



Living Well with MS:
**Medical
research
and hope**



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Introduction

Over the past decade, several important new therapies have become available in Canada to treat multiple sclerosis. Both of the two main classes of treatment — the beta-interferons (Avonex, Betaseron, Rebif) and glatiramer acetate (Copaxone) — have been shown to be effective in reducing the frequency and severity of MS relapses.

These therapies have revolutionized the management of MS — but they are not a cure and they are not necessarily effective for everyone. For people living day-to-day with their disease, the prospect of eliminating MS seems a long way off.

While the proverbial glass may appear half-empty, it doesn't mean that there is no reason for hope. Each year, over 2,000 research papers are published on MS — about seven studies every day — and doctors are gaining new insights into the disease process, how to control it, and how it might be possible one day to reverse some of the damage caused by the illness.

Over the past few years, the Multiple Sclerosis Society of Canada, with the assistance of an unrestricted educational grant from Teva Neuroscience, has presented a series of educational sessions called *Living Well with MS*. This booklet is the latest in the series, and summarizes some of the ongoing research in MS, the new ideas that are being explored, and some of the many reasons why there is hope for Canadians living with MS.

This booklet is based in part on information provided by the neurologists, researchers and other health professionals involved in the *Living Well with MS* series.

Nothing can be done about the diagnosis of MS. But the prognosis of MS — what we can look forward to — can be changed. In the medical research being done today are tomorrow's solutions to the challenges of living with MS.

What is MS?

Multiple sclerosis is believed to be an autoimmune disorder, in which a person's immune cells attack other cells in the person's own body. The causes of this attack aren't well understood. The immune system has a number of highly complex mechanisms to help it distinguish between the body's own proteins and those belonging to a foreign invader, such as a bacterium or virus. But in autoimmune disorders, such as MS, Type 1 diabetes, arthritis or lupus, some unknown factor triggers the immune system and starts a cascade of events. Many possible triggers (e.g. viruses and toxins) have been investigated. In MS, the most probable trigger is fragments of myelin, the protein "insulation" that covers nerve fibres. The immune system detects these as foreign and attacks them.

MS appears to cause damage to the myelin and nerve fibres (axons) early, even before there are any symptoms. This damage — called nerve degeneration — may be too subtle to detect or the body may be able to repair the damaged tissue.

In association with nerve degeneration, immune system activation produces an inflammatory response, in which immune cells cross from the blood into the central nervous system (the CNS, the brain and spinal cord). Inflammation can be beneficial or detrimental. As with other injuries to the body (e.g. a sprained ankle), inflammation is the body's way of healing damaged tissue. In the CNS, inflammation initiates repair mechanisms such as neurotrophic factors, which stimulate regrowth of myelin and axons. However, inflammation also stimulates the release of a number of toxic elements that damage the myelin and the nerve fibres. During an immune flare-up, damage is typically experienced as MS symptoms, such as tingling, pain, muscle weakness, and other problems.

Following such relapses, the symptoms typically go away, or remit, at least partially. That is why this type of MS is called relapsing-remitting MS (RRMS). In RRMS, symptoms appear to get better as the body's repair mechanisms undo some of the damage caused during the inflammatory flare-up.

Unfortunately, in MS the autoimmune assault doesn't switch off, and repeated episodes of inflammation exhaust the body's repair mechanisms and start to cause irreversible damage. This may not be immediately apparent because the brain has the ability to adapt, shifting the way it performs its tasks to other areas of the brain. This is known as *brain plasticity*. However, if a critical threshold of damage is reached and the brain can no longer adapt, there is a steady accumulation of disability.

What Do MS Therapies Do?

While inflammation and nerve degeneration in MS are complex, there are many opportunities to intervene in these processes to try to prevent ongoing damage to nerve fibres in the brain and spinal cord.

The different components of the disease process interact and can develop simultaneously or at different times during the course of MS. Some of these components include:

- **The trigger.** Ideally, a treatment would remove the trigger that initiates the immune system response. Researchers are looking into possible triggers but none has been identified yet.
- **The inflammatory response.** *Corticosteroids* are often used to control the immune system during severe MS relapses and are effective in the short term to suppress flare-ups. However, the chronic use of steroids can cause many unpleasant side effects so they cannot be given on a regular basis for a life-long illness like MS.
- **Invasion of the central nervous system (CNS).** *Beta-interferons* (Avonex, Betaseron, Rebif) block the passage of activated immune cells into the CNS. As a result, inflammatory flare-ups (relapses) in the brain/spinal cord are reduced, as seen on magnetic resonance imaging (MRI).

