

# Immunology for the Rest of Us

by Martha King

You are not your illness. If you live with MS, this is a cardinal concept. But for most people, MS is a foreign country at first, with its own language. Just learning to pronounce “multiple sclerosis” is a task.

At the Society, we say, “knowledge is power,” and consider learning to be a wise way to cope. Most doctors offer people with MS treatment choices or say things like “I’d like to try you on  $x$  because...” People who volunteer for clinical trials must give their “informed” consent. Without some basic knowledge, how can you make a choice, be informed, or assess risks and benefits?

## **Even the beginning is complicated**

We’re told MS is almost certainly an “autoimmune” disease: the kind of dis-

ease in which a person’s immune system attacks portions of the person’s own self. In MS, the target is a fatty protein called myelin that insulates nerve fibers (or axons). While this takes place, there’s inflammation in the brain or spinal cord. Later, two things may or may not happen: limited myelin repair, called remyelination, and scarring where healthy myelin once was.

Both inflammation and scarring lead to MS symptoms, but the relationship between them isn’t neat or predictable. Inflammation comes and goes silently—or may accompany a major exacerbation, or MS attack. Scarring is also silent and it is permanent. Remyelination means the myelin regrows, which often leads to recovery of



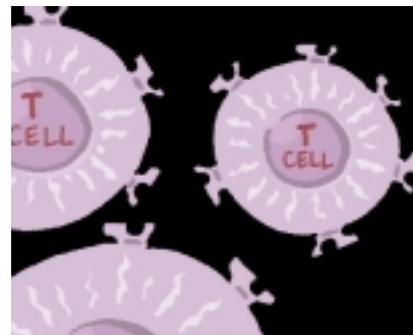
Illustrations  
by Josh Neufeld

some lost abilities. Natural remyelination is often incomplete and over the years tends to stall altogether. Some recovered functions may be due not to myelin repair but to the fact that other nerve cells have taken over the work done by the damaged ones. All three processes— inflammation, de- and remyelination, and scarring—offer opportunities for therapy.

- The current FDA-approved “disease-modifying” drugs can moderate the inflammation part of the process.
- Ways to protect nerves from the destructive effects of inflammation and other aspects of the immune attack are being investigated.
- Remyelination experiments are underway. The myelin-making cell (the oligodendrocyte) was ID’d years ago, but scientists thought it was inactive in adults. Findings now show that these cells are turned on or off by various chemical messengers excreted by other brain cells. Can the system be tricked into making larger amounts of the “turn-on” messengers? Or can the cells themselves be increased? (Last summer, Yale University neurosurgeons implanted new myelin-making cells in a patient. Later this spring, they may be able to tell if those cells made myelin.)
- It’s now known that the scar-making cells (called astrocytes) are turned on and off by specific chemical messengers, too. Since scars slow or block nerve conduction

after inflammation has cooled down, investigators are looking for ways to prevent scar formation, as this might damp down some MS symptoms.

In an autoimmune disease, the immune system attacks the healthy self instead of aliens or cancerous oddballs. It’s friendly fire, in military terms. Autoimmune diseases include rare ills like lupus, and more common ones, like rheumatoid arthritis. Even arteriosclerosis now appears to have autoimmune aspects.

