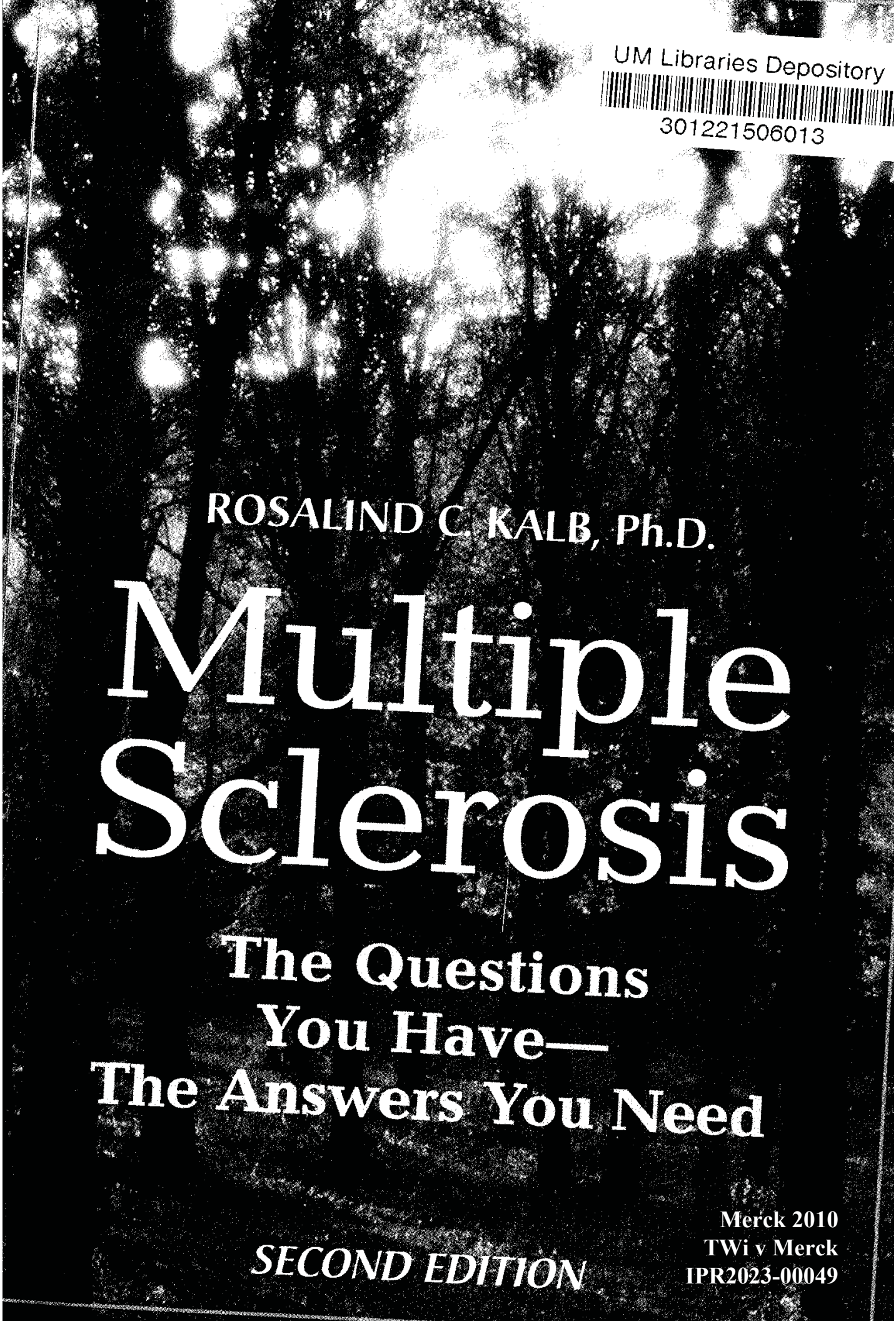


ROSALIND C. KALB, Ph.D.

Multiple Sclerosis

The Questions You Have— The Answers You Need

SECOND EDITION

Multiple Sclerosis

The Questions You Have— The Answers You Need

Second Edition

Edited by Rosalind C. Kalb, Ph.D.

Demos

New York

Demos Medical Publishing, Inc., 386 Park Avenue South, New York, New York 10016

Library of Congress Cataloging-in-Publication Data

Multiple sclerosis : the questions you have, the answers you need / edited by Rosalind C. Kalb.—2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 1-888799-43-9
1. Multiple sclerosis—Popular works. 2. Multiple sclerosis—Miscellanea. I. Kalb, Rosalind
RC377.M564 2000 00-035857
616.8′34—dc21

Printed in Canada

Annual updates to this book can be downloaded from our Web site: demosmedpub.com. This site also contains information about Demos's other publications on multiple sclerosis.

Contents

Multiple Sclerosis

The Questions You Have— The Answers You Need

Edited by ROSALIND C. KALB, Ph.D.

"This book is trustworthy! It is factual! It is honest! It is a jumping-off point to learning more about MS and with that knowledge developing new and better coping skills to deal with the ups and downs of the mysteries of MS."

From the Foreword by RANDALL T. SCHAPIRO, M.D.,
Fairview Multiple Sclerosis Center, Minneapolis

Here is the definitive guide for anyone concerned with multiple sclerosis—those who have the disease, those who share their lives with someone who has it, and health care professionals involved with its management. *Multiple Sclerosis: The Questions You Have—The Answers You Need* covers a wide range of topics in a question and answer format that is readily accessible and easily understood. Experienced clinicians provide answers to the questions that they have been asked repeatedly. Readers can quickly find information about specific topics and questions based on their individual needs.

Each chapter contains a list of references and recommended readings for those interested in pursuing more detailed information on a particular topic. The guide also contains a comprehensive glossary of all terms commonly used in MS management and a list of relevant resources for individuals with MS and their families. The chapter on treatments describes all medications commonly used in the treatment of MS and the management of its symptoms.

Demos

DEMOS MEDICAL PUBLISHING
386 Park Avenue South, Suite 201
New York, New York 10016

ISBN: 1-888799-43-9
$39.95

Cover Design Darby Downey

ISBN 1-888799-43-9
9 781888 799439

Multiple Sclerosis

The Questions You Have— The Answers You Need

Second Edition

Edited by Rosalind C. Kalb, Ph.D.

Demos

New York

Demos Medical Publishing, Inc., 386 Park Avenue South, New York, New York 10016

Library of Congress Cataloging-in-Publication Data

Multiple sclerosis : the questions you have, the answers you need / edited by Rosalind C. Kalb.—2nd ed.

p. cm.

Includes bibliographical references and index.

ISBN 1-888799-43-9

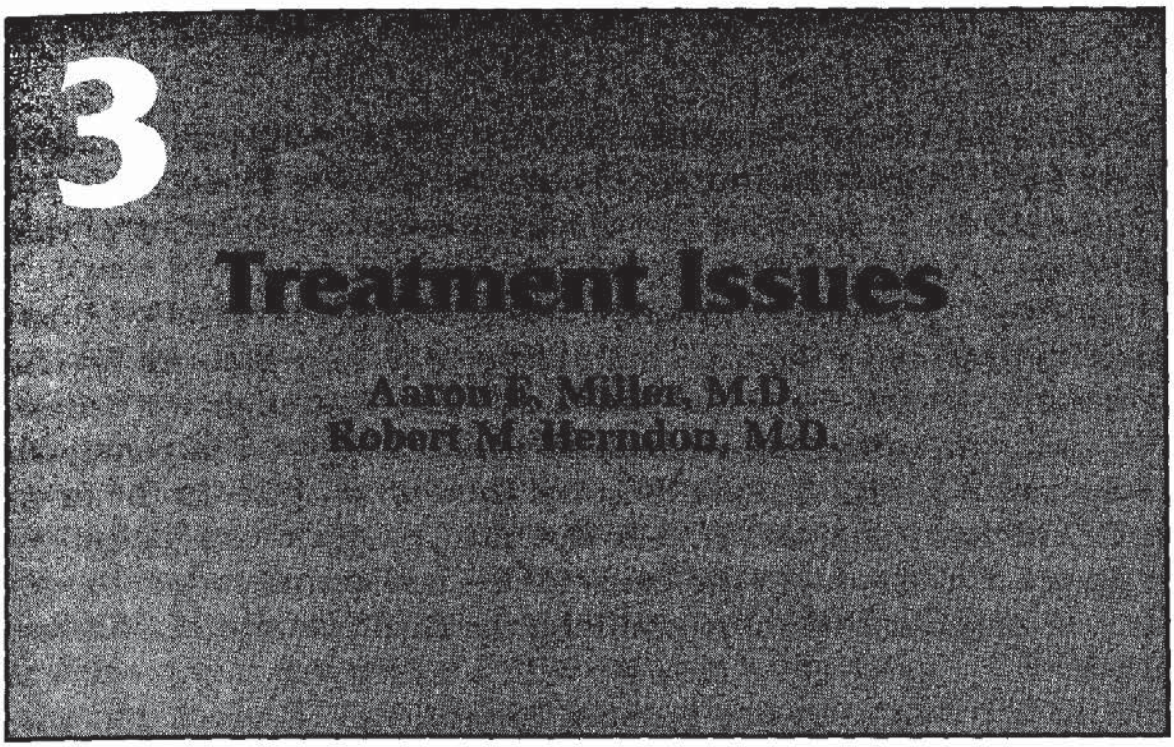
1. Multiple sclerosis—Popular works. 2. Multiple sclerosis—Miscellanea. I. Kalb, Rosalind

RC377.M564 2000 00-035857

616.8′34—dc21

Printed in Canada

Annual updates to this book can be downloaded from our Web site: demosmedpub.com. This site also contains information about Demos's other publications on multiple sclerosis.



