findings have led researchers to conclude that both genetic susceptibility and environmental influences affect the development and clinical manifestations of MS.<sup>24</sup>

## Do Sex Hormones Have Anything to Do with MS?

It is well known that MS is more common in women and it has been observed that MS symptoms are affected by the normal ebb and flow of hormones during the menstrual cycle.<sup>16</sup> Sex hormones play a central role as modulators of immune responses and autoimmune diseases. Use of hormone replacement therapy may be associated with a lower risk of MS, suggesting that sex hormones may have a role in the decreased relapse rate observed during pregnancy and the increased relapse rate following delivery. Indeed, research by Sicotte et al found that administration of estriol at pregnancy levels decreased production of inflammatory cytokines and reduced the mean number of contrast-enhancing lesions seen on magnetic resonance imaging (MRI) by 80%.<sup>25</sup>

Early animal and human studies of the effects of sex hormones on MS have had somewhat conflicting results. In animals with MS, estriol significantly reduced disease severity, whereas progesterone had no effect.<sup>26</sup> In a human study, patients with high estradiol and low progesterone levels had more MS lesions than those who had low levels of both hormones, whereas patients with a high estrogen to

progesterone ratio had a significantly greater number of active lesions than patients who had a low ratio.<sup>27</sup>

More recently, Italian researchers investigated the relationship between serum sex hormone concentrations and characteristics of tissue damage on conventional MRI.<sup>28</sup> They found an inverse correlation among patients with relapsing-remitting MS, in that serum testosterone levels were significantly lower in women with MS than in controls. There was also an inverse correlation between estrogen levels and the number of gadolinium-enhancing lesions—i.e., the lowest levels were found in women with a greater number of gadolinium-enhancing lesions. In contrast, there was a positive correlation between testosterone concentrations and tissue damage on MRI and clinical disability. In men, the researchers found a positive correlation between estradiol concentrations and brain damage. They concluded that hormone-related modulation of pathological changes supports the theory that sex hormones play a role in the inflammation, damage, and repair mechanisms typical of MS.

More studies are needed to determine the precise relationship between MS and hormonal imbalances.<sup>29</sup> A better comprehension of how sex hormones exacerbate and suppress the harmful immune responses seen in MS may lead to novel therapeutic approaches to combat this and other autoimmune or immune-mediated diseases.<sup>30</sup>

## Understanding the Processes

Major progress has been made in helping us understand what happens when a person has MS. Until relatively recently, the dominant theory was that MS is an autoimmune disease that triggers inflammatory attacks on the myelin within the central nervous system (CNS). However, in recent years, researchers have developed a neurodegenerative model of MS that in some ways complements the inflammatory model.<sup>31</sup>

### The Inflammatory Model

For many years, it has been widely accepted that MS exacerbations and CNS damage are the result of inflammatory activity.<sup>32</sup> The basis of the inflammatory model is an immune response involving a number of

different immune cells, including T cells, B cells, macrophages, and brain microglia.<sup>32</sup>

The immune system protects us from pathogens and responds to injury. The immune system has several important characteristics: diversity, specificity, the ability to distinguish self from non-self, and memory. Thus, the normal immune system can recognize a wide variety of potential pathogens, leave its own tissue alone, and remember a previous exposure and response. Some of the T and B cells also have the ability to react to self-antigens. A normally operating immune system keeps these autoreactive immune cells in check so that they do not

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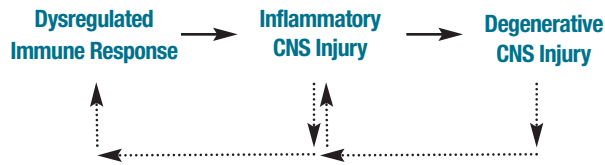
*In recent years, researchers have developed a neurodegenerative model of MS that in some ways complements the inflammatory model.*

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provoke an unwanted response. However, if the immune system is dysregulated, tolerance to some self-antigens may be disrupted and the autoreactive T and B cells will spring into action, mistakenly damaging a person's own tissues.<sup>33</sup> Hence, the term “autoimmune disease,” which is frequently used to describe MS. Although MS does not fulfill all autoimmune criteria, it is generally thought to be an immune-mediated disease.<sup>33</sup>

Evidence suggests that there is dysregulation of the immune system response in MS. The immune system in MS is unable to distinguish self-antigens from foreign antigens and seems to be imbalanced in favor of an inflammatory response. In MS, peripherally activated immune system cells are attracted to the cerebral blood vessels. Adherence to blood vessel endothelium and enzyme disruption of the extracellular blood vessel matrix allows immune cells to gain entry into the CNS. When these cells are presented with a recognizable CNS protein, they become reactivated and an inflammatory response begins, causing demyelination and axonal damage.

