MULTIPLE SCLEROSIS (MS) IS THOUGHT TO be an autoimmune disease in which the body’s immune system attacks the central nervous system (CNS), specifically by gradual destruction of the myelin sheath that surrounds nerve fibers. Its name is derived from the scarring (sclerosis) caused by attacks at multiple sites in the CNS.

The characteristic features of MS lesions are inflammation with activated T cells, monocytes and B cells and demyelination and axonal damage. Traditionally, MS was thought to be purely a demyelinating disease. The “insulation” around the axon “cables” was stripped off by the immune system. Inflammation is now known to be a significant part of the disease. Studies have shown that significant axon injury and death can occur in active sites of inflammation. This is the basis for the progressive atrophy and accumulation of disability that can develop in MS patients. Lesions can develop and brain atrophy can occur in patients not experiencing clinical relapses. Irreversible changes to axons can occur during early relapses thus affecting prognosis. Relapses and increased magnetic resonance imaging (MRI) lesions are related to increased disability.1

MS is the leading cause of neurologic disability in young adults in the United States with approximately one million diagnosed cases of the disease.2 The usual age of onset is between 20 and 50, but childhood and older onset MS can occur.

SUMMARY
With advances in the understanding of the dual nature of multiple sclerosis (MS) – inflammation and nerve fiber destruction, treatment is now recommended in earlier phases of the disease. Early treatment after the first attack of symptoms highly suggestive of MS with disease modifying medications can delay progression to clinically definite MS. Early treatment also can significantly delay the development of disability. Because of the effects on progression and disability, overall cost savings should occur with early treatment.

Key Points
• Early treatment with disease modifying medications delays the progression from clinically isolated syndrome to clinically definite MS.
• Early treatment also delays the development of disability.
• Disease modifying medications are a small part of the overall costs of MS management.

EXHIBIT 1: A DUAL-PHASE DISEASE?

Dhib-Jalbut, S. Pharmacology & Therapeutics. 2003: 98(2):245-255

Reference: 3
The risks for MS involve many factors such as age, gender, race, geographical location (especially during childhood), and genetics. While no specific “MS gene” is likely to be discovered, the risk of MS is increased within families, and the concordance rate for MS in monozygotic twins is much greater than in dizygotic twins. There is a higher rate in women (3:1), and Caucasians.

MS appears to be a dual phase disease (Exhibit 1). Despite the heterogeneity of disease patterns, most individuals with MS exhibit a dual-phase pattern of disease activity, dominated in the early phase by inflammation (with some axonal transection) and then transitioning to a later phase dominated by neurodegeneration (as inflammation subsides). Axonal loss and cognitive changes begin in the early phase. It is estimated that for every attack symptomatic enough for a patient to seek care, there are 10 attacks that can be documented on an MRI (Exhibit 2). Thus sub-clinical damage is ongoing. The latter phase of MS is characterized by increasing disability as the process of irreversible nerve damage continues. As neurodegeneration progresses, the disease becomes increasingly more difficult to treat.

Left untreated, MS can have a devastating effect on the patient. Eighty to 90 percent of untreated MS patients will have substantial disability after 20 to 25 years of disease. No treatment is reparative, so we must prevent damage as much as possible. Given our updated understanding of the effects of MS on the central nervous system, early treatment with effective disease modifying medications should be used when possible.

Traditionally, two clinical attacks were required for diagnosis. MRI scans are now being used to show all the attacks, not just those, which are symptomatic. The National MS Society treatment recommendations emphasize early treatment with interferon beta (Betaseron®, Rebif®, Avonex®) or glatiramer acetate (Copaxone®) and are summarized in Exhibit 3.

In addition to interferon beta and glatiramer acetate, natalizumab (Tysabri®) is approved for remitting relapsing MS (RRMS) and mitoxantrone is used as rescue therapy. Treatment decisions are best guided by using the principals of evidence-based medicine combined with the experience of the phy-
Physician and the individual circumstances of the patient. Exhibit 4 lists the American Academy of Neurology evidence based evaluations of the various treatments.\(^8,9\) One medication does not work for all patients. The medications also do not work as well when stopped and restarted.

In the majority of patients with MS, the first clinical neurological manifestation is a clinically isolated syndrome (CIS). CIS can be defined as a solitary, inflammatory, demyelinating syndrome of acute onset in the central nervous system in an individual with no prior history of demyelination, and in whom alternative diagnoses have been excluded with appropriate clinical and laboratory investigations. Therefore, it is beneficial to determine those characteristics of CIS that predict future development of MS. Several patient characteristics and neurological signs and symptoms are more frequently associated with the development of MS. In general, age can help identify those patients with CIS who will develop clinically definite MS (CDMS), thereby excluding those patients at the extremes of age. The predictive symptoms associated with a first attack of MS include optic neuritis, brainstem dysfunction, and myelitis.\(^10\) The cases of optic neuritis tend to be unilateral, retrobulbar, and painful in nature. Brain-
stem dysfunction is most often an ocular motor syndrome such as intranuclear ophthalmoplegia and nystagmus. Hemisensory abnormalities as well as hemiparesis and trigeminal neuralgia may be seen. In the cases of myelitis, more often partial sensory loss occurs rather than partial motor, with bowel and bladder dysfunction being common abnormalities.