3 Treatment Issues

Aaron E. Miller, M.D.
Robert M. Herndon, M.D.

Any discussion of treatments for multiple sclerosis must start with a careful look at what we mean by the word *treatment*. To most people, being "treated" for an illness means that they report their symptoms to a physician, are prescribed a medication (an antibiotic, for example), the symptoms go away, and they are cured. In another familiar scenario, the person gets the flu or some other viral infection, goes to the doctor or the pharmacy for some medications to relieve discomfort, and waits patiently for the virus to run its course and go away. In the case of physical injury, the treatment may be even more direct and clear-cut. The person who temporarily cannot walk because of a broken leg is treated for the injury, and walking ability is restored. Of course, the best strategy of all is a vaccine to prevent the disease in the first place.

At the present time, none of these familiar notions of treatment applies in MS. We are unable to prevent the illness from occurring, we do not know how to cure it, we have not found a way to restore damaged ***myelin, axons***, or lost functions, and the disease is a chronic one that refuses to run its course and go away. While efforts continue in the scientific community to find a cure for MS and restore damaged myelin, the primary

focus of day-to-day medical care in MS is symptom management (see Chapter 2) and efforts to stabilize the disease course. These efforts to stabilize the disease are the main focus of this chapter.

In order to understand why efforts to find an effective treatment for MS have been so frustrating, it is important to review some of the characteristics of the disease. Although we believe MS to be an ***autoimmune disease*** that is triggered in genetically susceptible individuals by some infectious agent in the environment (see Chapter 2), we do not yet have any definitive answers. Not knowing the cause of a disease makes looking for its cure significantly more challenging. Additionally, the disease tends to progress quite slowly, with a symptom picture that is highly variable from one person to the next. These characteristics make it difficult for researchers to know how to evaluate the efficacy of any particular treatment. If the disease manifests itself differently from one person to the next, what symptom or other aspect of the disease should be looked at to determine if a treatment is working?

Furthermore, although a review of treatments used in MS over the 15-year period from 1935 to 1950 indicated that 66 percent of the patients improved, none of these interventions has been shown *over time* to be any more effective than no treatment at all. Other studies have demonstrated that 70 percent of individuals treated for a recent worsening of their disease will improve, at least temporarily, with a ***placebo***, or inactive, medication. Thus, treatment of a recent ***exacerbation*** in MS can only be considered effective if it leads to long-lasting improvement in significantly more than 70 percent of people who are given it.

This brings us back to the question of measuring the outcomes obtained when evaluating experimental treatments. Recent research efforts have targeted the number of exacerbations, length of exacerbations, length of time between exacerbations, severity of exacerbations, and the total area or volume of lesions shown on ***MRI*** as reasonable indicators of treatment impact in ***relapsing-remitting*** multiple sclerosis. In 1981, at the first international conference on therapeutic trials in MS, it was clear that there had been only one successful treatment trial in MS that met the scientific standards of its time. In that trial of ***adrenocorticotropic hormone***

(ACTH), it was demonstrated that ACTH could shorten attacks even though it had no effect on the ultimate degree of recovery or long-term disability.

Since that time, there have been several high-quality drug trials in MS. There currently are more trials in progress in North America and Europe than at any time in the history of the disease. These include small-scale (fewer than 20 patients) and large-scale (several hundred patients) trials, targeting acute relapses, as well as ***exacerbating-remitting, secondary progressive***, and ***primary progressive*** MS. They involve experimental therapies designed to affect immune function, fight infectious agents, restore myelin, and improve symptoms. The trials are evaluating new drugs, old drugs, and drugs used in various combinations. In addition, treatments that have already been approved for use in MS are beginning to be compared to one another.

Based on data from recently completed European trials of mitoxantrone, an advisory panel for the ***Food and Drug Administration*** (FDA) recommended that the FDA approve Novantrone® (mitoxantrone for injection concentrate) to slow worsening of neurologic disability in secondary progressive and relapsing-remitting forms of MS. In recently completed trials of oral myelin, cladribine, and sulfasalazine, these agents were found not to be of benefit. Roquinimex (linomide) proved to be toxic so the trial was stopped. *As the results from new or ongoing trials become available, the information will be incorporated into periodic updates available from the publisher.*

This is an exciting time for both individuals with MS and their health care providers. Interferon beta-1b (Betaseron®), the first drug approved by the FDA for treatment of MS, became available for relapsing-remitting MS in the fall of 1993. Betaseron® has had a noticeable impact on the frequency and severity of attacks in many of those receiving the drug. In 1994, reports were made of successful trials of interferon beta-1a (Avonex® and Rebif®) and glatiramer acetate (Copaxone® formerly known as copolymer 1) for exacerbating-remitting MS. Avonex® and Copaxone® are now approved and in wide use. In February of 2000, Biogen, Inc. announced the early termination of its clinical trial of Avonex® for individuals with initial signs of demyelinating disease who are at risk for developing clinically definite MS. When used at the stan-

dard dose of 30 micrograms in once-weekly intramuscular injections, Avonex® (in comparison to a placebo treatment) significantly delayed development of a second objective sign that would signal clinically definite MS. [Publication of these data, and their review by the FDA had not yet occurred when this book went to print.] Rebif® has already been approved in Canada and Europe, and is expected to become available in the United States within the next few years. While these offer neither a cure nor any restoration of lost function, they do represent a significant advance in our efforts to stabilize the disease process.

What makes it so difficult for scientists to find a cure for multiple sclerosis?

Physicians and researchers have found it difficult to find a cure for MS because the underlying cause of the illness is not known. Current thinking is that some "environmental" trigger (a viral infection, for example) initiates a process in which the individual's ***immune system*** inappropriately attacks the myelin in his or her own ***central nervous system***. This process probably occurs more readily in people born with a genetic predisposition to the disease. Since we do not know the exact triggers for the initial and ongoing immunological assault, it is difficult to devise specific treatments to prevent it.

The ultimate result of the immunologic process in MS is damage to the myelin and destruction of nerve fibers or ***axons***. While myelin has the potential to regenerate to some degree, and does so early in the course of the disease, damaged axons do not regenerate. Once this damage has proceeded beyond a certain point, there are insufficient nerve fibers left to carry out normal functions, and permanent weakness, numbness, or visual loss begins to occur. Thus, much of the function lost during acute attacks early in the disease tends to be recovered, with the remaining fibers compensating for those that are lost. As the disease progresses, cumulative damage to myelin and nerve fibers leads to increasing, persistent neurologic dysfunction. Research has also demonstrated that some degree of brain atrophy, or shrinkage, occurs in MS, even in the early years of the illness. However, the cause or causes of this atrophy remain to be determined. At present, we do not know how to repair or restore myelin and are, therefore, unable to reverse the neurologic

symptoms, i.e., cure the disease. One hopeful sign is that we have recently come to realize that mammals, including humans, do have the capacity for spontaneous repair of central nervous system myelin and there is experimental evidence that this process can be favorably influenced.

When I have an exacerbation my doctor prescribes *intravenous* steroids (e.g., Solu-Medrol®). Why are steroids prescribed and what is the difference between steroids taken orally and those taken intravenously?