**Figure 2. Disease initiation in multiple sclerosis.**



The model of primary autoimmune disease suggests that dysregulated peripheral immune activation is the initiating event, resulting in inflammatory central nervous system (CNS) injury. The CNS then may be subject to additional waves of immune attack and to a partially independent process of degeneration. Adapted from Bar-Or A. *Neural Clin.* 2005;23:149-175.<sup>33</sup>

Each new wave of inflammation manifests itself as an exacerbation and/or as newly evolving lesions on MRI.<sup>33</sup> Inflammation in the CNS is believed to trigger a more degenerative process that leads to progression of disability, which may or may not, in turn, lead to further inflammatory responses (**Figure 2**).

**Figure 3** outlines the key steps in the inflammatory model of MS.<sup>33</sup> The first step is peripheral activation of T cells that recognize antigens in the CNS. T-cell activation involves T-cell recognition of antigens that bind to receptors on T cells. For this to happen, an antigen fragment must be presented to the T-cell receptor enfolded in the MHC, which is expressed on antigen-presenting cells (APCs). APCs include dendritic cells, monocytes, macrophages, CNS microglial cells, and B cells.<sup>33</sup> Activated T cells upregulate surface molecules that help them adhere to the endothelial cells of the blood-brain barrier (step 2). These molecules also help T cells respond to soluble proteins in the blood-brain barrier (step 3). Secretion of matrix proteases, enzymes that play a role in degrading the blood-brain barrier, helps the T cells invade the CNS (step 4), where they become reactivated (step 5) and injure myelin (step 6).<sup>33</sup>

Activated T cells differentiate into subsets, known as helper cells, distinguished by the cytokines they secrete. Cytokines associated with T-helper cells type 1 (Th1) include interleukin (IL)-12, IL-23, interferon (IFN)- $\gamma$ , and tumor necrosis factor (TNF)- $\alpha$ . Th1 cells are part of the normal antiviral response.<sup>33</sup> Th2 cells are associat-

ed with IL-4, IL-5, IL-13, and possibly IL-10, and act against parasitic infections.<sup>33</sup> It is generally believed that Th1 responses may be proinflammatory and thus cause damage, and that Th2 responses may be anti-inflammatory and protective.<sup>33</sup> In patients with MS, the balance is tipped toward Th1 responses. Thus, one of the therapeutic approaches researchers have explored is to induce immune deviation from Th1 to Th2 responses.<sup>33</sup>

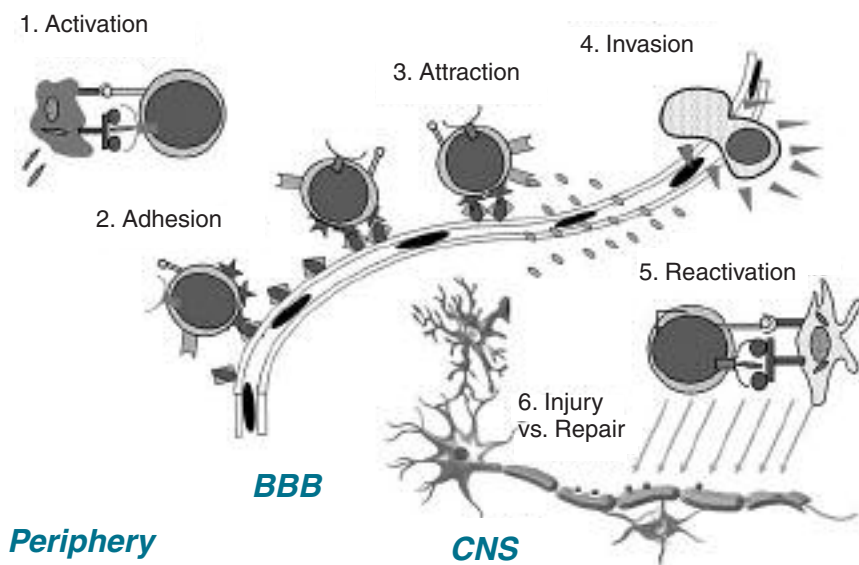
According to the inflammatory model, persistence and progression of neurological disability in MS may be the result of chronic activation of CNS glial cells, such as microglia and astrocytes.<sup>33</sup> The presence of activated cells within the CNS may contribute to “smoldering tissue injury.”<sup>33</sup> In addition, loss of oligodendrocytes (a type of glial cell responsible for producing myelin) could be the result of earlier sublethal inflammatory insults. It has been postulated that the lack of remyelination seen in chronic MS lesions may be the result of loss of progenitor oligodendrocyte cells because of immune-mediated injury. Oligodendrocytes provide trophic support for axons. Without adequate and functioning oligodendrocytes, axons become vulnerable to injury.<sup>33</sup>

### The Neurodegenerative Model

As we have seen above, MS relapses are generally believed to be associated with acute inflammation within the CNS from an autoreactive immune response. However, it is still not entirely clear whether disability progression is the result of a primary inflammatory mechanism.<sup>34</sup> Does one process depend on the other or are they independent of one another? Some researchers suggest that MS is triggered by neurodegenerative processes that result in inflammation and its consequences.