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- **Preventing myelin/nerve damage.** A medication such as *glatiramer acetate* (Copaxone) reacts with immune cells (T cells), which then cross over from the body into the CNS and induce an inflammatory response that is less damaging to myelin and nerve fibres. This beneficial effect spreads to other inflammatory cells in the CNS, making them less damaging as well (called “bystander suppression”). An oral formulation of Copaxone is currently being examined in phase II studies.
- **Nerve degeneration.** As mentioned previously, nerve degeneration may begin even before there is inflammation as well as after an immune system flare-up. Ideally, a treatment would be able to prevent this from happening and would provide **neuroprotection** so that nerve damage and disability would not occur. This topic will be explored in greater depth later in this booklet.

New and Emerging Therapies

Over 150 new therapies are now being studied in MS (see **TABLE 1**, page 7). The hope is that these medications, used either alone or in combination with existing treatments, will achieve even better control of the disease process than our current medications. It is important to note that these therapies are under investigation; their effectiveness and safety have not been fully determined so they have not yet been approved for use in MS.

If you refer to the previous page, you’ll see that many of the treatments listed below target one or more of the five steps outlined in the MS disease process.

Suppressing CNS inflammation

Mitoxantrone (Novantrone) is a potent immunosuppressant that is used as a cancer treatment. While not approved in Canada specifically for MS, doctors sometimes use it for worsening cases of RRMS or to treat secondary-progressive MS. However, mitoxantrone cannot be taken long-term because higher cumulative doses can damage the heart. Studies are now underway to see if lower doses of mitoxantrone are effective and less toxic when used in combination with other therapies. A less toxic compound, *pixantrone*, is also in development. The immunosuppressants *cladribine* (Leustatin) and mycophenolate mofetil have undergone preliminary studies in progressive MS but additional trials are needed. A promising agent, *FTY720*, has been shown in early studies to reduce the relapse rate and the number of inflammatory lesions in people with MS. A larger study is now ongoing.

Blocking CNS inflammation

Monoclonal antibodies: These “designer” antibodies target specific proteins involved in the inflammatory process. Among the monoclonal antibodies being studied in MS include *daclizumab* (Zenapax), which blocks a chemical in the body that inflammatory cells (T cells) need to grow; *rituximab* (Mabthera), which attaches itself to a protein on the surface of a different type of inflammatory cell (a B cell) to reduce the inflammatory response; *adalimumab* (Humira), which targets inflammatory proteins; an experimental compound (*ABT-874*), which blocks part of the immune system reaction at the site of MS brain lesions; and *alemtuzumab* (Campath-1H), which targets antigens on immune cells and has been shown to reduce MS disease activity. The future of the monoclonal antibody *natalizumab* (Tysabri) is uncertain. It was initially approved in the U.S. to treat MS but has been withdrawn due to safety concerns.

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Anti-inflammatory agents

Statins: These medications are currently used to lower cholesterol levels, but experiments have shown that they also reduce inflammation. Preliminary investigations have indicated that statins may also be able to slow the passage of inflammatory cells into the brain. To date, one study has shown that statins can reduce the number of inflammatory brain lesions seen on MRI. Additional studies are now ongoing.

Minocycline: This antibiotic, which is usually used to treat acne, may also block inflammatory cells from entering the brain and may protect nerve cells from damage. One small study has shown that minocycline may reduce MS brain lesions. A larger trial is now underway at four centres across Canada.

Laquinomod: This new medication has been shown to reduce inflammation and regulate the immune response in animal studies and is now being tested in humans.

Teriflunomide: This is a new oral agent that has been shown in preliminary studies to reduce the rate of inflammatory lesion development in the brain and relapses in MS. It is similar to another oral medication (Arava) approved to treat rheumatoid arthritis. Larger studies of teriflunomide are now ongoing.

Reducing inflammatory damage

Antioxidants: It has long been suggested that nerve damage may be caused, in part, by chemically reactive forms of oxygen in the brain; these molecules are called “reactive oxygen species” or, more commonly, “free radicals”. Free radicals are formed from normal metabolism in the brain. It has been speculated that reducing these free radicals might protect nerve cells. Two drugs, NAC (N-acetyl-L-cysteine) and inosine, are now being investigated in combination with glatiramer acetate and beta-interferon, respectively.

TABLE 1. Some of the treatments available and in development for MS. CNS=central nervous system (brain and spinal cord). For more information on MS medications in development, consult the MS Society of Canada website at www.mssociety.ca.