Steroids are a group of chemicals, some of which are naturally occurring hormones. They have many important hormonal functions but they have various additional effects when administered as medications (usually in synthetic preparations). Their utility in MS stems from their ability to decrease inflammation in the central nervous system, at least in part by closing the damaged ***blood-brain barrier.*** The steroids used in MS should not be confused with the anabolic steroids used by athletes to build muscle; the corticosteroids used in MS suppress inflammation.

Under normal circumstances, many potentially damaging substances are prevented by the blood-brain barrier from passing out of the blood stream into the brain and spinal cord. During attacks of MS, this barrier can break down and begin to allow damaging chemicals and cells to leak into the central nervous system. Inflammation then ensues, resulting in both ***acute*** neurologic injury—sometimes with accompanying symptoms—and ***chronic*** damage to myelin and axons. Steroids appear to decrease this inflammation.

Most neurologists caring for MS patients believe that steroids work best when given directly into the veins in high doses. We do not know whether equivalently high doses given orally would be equally effective, but some MS centers are taking this approach. In the past, it has been more common to prescribe lower doses of steroids orally. However, recent studies in patients with ***optic neuritis***, a condition that is often the first sign of MS, suggest that this strategy is less effective than high doses given intravenously.

Do steroids have any long-term benefits? I feel much stronger while I'm taking steroids but my doctor says they should not be used frequently or for very long periods. Why not?

Continuous administration of steroids has never been shown to provide long-term benefits for people with MS. There is some suggestion that short courses of high-dose intravenous steroids may have a longer-term benefit in delaying further disease activity. Many people feel better while taking steroids, in part because these drugs can have a mood-elevating effect. However, the chronic use of steroids is fraught with many potentially dangerous side effects and is currently thought to be unwise in the treatment of MS. Their long-term use can be associated with such side effects as hypertension, diabetes, bone loss (***osteoporosis***), cataracts, and ulcers. These potential detrimental effects outweigh the possible benefits when steroids are used on an extended basis.

When I take steroids I get very emotional and have intense mood swings. I also feel very down or depressed toward the end of the treatment. Why does this happen and is there anything to do about it?

Short courses of steroids, even in very high doses, are usually well-tolerated. Many people, however, do have some minor mood changes, both highs and lows. Others may have difficulty sleeping. A much smaller group of individuals may have more severe disturbances in mood or behavior. Lithium, a medication often prescribed for people with bipolar disorder (formerly called manic-depressive disorder), is sometimes used to prevent or manage these mood swings. Carbamazepine (Tegretol®) and divalproex (Depakote®) have also been shown to be very effective. On occasion, antidepressant medications may be prescribed, but they are seldom needed because the "blues" associated with a short course of steroids usually disappear spontaneously before the antidepressants would begin to take effect (usually a few weeks).

Once a promising new treatment has been identified, why does it take such a long time for it to be available for patients?

Unfortunately, the process of new drug development is very slow, particularly for a chronic disease like MS. The typical sequence initially begins with animal studies (see Fig. 3-1). This is a crucial first step because an experimental model for MS, ***experimental allergic encephalomyelitis (EAE)***, exists in laboratory rodents (as well as other species). This allows a quick

Figure 3-1. Summary table of steps involved in the development of a new drug

◇ Preclinical Phase	Animal studies
◇ Phase I	Preliminary human clinical trials ✣ small, unblinded, open label trials (for safety)
◇ Phase II	✣ small, often double-blind, for additional safety and efficacy information
◇ Phase III	Multicenter, randomized, double-blind, placebo-controlled trials needed for FDA approval
◇ Data Analysis	
◇ Application for approval of drug by the FDA	
◇ Pharmaceutical company brings drug to market	

assessment of the possible benefits of a treatment, as well as the preliminary evaluation of its safety. A promising agent then moves into human clinical trials.

Human clinical trials begin with very small "open label" (unblinded) trials in which the physicians *and* subjects know what drug is being taken. Initially, these are usually done in normal individuals without known disease. An unblinded trial is aimed at demonstrating the safety of a treatment and may be followed by an open trial in a few patients with known disease. These trials are typically of much shorter duration than later studies, but still take many months to a year or longer because of the variable nature of MS. The open label trials are then followed by relatively small, usually ***double-blind***, pilot trials designed to give stronger evidence suggesting that a new treatment may be effective as well as safe. "Double-blind" means that neither the subject nor the investigators know which subjects are receiving the real medication and which are getting the placebo (an inactive substance). This procedure is followed in order to prevent hopes and expectations on the part of researchers or subjects from affecting the course or evaluation of the treatment.

If the drug still appears promising, testing will move into Phase III, involving large, multicenter, randomized, placebo-controlled, double-blind trials. In this stage of drug development, typically hundreds of subjects are entered into a study in which some are randomly assigned to receive the medication and others to get placebo. Because MS is a chronic disease in which changes occur relatively slowly in most people, these

Phase III trials typically last for several years in order to obtain enough information on which to base fair and statistically valid conclusions. These trials are expensive, costing many millions of dollars that are essentially wasted if the drug does not work. This accounts, in large part, for the high cost of new drugs.

Following the completion of the trial, another six months may be necessary to analyze the large quantity of data and prepare submission of documents to the Food and Drug Administration (FDA). The FDA, which is ultimately responsible for the approval of new drugs, carefully reviews both the data and the methodology of the trial. This agency must be convinced of both the *effectiveness* and *safety* of the treatment before giving its approval. The review process typically takes another six to twelve months. Finally, after approval of a drug, the pharmaceutical company typically needs a few more months to get the drug to market.

Thus, the process is extremely long and arduous, as well as very frustrating for people with MS and their families. However, it is a process designed to assure that everyone receives safe treatments and that no one misses out on the opportunity to take other, potentially useful treatments while taking something that is ineffective. The problem with many of the publicly acclaimed "treatments" that receive so much attention in the press (e.g., snake venom and the removal of tooth amalgams) is that they have not been through this process. In other words, they have not been proven to be safe or effective in a clinical trial and can sometimes be quite harmful.

What is the "placebo effect?"

A placebo is a non-active substance that is designed to look just like the drug that is being evaluated in a research protocol. Investigators repeatedly find that a substantial proportion of patients with a variety of diseases experience some benefit even when they are treated with a placebo. This phenomenon is known as the ***placebo effect***. Although this effect may occur in part through unconscious psychological mechanisms, some studies have also demonstrated the production of certain chemicals in such individuals that may contribute to this improvement. Even though the benefits are not usually sustained, this short-lived effect confounds the study of new drugs. Randomized, placebo-controlled, double-blind trials are used in order to

determine the advantage (if any) that the new drug shows over placebo effects. Thus, to demonstrate the value of a new treatment, it must be proven to have a benefit *superior* to that offered by a placebo.

It is important to remember that being treated with a placebo is not the same as receiving *no* treatment. Taking the placebo fosters certain expectations for improvement that are not present when no treatment is given. That is why new drugs are always compared with a placebo rather than with no treatment at all. The drug must demonstrate a specific benefit beyond the placebo effect or the improvement that might occur spontaneously with no treatment, or with an existing treatment. Now, with the availability of several treatments for relapsing-remitting MS, many future trials will probably compare a new drug with an existing drug rather than with placebo.

If alternative treatments like bee stings and cobra venom work well for some people, why aren't they more widely prescribed?

Alternative treatments for MS such as bee stings are often touted as helping people with MS. The problem is that these reports are always "anecdotal"; they consist mostly of individual *claims* of success, without any scientific study. It is well-known that MS often undergoes spontaneous improvement or remission. Furthermore, as discussed previously, virtually every study of MS indicates a significant placebo effect, whereby people taking placebo (non-active substance) do better than they would with no treatment. Therefore, claims of success with any therapy, including alternative treatments, must be regarded with considerable skepticism unless controlled clinical trials are done. Additionally, some of these treatments, such as bee stings, carry potentially severe risks. Specifically, fatal allergic reactions can occur in some individuals receiving bee stings. These comments are not to suggest that there might not be merit to some alternative treatments, but rather to emphasize the importance of proper scientific investigation under controlled and *safe* conditions.

Who designs clinical trials and decides when and where they will take place, and who can participate?

Clinical trials may originate from several different sources. Early trials are often initiated by investigators interested in MS, whereas more definitive trials of promising new treatments are

generally undertaken by pharmaceutical companies interested in marketing a product. Although these companies often have physicians and basic scientists in their direct employment, they usually recruit outside investigators to help plan a clinical trial. Then, depending on the size of the study, additional investigators are invited to participate in the trial in order to enter the required number of subjects as quickly as possible. The lead investigators design the protocol or format for the trial, deciding how the trial will be carried out and who will be eligible to participate. The design of the trial is then submitted to the Food and Drug Administration for approval before the trial is begun.