Early treatment focuses on patients with CIS suggestive of MS in an effort to delay progression to CDMS. By intervening early, it may be possible to delay progression to CDMS, and ultimately to reduce disease severity and disability. The vast majority of patients with CIS suggestive of MS will progress to CDMS within a couple of years. In one study, up to 51 percent of placebo treated patients had converted to CDMS at six months, and 85 percent by two years (Exhibit 5). The vast majority of patients with CIS suggestive of MS will progress to CDMS within a couple of years. In one study, up to 51 percent of placebo treated patients had converted to CDMS at six months, and 85 percent by two years (Exhibit 5).

Trials using the available agents early in the disease have shown benefits in delaying progression of MS. In the BENEFIT trial, early interferon use in patients presenting with CIS suggestive of MS reduced the risk for confirmed disability progression, using the Expanded Disability Status Scale (EDSS), at three years from 24 to 16 percent (Exhibit 6). This was statistically significant with a relative risk reduction over the total time period of 40 percent. Delayed progression appears to increase over time especially in the third year of the study. This suggests a long-lasting and true disease-modifying effect. Waiting to treat a patient with interferon treatment resulted in greater sustained disability progression. In other words, if treatment is delayed until the second attack, the patient’s risk of developing CDMS is increased 40 percent. This trial also showed improved quality of life, cognition, and MRI results with early treatment.

Some have questioned the use of disease modifying agents in the later stages of MS because inflammation is not predominant. It is important to note that secondary progressive MS (SPMS) is NOT a different disease from RRMS; it is a different phase of the disease. All interferons are approved for relapsing forms of MS, which includes SPMS with relapses. SPMS trials with the interferons all showed benefit by reducing relapses and MRI activity. The effectiveness of the medications during the SPMS phase is likely due to suppression of residual inflammatory activity. Glatiramer has not been studied in SPMS but failed to show benefit in a trial of primary progressive MS (PPMS).

In the one trial of interferon in SPMS, sustained disability could be delayed by 12 months. A similar trial was conducted in the United States that found no change in disability but did find decreases in relapse and MRI findings. The patients in the United States trial were treated later in the disease process, which may account for the difference in outcomes.

One of the problems with assessing medications for MS is the pivotal trials have been two years in duration and MS is a lifelong disease. Extended follow-up studies of patients who have used disease-modifying agents are now being published. These extension studies are incomplete and suffer from the fact that many patients have been lost to follow-up. Additionally, none of these are blinded prospective.

In a long-term follow-up of glatiramer in patients with RRMS, of those patients who started on therapy, 47 percent stayed on therapy for 10 years.
those long-term patients, the relapse rate decreased 80 percent and the EDSS increased by only 0.5 points. At the end of 10 years, more than 90 percent of the patients were still ambulatory. Fifty-three percent of the patients originally started on glatiramer withdrew from the study. Unfortunately, there is no information on what happened in terms of relapse or disability in patients who stopped therapy. In a 16-year follow-up of patients treated with interferon, there was a six year delay in progression to an EDSS of 6 (needing a cane to walk).

Although the agents discussed here are truly disease modifying, they will not work if not taken appropriately. MS was previously thought to be a disease that was intermittently active. We now know that MS is a continuously active disease which means adherence to medication is necessary to maximize the effectiveness of the treatment. Adherence programs can be helpful in improving adherence rates with these agents.

Additionally, all the medications have side effects that may affect tolerance and long-term adherence. Side effects need to be recognized and treated. Long-term studies do show that these agents are safe and tolerable in the majority of patients.

MS is a costly disease. When untreated, mean total lifetime cost per patient is estimated at $2.4 million in 1994 dollars. Observational burden of illness studies conducted in the United States and European countries find that the major costs of MS lie outside the health care system with productivity loss, non-medical costs, and assisted care by caregivers dominating. These costs are correlated with the level of disability and increase with increasing disability. Analysis of managed care claims in several studies have found that disease modifying drugs account for 65 to 80 percent of medical cost of MS care. However, these studies do not take into account the severity of the disease, the degree of disability, or the total cost of care.

In a cross-sectional study of patients with MS treated with disease modifying medications in the United States, the overall cost driver for MS was the indirect cost of early retirement (Exhibit 7). The cost of all medications represented 28 percent of total costs of MS and 50 percent of direct costs. Disease modifying medications represented a minority (21 percent) of total costs. Total costs are highly correlated with an MS patient’s disability level or functional status. Indirect, informal care, and other direct costs related to inpatient status and nursing care represent a higher proportion of costs at moderate and severe disease levels. While the cost of care rises dramatically with the degree of disability (EDSS), the actual cost of disease modifying medications remains flat.

As MS progresses and the level of disability increases, both the direct and indirect cost of care will increase (Exhibit 8). The objective of early treatment is to lessen the development of disability, and thereby reduce the overall cost of care.

There are many new biologic therapies for MS under study. Some of these have new mechanisms of action and some are given orally rather than by injection. Some non-biologic therapies also are being evaluated, including minocycline, fluoxetine, lipid lowering agents, and vitamin D. Very positive data have recently been published with monoclonal anti-
Conclusion
MS is a disabling long-term disease that begins early in life. Evidence-based medicine has shown that all current treatments are disease-modifying agents. Treatment early of CIS reduces attacks and slows disability. Long-term treatment is safe and well tolerated and also can affect disease course. Financial analysis shows that treated patients cost less. The physician and patient, deciding together on therapy, maximize adherence and efficacy of the medication. JMCMS

Jack Burks, MD, is Clinical Professor of Medicine, University of Nevada School of Medicine and Chief Medical Officer for the MS Association of America.

References