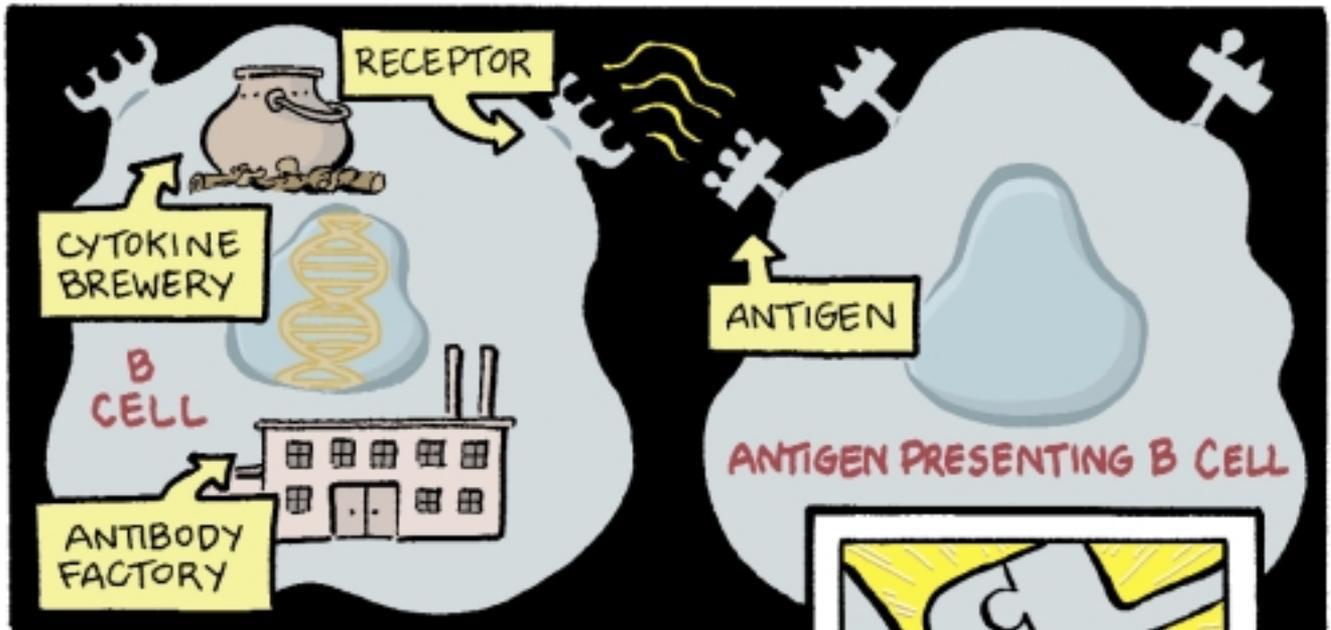


**Vast, complicated, only partly understood**

That’s the immune system. Scientists learned to activate some of it with vaccinations, a major medical breakthrough in the 19th century. Today, scientists can suppress some of it, which makes organ transplantation possible, and boost or tamp down certain functions. Understanding it in full is the ultimate goal of international research in fields ranging from fertility, through cancer and AIDS, to animal health.

Not surprisingly, the immune system looms large in our minds. We’re constantly advised to make our immune systems healthy or strong. But for people with an autoimmune disease, a strong

# A B CELL IS ACTIVATED BY ANTIGEN



OUR ACTIVATED B CELL WILL **DIVIDE** RAPIDLY. THE ANTIBODIES HELP OTHER IMMUNE CELLS **ZAP** GERMS. THE CYTOKINES **CALL UP** OTHER DEFENDERS.

immune system might not be an advantage. A “strong” immune system is sensitized, alert, quick to react. In MS and other autoimmune diseases, some part of the immune system has lost tolerance for a healthy tissue. It is too alert, and it attacks aggressively when it should stay calm.

### **What is the immune system, anyway?**

A body-wide defense system, sure. It’s everywhere, in every tissue. The outer perimeter includes things like skin, tears, and stomach acids that block or neutralize invaders.

The second line of defense is a generalized immune alarm. It makes us sneeze, cough, and itch to encircle and eject invaders. The immune system we’re concerned about here is a sophisticated inner defense against germs that have evaded the other two.

The system is the product of an arms race. The war between complex organisms like us humans and the germs that attack us is very old indeed; there was war between germs and dinosaurs. Attack and counter-attack measures have been refined over millions of years.

**Opposite shows a key event in normal immune system activity: activation of a type of white blood cell called the B cell.**

### **The basic process**

The basic process is largely the task of white blood cells. Through continual adaptation, a dizzying number of

our white blood cells learn to recognize a specific bacterium, virus, fungus, or even a normal cell that has become cancerous, by responding to unique proteins on the cell surfaces. All proteins have characteristic folds and wildly complex shapes. All cells have surfaces crowded with proteins. Among them, immunologists tell us, is a set of unique signature proteins that distinguish “self” from everything else.