How can I get into a clinical trial?

Various sources of information about clinical trials are available. The best place to start is with your own physician, who will often be able to direct you to a particular trial. The National Multiple Sclerosis Society can also provide information about the sites participating in particular clinical trials. Some of the local chapters of the National Multiple Sclerosis Society publish newsletters in which they announce trials in their area. Many of the member centers of the Consortium of Multiple Sclerosis Centers (see Appendix E, Resources) participate in one or more clinical trials. It is important to remember that each trial has a very specific protocol that details the types of patients who are eligible to participate. For some trials, the eligibility criteria are quite restrictive; for others, the criteria are more liberal. Your willingness to participate in a clinical trial is greatly appreciated by investigators because successful completion of such studies is the only way that we will definitively identify effective new treatments. Do not be discouraged if you do not meet the entrance criteria for a particular trial. Keep informed—the next one might be right for you.

Why should I participate in a clinical trial if I have a significant chance of getting the placebo instead of the real drug?

There are several reasons to participate in clinical trials.

- ◇ It has been demonstrated repeatedly in MS trials that even those subjects who receive the placebo usually do better than they would have done without any intervention. The quality of medical care in trials tends to be very high, and is provided without cost to the participants.

- ◇ Clinical trials are the best mechanism currently available to identify effective treatments; therefore, your participation ultimately helps investigators answer important questions.
- ◇ Standard, accepted treatments continue to be allowed under the research protocols of most placebo-controlled trials. For example, acute exacerbations could be treated with steroids in the interferon beta-1b (Betaseron®) and interferon beta-1a (Avonex®) trials.
- ◇ With Betaseron®, Avonex®, and Copaxone® currently available in the United States, Rebif® available in Canada and Europe, and Novantrone® recommended for approval by the FDA, it is likely that we will shift away from placebo-controlled trials to drug comparison trials in which a proposed new drug will be compared with the most effective available drug. Thus, any proposed new drug would have to demonstrate its superiority over those that have already been approved for use. Participants in this type of drug comparison trial would therefore be randomly assigned to either the proposed drug or one that has already been shown to be effective in treating MS.

Why do so many clinical trials require that participants be able to walk?

The entrance criteria for particular trials are very specific. Many of the trials require that subjects be able to walk, sometimes without the use of aids. This requirement is made because it is often more difficult to detect changes in disease activity in individuals whose illness is more advanced, and the inclusion of people with more advanced disease might cause investigators to discard potentially useful treatments because they erroneously failed to detect a benefit.

Why were the disease-modifying agents (Betaseron®, Avonex®, Copaxone®, and Rebif® [not available in U.S.]) originally tested on people with relapsing-remitting disease?

These agents (see Appendix B) were originally tested on people with relapsing-remitting MS because investigators thought those with milder disease would be more likely to show a benefit from the treatment. Also, previous studies had shown that it might be

easier to demonstrate an effect by measuring a reduction in attack rate than by showing a reduction in disease progression.

How does Copaxone® differ from the interferon medications, Betaseron®, Avonex®, and Rebif® [not available in U.S]?

Betaseron®, Avonex®, and Rebif® are interferons, a group of immune system proteins, produced and released by cells infected by a virus, which inhibit viral multiplication and modify the body's immune response. Copaxone® is unrelated to the interferons. It is a synthetic polypeptide (like a protein) that may act by fooling the immune system, and by suppressing the immune attack on myelin that is believed to occur in MS.

Copaxone® is administered by daily subcutaneous (under the skin) injection. Unlike Betaseron®, Avonex®, and Rebif®, it does not cause flu-like reactions. Injection-site reactions are generally minor. Depression, which has been associated with all interferons administered in high doses for human disease, does not occur with Copaxone®. However, people who are taking Copaxone® should be aware of one peculiar reaction that, although infrequent, can be quite alarming. On rare occasions (perhaps once in 800 to 1,000 injections), a person taking Copaxone® may experience an immediate post-injection reaction involving sensations of tightness in the chest and flushing of the face, perhaps accompanied by palpitations, shortness of breath, or anxiety. This reaction passes within 15 to 30 minutes and has never proved to be serious.

Table 3-1 compares the four drugs currently approved for the treatment of relapsing-remitting MS. *Note: Betaseron®, Avonex®, and Copaxone® have been approved in the United States and Canada. Betaseron® is approved in Canada and Europe for both relapsing-remitting and secondary-progressive MS. To date, Rebif® has been approved only in Canada and Europe.*

At a recent MS educational meeting, sponsored by my local chapter of the National Multiple Sclerosis Society, I heard about a drug named Rebif®. What is it, and why isn't it available in the United States?

Rebif®, like Avonex®, is beta interferon-1a. In a multicenter trial in Canada, Europe, and Australia, for relapsing-remitting disease, Rebif® was found to reduce the number and frequency of MS attacks, slow the progression of disability, and reduce the

number of brain lesions as measured by magnetic resonance imaging (MRI). It also reduced the number of hospitalizations and steroid use. The drug was tested in two dose strengths, administered subcutaneously three times per week. In this study, amounts of interferon beta-1a were higher on a weekly basis (by weight) at each dose than the weekly amount of Avonex® that has been approved by the FDA for use in relapsing forms of MS. In addition, people with a broader range of disabilities were studied, and shown to benefit.

In a separate, three-year, controlled clinical trial of (Rebif®) for secondary progressive MS, two doses of the drug were compared to placebo. Compared to placebo, neither dose of Rebif® delayed progression of disability (the primary goal of the study). However, both treated groups had significantly fewer and less severe relapses, fewer hospitalizations, reduced use of steroids, and fewer total lesions and new lesions in the brain as detected by MRI. The manufacturer of the drug has suggested that the failure to delay progression of disability in these secondary-progressive patients (in contrast to their positive findings in relapsing-remitting disease) may be due to the fact that the patients in this study started with higher levels of disability and had had the disease longer than the patients in previous studies.

Rebif® is now available for use in some countries. The trial sponsor, Ares Serono, has applied to the FDA for approval to market Rebif® in the United States as a treatment for relapsing-remitting MS. The FDA ruled that Rebif® was not sufficiently different from Avonex® to be marketed in the United States at this time. Under the provisions of the U.S. Orphan Drug Act, which provides financial incentives to the developers of drugs for rare diseases, Rebif® may not be allowed to compete with Avonex® on the U.S. market until 2003 unless Rebif® can be shown to be clinically superior to other products currently on the market. This ruling was made to allow the manufacturers of Avonex® time to recoup some of their costs. While this is frustrating for people with MS in the United States, the importance of the Orphan Drug Act should not be underestimated. Without the protections provided by this law, pharmaceutical companies would be unable, and unwilling, to undertake the development of new drugs for diseases like MS that affect relatively small numbers of people.

Table 3-1

BRAND AND GENERIC NAME			
Betaseron® Interferon beta-1b	Avonex® Interferon beta-1a	Copaxone® Glatiramer acetate	Rebif® Interferon beta-1a
MANUFACTURER/DISTRIBUTOR			
Berlex	Biogen	TevaMarion Partners	Serono Laboratories (U.S.), Serono Canada
APPROVAL			
1993 U.S. 1995 Canada (R-R) 1999 Canada (S-P)	1996 U.S. 1998 Canada	1996 U.S. 1997 Canada	1998 Canada
FREQUENCY/ROUTE OF DELIVERY			
Every other day; subcutaneous injection	Weekly; intramuscular injection	Daily; subcutaneous injection	Three times per week; subcutaneous injection
COMMON SIDE EFFECTS			
Flu symptoms following injection, which lessen over time for many people; injection site reactions, about 5% of which need medical attention. Rarer: elevated liver enzymes, low white blood cell counts.	Flu symptoms following injection, which lessen over time for many people. Rarer: mild anemia, elevated liver enzymes.	Injection site reactions. Rarer: a reaction immediately after injection which includes anxiety, chest tightness, shortness of breath, and flushing. This lasts 15–30 minutes and has no known long-term effects.	Flu symptoms following injection, which lessen over time for many people; injection site reactions; Rarer: elevated liver enzymes, low white blood cell counts.