MRI studies suggest that the underlying structural damage associated with exacerbations on the one hand and disability progression on the other hand is different. With exacerbations, recent lesion activity is visible with a gadolinium enhancement, whereas disability progression is more associated with black holes seen on T1

**Figure 3. Inflammatory model of multiple sclerosis immunopathogenesis.**



Immune cells activated in the periphery (step 1) upregulate surface molecules that enable them to adhere more efficiently (step 2) to the endothelial cells of the blood-brain barrier (BBB) and respond to local chemokine gradients (step 3). Active secretion of matrix proteases (step 4) facilitates immune-cell invasion into the central nervous system (CNS) where they may become reactivated (step 5) and have an impact on the biology of CNS elements (step 6). Adapted from Bar-Or A. *Neurol Clin.* 2005;23:149-175.<sup>33</sup>

disease but also in patients with relapsing-remitting MS.<sup>36</sup>

To further support their theory, proponents of the neurodegenerative model of MS cite animal studies suggesting that axonal degeneration may, in fact, be the result of disturbed trophic support rather than of demyelination per se.<sup>34</sup> In addition, the fact that lesions found in the gray matter of patients with MS exhibit considerably less infiltration by lymphocytes and macrophages than do white matter lesions offers further evidence for a non-inflammatory basis of the disease, or at least for the progressive component.<sup>34</sup>

Autopsies of patients with MS who had undergone autologous bone marrow transplants revealed that although there was almost a

sequences, which reflect axonal loss and brain atrophy.<sup>34</sup> Researchers have concluded that the processes of acute relapse and disability accumulation are dissociated in time, between patients, and on MRI, suggesting differences in underlying pathology.<sup>34</sup>

Only recently, researchers have realized that axonal damage is an integral and early pathological feature of MS lesions.<sup>34</sup> Axonal damage is visible in both active and inactive lesions on MRI scans. This persistent damage can lead to significant loss of axons over the years, in spite of the absence of acute inflammatory activity.<sup>34</sup> While conventional MRI allows us to see the focal damage of MS, non-conventional MRI techniques such as magnetic resonance spectroscopy and magnetization transfer imaging allow us to appreciate the diffuse nature of the disease. Axonal and neuronal loss develop in areas of the CNS well beyond the focal inflammatory lesions typical of MS.<sup>35</sup> This damage to so-called “normal-appearing white matter” is found not only in patients with secondary-progressive

complete absence of inflammatory markers in the brain, there was significant evidence of acute axonal damage. This suggests that neurodegeneration continues, even in the absence of inflammation.<sup>34</sup>

Taking all of this information together, some researchers are now postulating that axonal damage may develop independent of inflammation and involve changes in trophic interactions among oligodendrocytes, microglia, and neurons.<sup>34</sup> Indeed, they theorize that these trophic disruptions may be the primary pathophysiological anomaly in MS, responsible for both the inflammatory process and neurodegeneration.

## Patterns of Disease and Implications for Treatment

There is emerging evidence that the mechanisms underlying inflammation and degeneration in MS have practical implications for the use of currently available disease-modifying therapies and ongoing and future research efforts.

It is clear that MS is a heterogeneous disease. Symptomatology and brain pathology differ among patients. Luchinetti and colleagues examined the brains from 82 MS patients and identified four distinct pathological patterns. Although more research is necessary to confirm these findings, clinical observations support the heterogeneous presentation of the disease.<sup>37</sup> These scientists suggest that based on brain pathology, there are distinct subgroups of patients and they may benefit from different therapeutic approaches. Although there is a great deal of overlap, the patterns differ from one another by the degree of inflammation, demyelination, remyelination, and whether there is damage to oligodendrocytes. Patterns I and II show cell-mediated damage, significant inflammation, and evidence of extensive remyelination. Pattern II is distinguished by the presence of antibody and complement, which are absent in the other patterns. In Patterns III and IV, the distinguishing features are oligodendrocyte damage and a lack of any remyelination. In summary, Patterns I and II appear to be inflammatory in nature and Patterns III and IV are more degenerative.