A subgroup of white blood cells called **B cells** manufactures and secretes **antibodies**, which are proteins with shapes that can latch onto other proteins, the way an M and a W can fit together. B cells become antibody-makers on command only. The command, or trigger, is another protein from a cell that seems to be foreign.

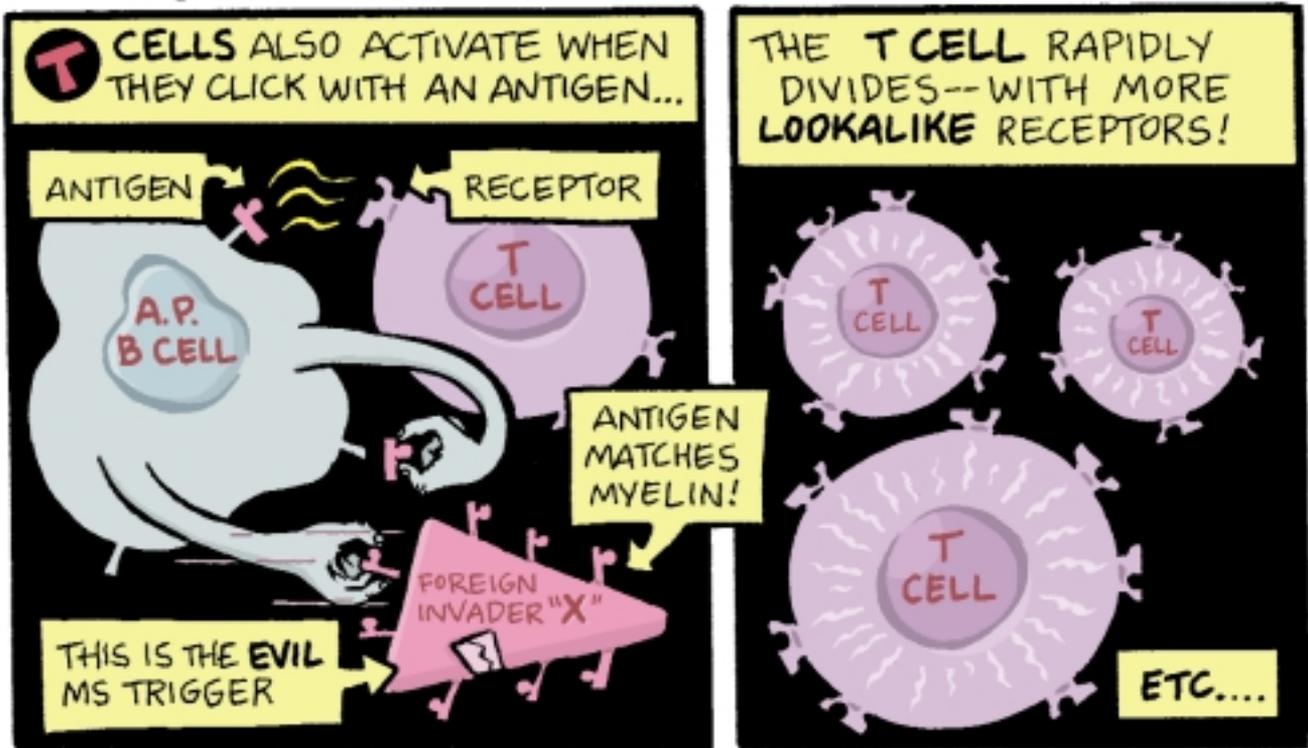
The trigger protein, no matter what it’s from, is called an **antigen**. To make sure that foreign antigens are identified, some B cells serve as **antigen-presenting cells** (or APCs), scooping up these fragments all over the body, and sailing around offering them on stick-like projections to the cells they pass.

Friend or foe? the APCs ask. Friends, ironically, don’t need a password. They are not supposed to be recognized. Instead, the cell surface receptors are primed to accept the shape of a protein that doesn’t belong.