RETAIL COST, APPROXIMATE
(SOURCE: WWW.DRUGSTORE.COM)

$10,800/year* (U.S.) $17,000/year (Canada)	$11,000/year (U.S.) $16,970/year (Canada)	$10,000/year (U.S.) $12,300/year (Canada)	$17,000/year (Canada)-lower dose $21,000/year (Canada)-higher dose

PATIENT INFORMATION AND FINANCIAL SUPPORT PROGRAMS

"Pathways" 1-800-788-1467; 1-800-948-5777 (financial issues) www.betaseron.com	"Avonex Alliance" 1-800-456-2255 www.biogen.com	"Shared Solutions" 1-800-887-8100 www.tevamarionpartners.com	"Multiple Support Service": 1-888-MS-REBIF www.ms-network.com

Once I start taking one of the disease-modifying drugs (Betaseron®, Avonex®, Copaxone®, or Rebif® [not available in the United States]), how long will I need to take the medication?

No one knows how long a person "needs" to take these medications. Since none of these medications completely prevents disease activity, the occurrence of an occasional attack in someone taking one of these medications does not necessarily mean drug failure. Data from the original three-year trial of Betaseron® indicated that, compared to the group receiving a placebo, the group treated with high-dose Betaseron® (the same dose that is currently prescribed for patients) had about a 30 percent reduction in annual exacerbation rate and showed no increase in total amount of lesion area in the CNS as detected with MRI. Follow-up data from the original group of 372 individuals with ambulatory, relapsing-remitting MS in the interferon beta-1b trial indicate the continued benefit and safety of Betaseron® for up to 10 years.

Additional clinical data on the safety and efficacy of glatiramer acetate (Copaxone®) were reported in 1998. Data for up to 35 months of treatment showed that the beneficial effects of daily subcutaneous injection of the drug persist for at least three years, and the benefit tends to improve as time progresses. These benefits, which include a further reduction in the relapse rate and extended time to first relapse, also suggest a slowing of the progression of disability. Safety continues to be acceptable, and the drug continues to be well tolerated. Experience with Avonex® now extends to at least five years and suggests continued efficacy and safety as well.

After a year or longer on Betaseron®, there is some evidence that approximately 38 percent of individuals develop substances in the blood called antibodies—proteins of the immune system that protect the body from foreign substances such as viruses and bacteria. The development of neutralizing antibodies was originally thought to be associated with a reduction in treatment benefits in some individuals. Follow-up data from the Betaseron® trial initially indicated that the exacerbation rate of the subgroup of treated individuals who developed the antibodies was significantly higher than the exacerbation rate for those who did not develop antibodies; in fact, it did not differ from the exacerbation rate for the group receiving a placebo. More recent data, however, indicate that the antibody level declines again, so

that after a number of years they are no longer found. This means that there is no simple way for a person to determine his or her likelihood of developing antibodies to Betaseron®, or the impact that these antibodies are likely to have. Although similar neutralizing antibodies were reported in some of the patients in the Avonex® trial, data from the extension study show only about 5% of individuals developing antibodies. In the Rebif® trial, the relapse rate of those who developed neutralizing antibodies in the two treatment groups did not differ from the relapse rate of those who did not develop antibodies.

In general, people taking these medications should remain on the medication unless they are clearly having frequent attacks, significant disease progression, or severe side effects. Of course, the availability of newer effective treatments will require continual reassessment of an individual's situation.

I have been taking one of the disease-modifying agents for more than two years and I still don't feel better. Does this mean that the drug isn't working for me?

In the clinical trials of interferon beta-1b (Betaseron®), interferon beta-1a (Avonex® and Rebif®), and glatiramer acetate (Copaxone®), there was no evidence that the drugs made the treatment groups "feel better." Betaseron® was found to reduce the frequency and severity of exacerbations in relapsing-remitting MS. Avonex® reduced the frequency of relapses and slowed disease progression. Copaxone® reduced the frequency of exacerbations. Rebif® was found to reduce attack frequency and slow progression of disability. And all four drugs showed a reduction in new or active lesions on MRI. Although a significant effort has been made to inform people about the possible benefits and limitations of these treatments, it is clear that many people harbor a hope that they will feel better as a result of taking one of these treatments. This is not particularly surprising since most people's life experience with medical treatment in general, and medication in particular, is that it is designed to make a person feel better.

In a study of 100 individuals eligible for Betaseron® (funded by the National Multiple Sclerosis Society at the University of California, San Francisco), a significant proportion of those surveyed had misconceptions about the drug's potential effects. More than 80 percent expected that the drug would reduce their

level of physical discomfort and improve their overall quality of life. Unfortunately, misconceptions such as these may cause people to become disappointed or dissatisfied with the effects of the drug they are taking and stop it prematurely, even if the drug is working for them in ways they cannot readily see or feel.

Since it is not possible to evaluate the extent to which any of these drugs is working for any one individual at any particular point in time, it is advisable for you to remain on the drug unless you are having frequent attacks, rapid disease progression, or severe side effects.

Why do all of these medications have to be taken by injection?

Injection is the only route of administration that has been shown to be effective at the present time. Betaseron®, Avonex®, and Rebif® are proteins, and proteins are degraded in the stomach and intestinal tract. The degradation products may not have the same effects in modulating the immune system that the intact molecule has. Copaxone® is a synthetic polypeptide (like a protein) that is unrelated to the interferons. An oral form of Copaxone® has been tested very successfully in EAE, the animal model of multiple sclerosis, and a major trial in MS is being launched. Oral and inhaled forms of interferons are also in development.

What will happen if I lose track of the date and forget to give myself a shot of Betaseron®, Avonex®, Copaxone®, or Rebif®?

Missing an occasional Betaseron® or Rebif® injection is not thought to be harmful. If that should happen, just give yourself the injection at the next most appropriate opportunity and continue the every-other-day routine from that point. The same holds true for Copaxone®. If you miss an injection, simply continue with your daily routine as soon as you remember. Do not, however, take two injections in one day. If you miss a dose of Avonex®, take it as soon as you remember and continue on a weekly schedule. Do not, however, take two doses within two days of each other.

Why are the disease-modifying medications so expensive and will the cost of these drugs ever come down?

These drugs are expensive for several reasons. First, the technology to develop and produce them is highly specialized.

Interferon beta-1b and interferon beta-1a are not naturally occurring substances. They are produced in the laboratory—grown in, and harvested from, bacteria and mammalian cells respectively. Glatiramer acetate is synthesized in a complex process that is difficult to standardize and requires precise control to maintain standardization. Manufacturing is thus complex and costly. More importantly, however, the costs of developing the products are extremely high and are passed along to the consumer. It is important to realize that for every drug that does reach the marketplace, dozens of others have failed to achieve that goal. The costs of testing those unsuccessful drugs must also be recouped through sales of the drugs that are successful.

Unfortunately for the public, pharmaceutical companies, like all other businesses, have a fiduciary obligation to their stockholders to try to maximize profits. Therefore, new drugs are generally quite expensive, especially those without similar competitive medications. With the approval of additional treatments, many people expect that competition may bring down the cost of these drugs.

I have recently been diagnosed with MS and have no apparent symptoms at this time. Should I start taking Betaseron®, Avonex®, Copaxone®, or Rebif® [not available in U.S.] right away?

The decision to begin one of these medications should be made with your physician, taking into account your history, current symptoms, exacerbation rate, and any evidence on MRI of new lesion development. In general, the person whose disease shows signs of relatively recent activity is the likeliest candidate to benefit from the treatment. Although people who are feeling and doing relatively well may see little reason to begin one of these medications, the fact is that multiple sclerosis is a very unpredictable disease. These medications are designed to reduce the number and severity of attacks in the hope that they will slow disease progression *over the long term*. Particularly in light of the new data indicating irreversible axonal damage, and possible brain atrophy even in the early stages of the disease, it is important to consider these medications carefully. Most MS experts now believe that one of the medications should be started early in the course of the disease, before significant, perma-

nent damage occurs. Thus, if there are clear signs on clinical examination or on MRI that the disease process is active, *even if you are not currently experiencing significant symptoms*, most experts would favor initiating treatment. The National Multiple Sclerosis Society has recently published a Consensus Statement of the Medical Advisory Board advocating early and sustained treatment with one of these medications for individuals with relapsing forms of MS (see Appendix C).

Recently there have been reports about axonal damage and brain atrophy that can occur even in the early stages of MS. Can you tell me what these terms mean?

It is generally believed that the inflammatory process in MS causes damage primarily to the myelin sheath surrounding the nerve fibers in the central nervous system. Since the earliest descriptions of MS pathology, however, it has been known that the nerve fibers (axons) themselves also sustain damage. While inflammation is probably responsible for this phenomenon as well, the details of how axonal damage occurs remain unclear. Recent research has confirmed that nerve fibers can be affected or even severed in MS, and that this damage can occur very early in the disease. There is some speculation that this damage to the axons may be responsible for the permanent symptoms or impairments that can occur in MS.