Approved medicatons	BRAND NAME	HOW THEY WORK
Beta-interferon	Avonex Betaseron Rebif	<ul style="list-style-type: none"> ● Reduce inflammation ● Reduce inflammatory cell trafficking into CNS
Glatiramer acetate	Copaxone	<ul style="list-style-type: none"> ● Reduces inflammation ● Shifts immune response from pro-inflammatory to anti-inflammatory
Emerging therapy		
Mitoxantrone	Novantrone*	<ul style="list-style-type: none"> ● Suppresses inflammation
Drugs being investigated		
Glatiramer acetate	Copaxone — oral formulation	<ul style="list-style-type: none"> ● Reduces inflammation ● Shifts immune response from pro-inflammatory to anti-inflammatory
Monoclonal antibodies – Daclizumab – Rituximab – Adalimumab – Alemtuzumab – Natalizumab	Zenapax Mabthera Humira Campath-1H Tysabri**	<ul style="list-style-type: none"> ● Block inflammation
Immunosuppressants – Pixastrone – Cladribine – Mycophenolate mofetil – FTY720	Leustatin CellCept	<ul style="list-style-type: none"> ● Suppress inflammation
Anti-inflammatory agents – Statins – Minocycline – Laquinimod – Teriflunomide		<ul style="list-style-type: none"> ● Reduce inflammation
Anti-oxidants	NAC Inosine	<ul style="list-style-type: none"> ● May reduce tissue damage

* not approved in Canada specifically for the treatment of MS but often used “off-label”;

**withdrawn due to safety concerns.

Neuroprotection

One of the most exciting topics in MS research is **neuroprotection**. The brain has the natural ability to repair itself by producing factors (called “neurotrophins”) that have the ability to repair myelin, regenerate nerves and stimulate new neural connections. Neurotrophic factors are released by activated immune cells during inflammatory flare-ups. As a result of these factors, some of the damage done during a relapse is repaired, which leads to a remission of symptoms. However, during the course of MS, repeated inflammatory episodes appear to exhaust the repair system and the damage starts to accumulate. An ideal treatment would stimulate or enhance the body’s own repair mechanisms at the beginning of this process and protect the brain and spinal cord from damage. That is why early treatment of MS is so important.

Neurodegeneration and neuroprotection are complex, but a great deal of research has helped doctors understand how damage occurs and how it might be repaired. By understanding the different components of these two processes, it is hoped that therapies can be developed that will specifically target them.

The following are the main strategies that are being investigated.

Prevent demyelination: Myelin is the covering around nerve cells, which provides “insulation” so that the electrical signals traveling along the nerves can be transmitted properly. In MS, this myelin becomes damaged and creates an interrupted signal — which may result in tingling sensations, pain, muscle weakness or other common MS symptoms. In MS, inflammation in the brain and spinal cord stimulates tissues to release a number of toxic chemicals that strip away the myelin — a process called demyelination.

Treatment with immunomodulatory drugs — the beta-interferons and glatiramer acetate — reduces the damaging effects of inflammation. Beta-interferons lower the number of immune cells entering the brain, thereby reducing the amount of CNS inflammation.

Glatiramer acetate acts somewhat differently: it shifts the immune system from a pro-inflammatory to an anti-inflammatory response. By reducing the degree of inflammation in the CNS, these therapies may prevent some of the demyelination that is occurring. Newer medications may be able to make the chemicals released during inflammation less toxic to myelin.

Stimulate repair cells: Oligodendrocytes are cells that produce myelin. Over time, it appears that these cells can’t keep up with the amount of myelin damage that is occurring. As a result, the underlying nerves become exposed and damaged.

This raises two intriguing possibilities: 1) there may not be enough of the cells that grow and mature into oligodendrocytes (called precursor cells); and/or 2) the ability of the oligodendrocytes in covering the nerves with myelin may become depleted over time.

Scientists are investigating both of these possibilities. If there aren’t enough precursor cells, there may be ways to stimulate the body to produce more. Alternatively, if the oligodendrocytes are no longer effective, it may be possible to transplant fresh myelin-producing cells into the brain to help with the repair work.

Promote remyelination and repair: The opposite of demyelination is remyelination — the process of producing new myelin to insulate and protect nerves. A number of steps are known to be involved in remyelination, although not all of them are fully understood.

One area that is receiving intense interest is neurotrophic (“nerve growing”) factors. The starting point for this line of research was the realization that not all inflammation is damaging. When you sprain your ankle, for example, the inflammation you see is part of your body’s natural healing process that serves to repair the damaged tissues. Similarly, it appears that neurotrophic factors play an important role in stimulating the brain to repair itself during MS flare-ups. Several of these factors, such as BDNF (brain-derived neurotrophic factor), have now been identified.

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Preliminary studies have shown that immune cells (T cells) that have reacted with glatiramer acetate cross into the brain and stimulate the body to produce more BDNF, which may help in the repair process. These early studies establish a “proof of principle”, but more studies are needed to determine the possible benefits of this enhanced BDNF production in the brain.