### **When antigen meets receptor...**

Once an antigen locks onto a cell surface receptor, like M onto W—or, more accurately, like a key fitting into a key-

## IN MS, "MOLECULAR MIMICRY" TRICKS THE SYSTEM



hole, because the shapes are quite intricate—the cell's system starts to cook. If the receptor is on a B cell, an antibody factory inside goes into high gear, and so does cell division. Soon the area is thick with antibody-making B cells and antibodies—antibodies that are primed to stick to the specific invader.

Coated with antibodies, an invader cell may stop functioning properly. More likely, it becomes vulnerable to yet another arm of the system, the hungry **phagocytes** that eat anything that has accumulated an antibody coating. Just like other white

blood cells, phagocytes are not confined to the blood stream. They patrol spaces between cells, they float in lymph, and one phagocyte, called the **macrophage**—or Big Eater—is implicated in the MS myelin feeding frenzy.

Macrophages normally remove debris. Without macrophages as biochemical garbage trucks, a body might look like Times Square on New Year's morning.

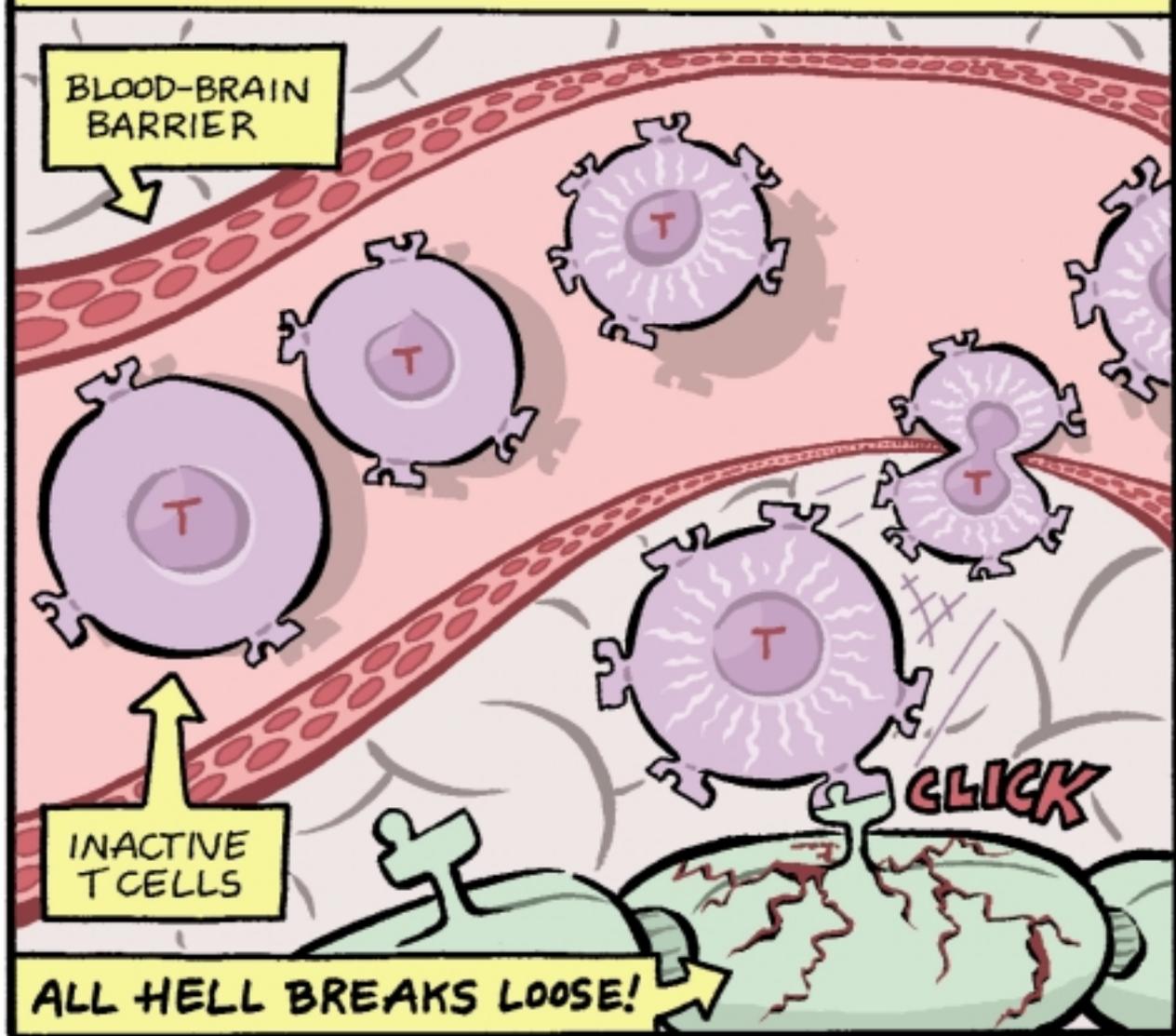
The B cell-directed arm of the immune system is formally referred to as **antibody-mediated immunity**.