Damage to nerve fibers and their loss may be partly responsible for the recently confirmed "atrophy" or brain shrinkage that occurs in MS. Loss of myelin and changes in brain fluids are also likely contributors. While myelin has the potential capacity to regrow, at least early in the disease, the regrowth of nerve fibers is much more problematic.

Perhaps the greatest significance of these findings lies in the fact that these irrevocable changes can occur early in the disease. It is in part because of these findings that MS experts are advocating early treatment, with one of the disease-modifying agents, for anyone with a confirmed diagnosis of relapsing-remitting MS. The goal is to slow the progression of the disease and prevent as much of this early, irreversible damage as possible.

What are the long-term side effects of taking the interferons (Betaseron®, Avonex®, and Rebif®) or glatiramer acetate (Copaxone®)? Will I get cancer because of these drugs?

No severe, long-term side effects have as yet been recognized with the use of these treatments. However, it is important to realize that only very small numbers of people have taken the drug for more than a few years. There is nothing at present to suggest an increased risk of cancer in people taking Betaseron®, Avonex®, Copaxone®, or Rebif®.

Follow-up data from the original group of 372 individuals with ambulatory relapsing-remitting MS in the interferon beta-1b trial showed a significant drop over time in the numbers of people experiencing flu-like symptoms and injection-site reactions. While 76 percent of the high-dose treatment group experienced flu-like symptoms during the initial months of the clinical trial, only 3 percent to 8 percent of this group reported these symptoms through the next five years. Similarly, the injection-site reactions experienced by 80 percent of the high-dose group in the early months of the trial were reported by 44 percent to 50 percent of this group in years four and five. Thus, most people taking Betaseron® over an extended period of time seem to be doing so with relatively little problem or discomfort.

In the Avonex® trial, 4 percent of patients discontinued the drug due to adverse effects. Modest side effects, including flu-like symptoms, muscle aches, fever, chills, and weakness, diminished with continued treatment. Four percent of patients experienced mild injection-site reactions.

During the two-year Rebif® trial, 3 percent of patients discontinued the drug due to adverse effects. The flulike symptoms and injection-site reactions tended to diminish with time. No long-term follow-up data on these subjects are yet available.

There are no long-term adverse effects known for Copaxone®.

If I have an exacerbation while I'm taking Betaseron®, Avonex®, Copaxone®, or Rebif®, can I still be given intravenous steroids?

Individuals taking any of these medications can still be treated with intravenous steroids in the same manner as those not on the medication.

I read on the Internet that some people with MS are being prescribed double doses of their injectable medication. Are double doses more effective that single doses, and will the insurance companies pay for them?

At the present time, little information is available to permit a reliable decision about what is the most effective, well-tolerated dose of the currently available injectable medications for MS. The recommended dose of Betaseron® was based on a very small pilot trial, which suggested that this was the maximum dose that was reasonably well tolerated. Nonetheless, recent trials of the drug in patients with secondary progressive MS have included some individuals who received slightly higher doses, based on their body weight.

It is difficult to compare doses of Betaseron® and Avonex®. Although both are interferon beta preparations, the drugs are chemically slightly different. In addition, their different routes of delivery (subcutaneous vs. intramuscular, respectively) can affect dose response. However, some experts do believe that the currently FDA-approved dose of Avonex® may not be maximally effective. Higher doses are likely to be tolerated, and are currently being tested in the Avonex® trial for secondary-progressive disease and in a dose-response study in Europe for relapsing-remitting MS. Rebif® (also interferon beta-1a) was recently tested successfully in Europe using three injections per week, thus providing a much larger, weekly dose of medication.

Despite the possibility that higher doses of the interferons may ultimately prove better, at the present time there remains insufficient information to justify their routine administration. Furthermore, it is extremely unlikely that insurance companies will be willing to pay for the higher doses unless and until there is more conclusive evidence of their effectiveness.

Very little is known about the optimal dose of Copaxone®. The current dose of 20 mg daily was rather arbitrarily chosen for the clinical trials. In one small trial in progressive MS, 30 mg was administered daily in two divided doses. This higher dose was well tolerated, but the trial did not show any convincing benefit for progressive disease.

My MS used to be relapsing-remitting. Now that it seems to be secondary progressive, would Betaseron®, Avonex®, Copaxone®, or Rebif® still be appropriate treatment for me?

In the United States, Betaseron®, Avonex®, and Copaxone® have been approved by the FDA solely for the treatment of relapsing-remitting MS. In Canada, Betaseron®, Avonex®, Copaxone®, and Rebif® are approved for relapsing-remitting MS. Following a

recent European trial that demonstrated the effectiveness of Betaseron® in secondary-progressive MS, the drug was also approved in Canada and Europe for secondary-progressive disease. A similar trial of Betaseron® in secondary-progressive MS is still underway in North America. The FDA is awaiting results of the North American trial before deciding whether to approve Betaseron® for use in secondary progressive MS. The Rebif® trial in secondary progressive MS did not show an effect on progression and its approval for the treatment of secondary progressive MS in Canada is still in question.

A study is currently underway with Avonex® to investigate its effectiveness in secondary progressive MS. One small trial of Copaxone® in progressive MS, done in the late 1980s, failed to show a statistically significant benefit, but the trial was too small to be conclusive. Currently, Copaxone® is being tested in a larger primary progressive trial.

From a theoretical standpoint, it is reasonable to believe that these agents may all be effective for secondary-progressive MS. Difficulty may be encountered in obtaining insurance coverage in the United States for treatment of secondary progressive MS with these drugs since the drugs have either not been tested or are not yet approved by the FDA for progressive disease. At the moment, the only choice available in Canada for those with secondary, progressive disease is Betaseron®.

I have progressive MS and I'm wondering what treatments are available for me.

The answer to your question depends, in part, on what you mean by "progressive MS." There are two recognized types of progression in MS: ***Primary progressive MS*** refers to a disease course that is characterized by progression of disability from the outset, without an early phase of acute attacks and remissions. This course is seen in only 15 percent or so of people with MS. ***Secondary progressive MS*** refers to a disease course that is initially relapsing-remitting but subsequently becomes more consistently progressive. Of the 85 percent of people with MS who start out with relapsing-remitting disease, more than half will develop secondary progressive within a period of 10 years, and 90 percent within 25 years.

Of the treatments that have already been approved by the FDA for relapsing-remitting MS, Copaxone® (glatiramer acetate) and

Avonex® (interferon beta-1a) are currently being studied in people with primary progressive disease. However, the results from these studies will not be available for a few years.

Avonex® is currently being studied in secondary progressive MS. A European trial of Betaseron® (interferon beta-1b) in secondary progressive MS was terminated prematurely due to overwhelmingly positive results, and the drug is now approved for this use in Europe and Canada. The results of a similar study in the United States are not yet available. The FDA's decision about the use of Betaseron® in secondary progressive MS is awaiting these results. A study of Rebif® (interferon beta-1a; not available in the United States) for secondary progressive MS showed no benefit on slowing progression of disease, although a positive effect on relapses was seen.

One immunosuppressive agent is likely to have an increasing role in the treatment of progressive MS. Novantrone® (mitoxantrone for injection concentrate) is a potent immunosuppressing agent that is approved by the FDA for use in adult myeloid leukemia and for pain associated with certain types of prostate cancer. Its modes of action include inhibition of cell division, suppression of immune system B cells and helper T cells, and modulation of other immune cells and substances.

In a large, multicenter, controlled clinical trial, 194 individuals with secondary progressive MS (*with or without relapses*) and mild to moderate disability were randomly assigned to a low-dose, high-dose, or placebo group. Treatment was delivered by intravenous infusion once every three months over 24 months. After two years of treatment, the high-dose group was significantly less likely than the placebo group to demonstrate increased disability on the EDSS rating scale. The high-dose group also experienced significantly fewer relapses requiring corticosteroid treatment. The beneficial effects of treatment continued through one year of post-treatment follow-up.

A second study, focusing on MRI findings in individuals with highly active MS, compared monthly infusions of Novantrone® plus intravenous steroids with intravenous steroids given alone, over a six-month period. Compared with those treated only with steroids, the subjects treated with Novantron® plus steroids demonstrated significantly lower numbers of active inflammato-

ry lesions in the brain, slower progression of disability, and reduced relapse rate.