Restore nerve function: Scientists once believed that damaged or dying nerves could not be rescued. Once they stopped functioning, that function was lost and could never be restored. But is this true?

Nerve regeneration is the most important issue facing neurologists today. It is crucial to restoring function not only in individuals with MS, but those with Parkinson’s disease, Alzheimer’s disease, as well as people suffering the after-effects of a stroke or spinal-cord injury.

Nerve damage is a highly complex process that involves macrophages (“eater cells”) that clear away the debris, genetic upregulation (“turning on”) of nerve growth factors, and the production of proteins. In addition, other chemicals are released that inhibit nerve regeneration. Many studies are attempting to understand how these processes interact. A number of different approaches have been taken to regenerate nerves, but a great deal of work still needs to be done. However, preliminary studies have suggested that nerve regrowth may be achievable by stimulating nerve growth factors either directly or through genetic mechanisms, blocking substances that impede nerve development, and/or novel techniques to support nerve re-formation.

Assessing Neuroprotection

In addition to the many therapies now being investigated, researchers are also working on new techniques to assess whether a medication is working effectively. At the time of diagnosis, most people with MS undergo a magnetic resonance imaging (MRI) scan — a “picture” of the brain that shows the areas of inflammation (lesions) caused by the disease.

But MRI is more than just a tool for diagnosis. It is also a useful technique in research to assess how lesions change. By repeating MRIs over time, doctors can obtain a series of “snapshots” of individual lesions to see if they heal or get worse, and the extent of damage they are causing. When a person starts a medication, it is also possible to determine to some degree what that therapy is doing. Is it reducing inflammation? Allowing lesions to heal? Can the treatment slow down or prevent the development of irreversible tissue damage, which are often called “chronic black holes” (because of their appearance on an MRI scan)?

In addition, more global assessments of the brain can measure the volume of brain tissue to evaluate if there is atrophy (shrinkage). While everyone experiences some degree of atrophy because of aging, this process appears to proceed more rapidly in people with MS. Atrophy is difficult to measure since many factors can confuse the picture; steroids, for example, reduce brain volume in the short term because they reduce fluid accumulation (edema), but this is not true atrophy. MS-associated atrophy appears to be due, in part, to the loss of nerve cells resulting from the disease. Many studies are now examining if MS medications can reduce the rate of atrophy and how this might benefit people’s ability to function day-to-day.

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Researchers are also developing new imaging techniques to try to get an even clearer picture of the effects of MS on the brain. MTR (magnetization transfer ratio) imaging is used in research as a more sensitive tool than MRI to detect changes in the brain; this can provide a clearer picture of lesions as they evolve. One limitation with conventional MRI is that the type of lesions seen on scans do not necessarily correlate with current MS symptoms or future disability. The hope is that MTR will be better able to predict the course of MS and the risk of disability.

MRS (magnetic resonance spectroscopy) is also used in research to identify the spectrum of different chemicals present in the brain. Of particular interest is NAA (N-acetyl-aspartate), a protein derivative that is found almost exclusively inside nerve cells (neurons). Changes in the concentration of NAA, as measured by MRS, provide an indication of the extent of nerve damage that is occurring in MS lesions and in other areas of the brain. This is very important to measure since it gives some indication of the severity of nerve damage and the risk of future disability.

These tools are providing important new insights into MS. It is hoped that being able to “see” how MS develops will allow researchers to target the illness more precisely and identify medications that slow the disease process. By understanding the process of MS nerve degeneration, researchers hope to reach the ultimate goal: the prevention of ongoing tissue destruction that can ultimately lead to disability.

What the Future Holds

One of the greatest challenges of MS is living with the uncertainty of what tomorrow will bring. Will I be able to raise my family? Can I keep working? Will I develop disabilities?

No one knows the answer to these questions. But that doesn't mean there is no opportunity for hope. In the past decade, MS has undergone a change from a disease with no effective treatment to one in which a number of therapies are now available.

We have started to bring the disease process under control. And that gives control back to everyone living with MS — to make plans, to raise a family, to pursue a dream.

Medical research — and hope — can transform tomorrow. We can expect that this progress will continue in the months and years ahead.

This new era is the result of ongoing research collaboration, much of it led by the MS Society of Canada and its related MS Scientific Research Foundation. Thanks to the leadership and commitment of MS Society divisions, chapters and units, donors and event participants, in 2004 the Society and Foundation funded an unprecedented \$11.9 million in MS research projects and scholarships.

Research projects range from basic laboratory studies of the intricate interactions between cells in the nervous system to examining whether vitamins combined with other therapies might stimulate myelin repair. Large multi-centre studies include the use of bone marrow transplantation as a possible MS treatment to the development of MS in children.