**Opposite, the blood-brain barrier keeps harmful substances, including T cells of any kind, out of the central nervous system.**

**Above, foreign invaders learned to fool the immune system by developing antigens that look like friends. See *Molecular mimicry* (p. 58).**



**S**OME OF THE T CELLS BECOME ACTIVATED. WE DON'T KNOW WHY OR HOW THIS HAPPENS. SO FAR, WE ONLY KNOW THIS: ACTIVATED T CELLS CAN SQUEEZE THROUGH THE CAPILLARY AND HEAD FOR THE MYELIN...



### A tougher call

Viruses present a tougher defense problem. Not only are they far smaller than bacteria, fungi, or aberrant cancerous cells, they disappear inside host cells and don't kill them initially. The debris from dead or dying cells quickly attracts immune system warriors. Viruses, like

the classic sci-fi aliens they resemble, lie low and subvert the cell's replicating machinery to make copies of themselves. Eventually the captured cell is full of new viruses that bud out and disperse. Since the viruses are hiding inside "self" cells, they could be impossible for immune surveillance cells to detect. But fortunately,

most host cells retain a few virus fragments on their surfaces. Viral antigens!

The defenders have to be extra vicious to kill virus-infected cells before they release more virus. **Cell-mediated immunity** does the job with a white blood cell called the killer, or cytotoxic, T cell. When viral antigens are presented to T cells that have a matching receptor, the result is dramatic: rapid replication of activated T cells. **T cells** have many functions. Some of the chemicals they release turn on B cells and signal other T cells. In the all-out attack, killer T cells commonly damage a lot of harmless territory, which is why virus infections make us feel horrible.

It may be important to know about these two arms of the inner immune system. The Society's MS Lesion Project is following clues that antibody-mediated immunity is at work in MS destruction in some people, while T cell-mediated immunity affects others. Earlier studies showed that the most destructive MS lesions are full of macrophages busy engulfing bits of antibody-coated myelin.

### **When recognition fails**

Both immunities depend on recognition, or, just as important, on ways to prevent recognition. For example, the system does not attack most of the foreign proteins that we eat. Something happens between the gut and the blood-

**Left, the blood-brain barrier fails. Myelin-sensitized T cells enter and orchestrate a myelin attack. Researchers hope to stop this.**

stream to make the molecules of your Burger King perfectly safe, provided they weren't accompanied by something yucky on your fingers.

The immune system doesn't attack the foreign proteins that make up a developing fetus, either, not even when that fetus has begun to display and excrete a lot of its own personal proteins. Tellingly, MS symptoms are calm and attacks quite rare in the third trimester of pregnancy, when the immune system is tolerating many "foreigners" within its territory.

MS researchers have been exploring both areas for possible therapies. Feeding people a myelin protein to induce "oral tolerance" to myelin hasn't worked well in enough people for unknown reasons. Studies of the hormones of late pregnancy are still in very early stages, but the preliminary results have been modest. These may or may not be dead ends, and it is way too soon to tell for certain. For example, a synthetic molecule made of protein components was studied for over 20 years before it was proven effective and approved for use in MS. It's known today as Copaxone.