The most common side effects in these two trials were nausea, hair loss, urinary and upper respiratory tract infections, and menstrual disorders. Cardiac toxicity has previously been reported, primarily in cancer patients exceeding a certain *cumulative* dosage level (i.e., accumulated level in the body over time). No cardiac toxicity was evident in the MS trials because none of the participants reached an equally high cumulative dose during the two years of the study.

Based on all of these findings, an advisory panel for the FDA recommended in January 2000 that the FDA approve Novantrone® to slow worsening of neurologic disability in people *with normal cardiac function* who have secondary progressive and relapsing-remitting forms of MS. Because of the dose-related toxicity that has been reported, its use will require cardiac monitoring above a certain cumulative dose and termination once the maximum cumulative dose is reached. Thus, Novantrone® will likely be prescribed to treat aggressive disease for a time-limited period, followed by one of the other available therapies. In fact, a trial is under way in Europe in which Novantrone® is being given in combination with methylprednisolone for six months, followed by interferon beta-1b for 27 months.

Although the FDA is not required to follow the advisory panel's recommendations, it usually does so. A final decision is expected in the near future. At the time of approval, the FDA will issue specific recommendations for the dosing and monitoring of Novantrone®.

Various other immunosuppressive agents (e.g., Imuran® (azathiaprine), Cytoxan® (cyclophosphamide), and methotrexate) have been used by some MS physicians to treat progressive disease; however, the clinical trials of these chemotherapeutic agents have not conclusively demonstrated their value for a broad spectrum of secondary progressive MS. A trial of cladribine failed to show benefit in progressive disease.

Thus, there is no simple answer to your question. Novantrone® is likely to be approved for the treatment of secondary-progressive disease very soon. While there are no currently approved treatments for primary progressive disease,

there is reason to be optimistic that some will become available in the not-too-distant future.

What is immunosuppressive therapy and will it make my MS better?

Immunosuppressive therapy utilizes treatment agents that dampen the body's natural immune response, which is designed to protect it from foreign substances. In MS, we believe the immune system mistakenly attacks the person's own myelin as if it were foreign. By suppressing the immune system, such therapy may reduce the severity of the attack and thus reduce further damage to the myelin in the nervous system.

Immunosuppressive drugs such as mitoxantrone, cyclophosphamide, methotrexate, and azathioprine have been shown to slow the progression of MS. An advisory panel to the FDA has recently recommended that mitoxantrone (Novantrone®) be approved by the FDA for use in secondary progressive and relapsing-remitting forms of MS to slow worsening of neurologic disability. Cyclophosphamide proved too toxic for widespread acceptance by physicians or their patients. Methotrexate has been used in cancer treatment, for immunosuppression in organ transplantation, and for the treatment of rheumatoid arthritis. In relatively low doses, it has been shown to slow the rate of progression in MS. However, methotrexate is potentially toxic to the liver, and treatment with this drug must be carefully monitored. It is not compatible with nonsteroidal antiinflammatory drugs (e.g., aspirin or ibuprofen) or with alcohol, so that the use of methotrexate involves a number of restrictions. It is currently being used in some individuals with progressive MS. There is some evidence that azathioprine may slow progression in MS, but the effect, if it exists, is small and somewhat controversial.

All treatments currently available or in advanced stages of testing are aimed to reduce further damage. Of course, individuals with MS often improve spontaneously. However, the longer symptoms of MS have been present, the lower the likelihood that this spontaneous improvement will occur.

Now that there are several disease-modifying treatments available, how will I know whether to continue with my current treatment or try one of the others?

This is a question to be answered by you and your physician. The three therapies currently available in the United States have similar effectiveness but somewhat different side effect profiles. If side effects are causing significant problems, one of the other medications may be better tolerated. If you are doing well on what you are taking, however, you probably should not change since there is a certain period of time required for any treatment to take effect in your body.

While the mode of action of interferon beta-1b (Betaseron®) and interferon beta-1a (Avonex® and Rebif®) are probably identical, the third drug, glatiramer acetate (Copaxone®), is completely unrelated to the interferons. It is believed to "fool" the immune system in some way and interfere with its ability to damage myelin.

We currently have no data comparing the relative effectiveness of the three drugs. Many MS specialists believe that the dose of Avonex® may be sub-optimal, and that some people will require higher doses of interferon. This conclusion is derived principally from studies of Rebif®, an identical interferon to Avonex®, produced by another pharmaceutical company. Clinical trials with this agent showed substantially better responses, both clinically and on MRI, when the drug was administered three times a week rather than once. A study funded by Serono (the makers of Rebif®) is currently under way to compare the relative efficacy of Avonex® and Rebif®.

My friend's doctor recently started him on a combination of Copaxone® and Avonex®. Does combining these drugs provide more protection than either one of them alone?

Many people with MS, as well as MS investigators, would like to see results of a trial combining one of the interferons with glatiramer acetate (Copaxone®). Although this pairing might be beneficial, it is also possible that the combination could pose unexpected hazards (as seen in animal studies using this combination) or be less effective than either drug used alone. A current small pilot trial is examining the safety of Copaxone® and Avonex® used together in humans with MS, by evaluating their effect on MRI scans over a six-month period. If this trial does not lead to disease worsening or other unforeseen problems, it is probably that a full-scale trial of the two drugs together will be undertak-

en. In the meantime, there does not appear to be sufficient safety and efficacy information available to warrant use of two agents simultaneously, making it highly unlikely that insurance companies will be willing to pay for two drugs at the same time.

My family is worried about my using Betaseron® because of the reported suicides. What is the risk of depression and/or suicide with this drug?

Depression is very common in people with MS. Fortunately, however, it is usually not severe and generally responds well to a combination of psychotherapy and medication. Nevertheless, suicide occurs more frequently among people with MS than among comparable groups of people without the disease. In the Betaseron® definitive trial, four suicide attempts and one completed suicide occurred. Because of the frequency of depression and suicide in the MS population (see Chapter 11) and the small number of events in the trial, one cannot conclude that these episodes of depression were caused by the drug. It is known, however, that very high doses of interferon, such as those used in cancer treatment, do cause depression. As a result of concerns about interferons and depression, the emotional state of patients receiving these drugs has been followed carefully since marketing. In addition, the subjects in the Rebif® trial, who were receiving higher doses of interferon than subjects in previous interferon trials, were carefully monitored for depression. Rates of depression and suicide did not differ between the two treatment groups (high and low dose) and the group receiving a placebo. Now that more experience with these agents has been gained, severe depression and suicide seem to occur among individuals taking interferons at the same rate as they occur in the general MS population.

The best recommendation is that people with a previous history of severe affective disorder (depression or bipolar [manic-depressive] illness), or previous suicide attempts, should probably not take either interferon beta-1b (Betaseron®) or interferon beta-1a (Avonex®). Individuals with milder forms of depression can probably safely take Betaseron® or Avonex® under close supervision. Family members, other loved ones, and caregivers should be advised to be alert to any changes in mood and report them promptly to the physician. Sometimes the physician will wish to

consult with a psychiatrist before starting a person on interferon beta-1b or interferon beta-1a, even though no suicide attempts or serious depression occurred in individuals in the Avonex® trial.

My doctor has recommended that I begin taking one of the interferons (Betaseron® or Avonex®). I've been reading about them on the Internet and hearing about the side effects people experience with these drugs. I'm reluctant to start an interferon because I don't want to feel worse than I already do.

The Internet has been a useful forum for people to exchange views and information about MS. It is probably a fact of life, however, that people tend to report side effects and problems more commonly than they "go on record" with positive feelings. Certainly, side effects do occur with Betaseron® and Avonex®. Most common are flulike symptoms that occur primarily in the first few months of treatment. For the majority of people, these are relatively mild and can be managed by taking injections at night and using minor analgesics (pain relievers), such as ibuprofen or acetaminophen. People taking Betaseron® also experience local injection-site reactions. Most typically these are confined to the appearance of red blotches and, perhaps, minor pain. Only infrequently do more severe reactions occur that may necessitate stopping the medication. We now have experience with many thousands of people taking Betaseron® or Avonex®. In general, with proper education and support from physicians and nurses, the medications are well tolerated and people can readily continue taking them. Overall, perhaps about 15 percent of people need to discontinue treatment for one reason or another and, certainly, not all of these are because of side effects.

One of the people in my MS support group is getting a treatment called IVIg. What can you tell me about it?

Intravenous immunoglobulin (IVIg) is a treatment that has been used in other autoimmune disorders, including neurologic diseases such as myasthenia gravis and Guillain-Barré syndrome, although the mechanism of action in any of these disorders is not known. IVIg, which consists of the antibody-containing portion of blood collected and fractionated from pools of donors, requires periodic intravenous administration. Several different

treatment schedules have been employed, but most have involved monthly infusions.