The current disease-modifying therapies are anti-inflammatory agents with varying mechanisms of action. It is likely that heterogeneous disease pathology is an explanation for their partial ability to modify the disease process. Their mechanisms of action are directed towards the cell-mediated inflammatory response, and none of the current therapies have demonstrated a profound effect on disease progression. As axonal loss is permanent, there is great interest in finding treatments that could be potentially neuroprotective. There are numerous trophic factors that may play a role in repair and protection, such as brain-derived neurotrophic factor (BDNF). BDNF is expressed by several subsets of immune cells, including T cells, B cells, and monocytes, and exerts potent effects on neuronal and axonal survival during development and after injury.<sup>38-41</sup> Recently, evidence has emerged that in addition to its anti-inflammatory effects, glatiramer acetate stimulates the production of BDNF.<sup>42,43</sup> Thus, it has been proposed that glatiramer acetate may contribute to neuroprotection and

regeneration, in addition to its well-characterized anti-inflammatory effects.<sup>44,45</sup> Interferons have been found to enhance production of nerve growth factor (NGF) by astrocytes. Thus, they too may have some neuroprotective properties.

In the research pipeline are numerous oral and injectable agents. Rituximab is a potent injectable monoclonal antibody with anti B-cell properties. Fingolamod (FTY 720) is an oral agent that interferes with the normal circulation of lymphocytes in the periphery. Alemtuzumab, a monoclonal antibody,

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prohibits T-cell proliferation in the periphery. Other potential treatment approaches include cytokine-promoting CNS progenitor cells, promyelinating antibodies, prostaglandins, lipoxins, and antithrombins.<sup>33</sup>

When counseling patients about therapies, it is important to remember that each individual is unique and may be subject to a different underlying pathological process. Currently, there is insufficient information to make treatment decisions based upon brain pathology, but patients need to understand that the disease is heterogeneous and the response to treatments is variable. Thus, if the response to one of the agents available to treat MS is suboptimal, an agent with a different mechanism may be needed.

## Conclusions

The pathophysiology of MS is a complex subject and our knowledge base is rapidly expanding as our understanding of the disease evolves. It is now widely believed that the mechanisms that underlie acute exacerbations and disability progression are distinct and may merit different treatment approaches.

When discussing these issues with patients, it is important to evaluate a patient's ability and need to understand them.

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# MS Counseling Points™

## *Pathophysiology of MS: What We Know, What We Think We Know, and What We Don't Know*

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- Before discussing the causes and pathophysiological underpinnings of multiple sclerosis (MS), always assess the individual patient's capacity to understand and need to know.
- The causes of MS are believed to be multifactorial, reflecting an interplay between viral, genetic, environmental, and, potentially, hormonal factors.
- No specific infectious pathogen to date has been identified as a causative agent.
- As yet, there are no genetic screening tests available that will identify individuals susceptible to MS; thus, when counseling patients regarding the risks of passing MS on to their children, elicit a thorough family history and be empathetic while emphasizing that there is no way to quantify the risk.
- Inflammatory processes, initiated in part by an autoimmune response, are believed to be the dominant feature of pathology of MS.
- There is growing consensus that the disability progression associated with MS is neurodegenerative in nature and is probably independent of the inflammatory cascade.
- All of the currently available disease-modifying therapies address the inflammatory component of MS; in addition, there is emerging evidence that glatiramer acetate may have neuroprotective properties in addition to its anti-inflammatory effects.

# MS Counseling Points™

*Pathophysiology of MS: What We Know, What We Think We Know, and What We Don't Know*

## Tell Us What You Think

We are anxious to hear your comments about this issue of *Counseling Points™*. We would also like you to share any suggestions you may have for future issues.

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Excellent ⑤    Good ④    Satisfactory ③    Fair ②    Poor ①

### How would you rate the:

Overall quality of <i>Counseling Points™</i>	⑤ ④ ③ ② ①
Readability of <i>Counseling Points™</i>	⑤ ④ ③ ② ①
Usefulness of the information presented in <i>Counseling Points™</i>	⑤ ④ ③ ② ①
Value of the <i>Counseling Points™</i> summary (page 10)	⑤ ④ ③ ② ①

Do you believe you will be better able to communicate with patients after having read the information presented in *Counseling Points™*?

Yes     No

We would appreciate your comments and suggestions on how we can improve future issues of *Counseling Points™*.

What future topics would you like to see addressed in *Counseling Points™*?

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Are there any other comments, suggestions, or thoughts about *Counseling Points™* that you would like to share?

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