### **When recognition works too well...**

Generally, our immune systems tolerate our "self" tissues by not recognizing them. But there is a set of cell surface proteins that impart a unique personal signature to each individual. In all higher species, these signature proteins are referred to as the **major histocompatibility complex**, or MHC. It may be worth knowing something about

“histo”—or tissue—compatibility because recent research indicates that some of the genes implicated in susceptibility to MS lie in sections of DNA that code for the MHC proteins. In other words, something that may suppress or enable cell recognition might be ever so slightly different in people who eventually develop MS. But even with cell recognition “enabled”—why would a person’s immune system “see” a self protein at all?

### **Molecular mimicry**

Immunologists suspect that “molecular mimicry” is involved. Germs learned long ago about immune recognition—and developed ways to evade detection. Viruses or bacteria may carry surface proteins deliberately evolved to mimic a protein that won’t be recognized by the host it invades.

So, the theory goes, when a person with slightly abnormal MHC proteins (perhaps enabling what ought not to be enabled) is exposed to a virus or bacterium with myelin look-alike antigens on board, a few T cells are primed to attack myelin wherever it is encountered again. At first very few cells are sensitized to myelin. But as time goes by, and exposures continue, the person develops troops of T cells geared to attack rather than tolerate this vital body protein.

Still, nothing bad might ensue. For the most part, T cells are kept out of the central nervous system—the brain, spinal cord, and optic nerves, where myelin is—by a protective layer of cells lining all the blood vessels that serve it.

This key defense protects the brain from all sorts of natural and foreign chemicals that might disrupt it. But in MS, T cells activated for a myelin attack are able to wiggle through this blood-brain barrier. Researchers are looking at this to learn exactly how it’s done.

### **What’s known about what works**

It’s comforting to remember that many diseases have been tamed without full understanding of their inner workings. The current crop of disease-modifying drugs is a case in point. It’s known that they help, but not in full detail how. Two of them—Betaseron and Avonex—are close copies of a naturally occurring human chemical called interferon beta. (So is Rebif, marketed in Europe and Canada, and soon to be in the U.S.) Since the first interferon was discovered in 1957 and named for its ability to interfere with viral replication, a collection of interferons have been identified. Interferons tune up or tone down inflammation, swelling, and the rapid proliferation of T and B cells. One of them, an activator called gamma interferon, makes MS dramatically **worse**.

The beta interferons specialize in slowing down the immune response action. They can stop T cells from releasing chemicals that damage myelin. They can block activated T cells from breaching the blood-brain barrier. They can’t suppress the immune defense system as a whole, so people taking them for MS can still resist infections. Most people taking a beta interferon drug have fewer and less

severe MS attacks. They have fewer and smaller damaged areas as seen on MRI. The rate of accumulated damage associated with permanent losses is slowed.

Copaxone has almost the same results. People taking this drug have fewer and less severe attacks, less damage seen on MRI, and a slower accumulation of the damage associated with permanent losses. But the mechanism is completely different. Copaxone apparently acts as a decoy antigen, because it mimics protein structures found on myelin. By clogging T cell receptors and by lacking the active molecules of the real antigen, Copaxone makes the T cell war machine reverse itself and produce anti-inflammatory chemicals.

While these drugs are the most exciting possibility ever available for people with MS, they are halfway effective at best. They delay, slow down, and “modify” MS. They don’t stop it cold.

### So what’s ahead?

Complications actually offer medical scientists opportunities to intervene. MS researchers are studying scar formation and how to control it. They are working on boosting natural remyelination, or using transplanted cells. Others hope to restore tolerance to myelin; to further

tighten the blood-brain barrier; to block or eliminate myelin-sensitized T cells, or to identify the invading germs that trigger the sensitizing process. These and other opportunities were unknown only a short time ago. More has been learned about the immune system, the central nervous system, and multiple sclerosis in the last 10 years than in the entire preceding century. There are powerful reasons for hope.

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*Martha King is the editor of InsideMS. Grateful acknowledgement for help in preparing this story goes to Dr. Cedric Raine of Albert Einstein College of Medicine (winner of the 1996 Dystel Prize for MS Research) and to Dr. Sansana Sawadikosol of Skirball Research Institute, New York University School of Medicine.*