Several reports have now indicated a beneficial effect in MS. All of these studies have evaluated the treatment with relapsing disease. No data have yet been reported for individuals with progressive forms of MS. Direct comparisons of the effectiveness of this treatment with those approved by the FDA—Betaseron®, Avonex®, and Copaxone®—are not available.

The treatment is generally well tolerated, although kidney problems may occur, and there is some concern about potential liver damage. Because IVIg is derived from natural blood products, there can be inconsistencies between batches and a potential risk from blood-borne viruses. For these reasons, IVIg is not considered by many North American experts in the field to be the treatment of choice for MS.

Insurance companies are likely to vary in their willingness to pay for the treatment, the costs of which tend to be higher than those for the other injectable medications.

I recently heard a news report about plasma exchange as a treatment for MS. I was just diagnosed and would like to know where I can get this treatment.

Although a recent study of ***plasma exchange*** (also called plasmapheresis) suggested a significant potential benefit for certain individuals with MS, its use is not appropriate for everyone. The study included 12 people with MS and 10 people with other disorders involving myelin destruction in the brain and spinal cord. *All subjects in the study were experiencing acute, severe attacks that had failed to respond to standard treatment with high-dose steroids.*

Before the plasma exchange, neurologists selected for each study participant one or two neurologic deficits or disabilities, resulting from the acute attack, that were to be the target of treatment. After plasma exchange, four of the 12 study participants with MS showed improvement in at least one of their targeted deficits and were considered treatment successes. For these individuals, plasma exchange was a major treatment intervention, resulting in a degree of recovery that would otherwise have been impossible

The investigators concluded that plasma exchange might contribute to recovery from an acute attack in people with MS or other inflammatory demyelinating diseases who have not

responded to standard steroid treatment. They recommend, therefore, that this treatment *only be considered for individuals experiencing a severe, acute attack that is not responding to high-dose steroids.* Since the vast majority (approximately 90 percent) of people experiencing acute attacks respond well to the standard steroid treatment, plasma exchange would be considered a treatment alternative only for the 10 percent or so who do not. For those 10 percent, however, plasma exchange may offer an important and beneficial treatment option.

The plasma exchange procedure can be performed at most major medical centers without hospitalization. It involves seven treatments over a 14-day period, and costs approximately $18,000. Because this treatment is considered experimental for MS, the cost is not likely to be covered by most insurance carriers. The procedure also carries with it certain risks, including anemia and infection.

What new drugs are currently being tested for MS and how do they differ?

The following is a partial list of current and planned drug trials, divided by the type of MS being studied. Because this list is an ever-changing one, it is provided here merely to give an idea of the range of potential treatments currently under evaluation.

Acute Attacks: *gamma globulin; monoclonal antibodies*

Relapsing Forms of MS: *glatiramer acetate (in oral form; in children with MS); interferon alpha (oral); interferon beta-1a + glatiramer acetate; monoclonal antibodies; peptide therapy; T cell vaccination; valacyclovir; vitamin D*

Progressive Forms of MS (including all forms of progressive disease, separately or in combination): *bone marrow transplantation; glatiramer acetate; interferon beta-1a; interferon beta-1b; mitoxantrone; T cell vaccination; valacyclovir*

Combined Relapsing and Progressive Forms of MS: *aspirin; gancyclovir; estriol*

Is it possible to replace or repair the myelin that has been destroyed by MS?

It is not currently possible to enhance or improve myelin repair in MS. However, recent animal and laboratory investigations

have shown that myelin repair occurs spontaneously in mammals and that this repair can be enhanced in animals. Some myelin repair occurs naturally in MS, particularly early in the disease, and this may be an important aspect of recovery from attacks. Further study is underway to try to find ways to enhance myelin repair in humans.

I have a friend who is taking 4-AP for his MS. What is 4-AP and is it likely to help me?

4-AP, which stands for 4-aminopyridine, is a chemical that acts on the channels in nerve fibers that control the passage of potassium. In so doing, it appears able to improve temporarily the transmission of impulses through these fibers. Some individuals with MS have experienced improvement in neurologic symptoms when taking 4-AP orally. In particular, it seemed to help some people whose MS was heat-sensitive. Although 4-AP has never had FDA approval, a physician could legally write a prescription for the chemical to be made up for a patient by a compounding pharmacy that would put the substance into a medicinal form.

Recently, however, the FDA recommended that pharmacies no longer be allowed to compound this substance because of significant safety problems and problems with inconsistency in products made by compounding pharmacies. 4-AP has a number of potentially serious side effects, most noteworthy of which are seizures. Furthermore, it has a low toxic-therapeutic index, meaning that the dose that may cause problems is not very much higher than that which may be beneficial. Because compounding pharmacies may not have the same high level of standardization controls that exist for prescription drugs marketed by regulated pharmaceutical companies, a lack of precision about dosage may pose significant risks to people who obtain the substance from compounding pharmacies.

Oral myelin is sold at my local health food store. Will this product help my MS symptoms?

Oral myelin did not produce detectable benefit in a recent therapeutic trial so it is unlikely that the product sold in your local health food store will be helpful. Unfortunately, preparations touted as containing oral myelin are presently being sold at

many health food stores. Such products are essentially unregulated. The amounts of oral myelin that they contain are unknown, but usually much smaller than that which was tested. Furthermore, the source of the product is generally not indicated. Certain herds of cattle, though not those in the United States, have harbored a fatal, transmissible disease that may pose risks to humans. Extreme precautions were taken to eliminate any risk to subjects in the FDA-approved trial of Myloral®, but the same cannot be said for these uncontrolled products distributed through health food stores.

One of my friends recommended that I try marijuana to relieve my MS symptoms. Is marijuana an effective treatment for MS?

Smoking marijuana has been reported by some individuals to benefit some of their symptoms, particularly spasticity. However, small clinical trials of orally-administered tetra-hydrocannabinol (THC), the active chemical in marijuana, have had mixed results. While some treated individuals reported feeling "looser" and less stiff, objective evaluations by physicians could not always confirm any change. Effects lasted less than three hours, and side effects included weakness, dry mouth, dizziness, mental clouding, short-term memory impairment, space-time distortions, and incoordination.

In March 1999, the National Academy of Sciences/Institute of Medicine released their White House-commissioned report on medical uses of marijuana. The report stated that the medical benefits of marijuana are modest, and that for most symptoms, more effective medicines are already available. The report did recommend, however, continued research on the biological effects of cannabinoids, the active compounds in marijuana, to determine if it is possible to derive their benefits without their detrimental side effects. In the meantime, the use of marijuana is not legal for the treatment of MS.

My friends and relatives are always pushing me to try different diets and vitamins. Does diet have any effect on this disease?

Many diets have been touted as being useful for MS, but none has ever demonstrated its efficacy in a controlled trial. While some of these (e.g., the popular Swank diet) are generally healthful if extremely demanding, others are inconvenient, and some

are possibly harmful. The same is true for vitamins and other supplements, none of which has been shown to help MS. It is clear, however, that maintenance of good health and physical condition is valuable and may help a person with MS cope better with the physical and emotional challenges of the neurologic disease. Thus, a diet such as the American Heart Association diet—which resembles the Swank diet but is a little less rigid—may be worthwhile if a person with MS wants to follow a nutritional regimen.

Recommended Readings

Giffels JJ. *Clinical Trials: What You Should Know Before Volunteering to Be a Research Subject.* New York: Demos Vermande, 1996.

Sibley WA. *Therapeutic Claims in Multiple Sclerosis (4th edition).* New York: Demos Vermande, 1996.

Selected booklets available from the National Multiple Sclerosis Society (800-344-4867):

- ◇ *Research Directions in Multiple Sclerosis* (ES 6017)
- ◇ *Clear Thinking About Alternative Therapies* (ECS 6038)

References in this area become outdated very quickly. The most accurate, up-to-date information about treatments and drug trials is available through the National Multiple Sclerosis Society Society (800-FIGHT-MS; www.nmss.org).

Recommended Resources

Avonex®: "Avonex Support Line" (800-456-2255); www.biogen.com
Betaseron®: "Multiple Sclerosis Pathways" (800-788-1467); www.betaseron.com
Copaxone®: "Shared Solutions" (800-887-8100); www.tevamarionpartners.com
Rebif®: "Multiple Support Program" (888-MS-REBIF); www.msnetwork.com
National Multiple Sclerosis Society (800-FIGHT MS); www.nmss.org