Happening Now

Bulletins from clinical trials of new MS therapies

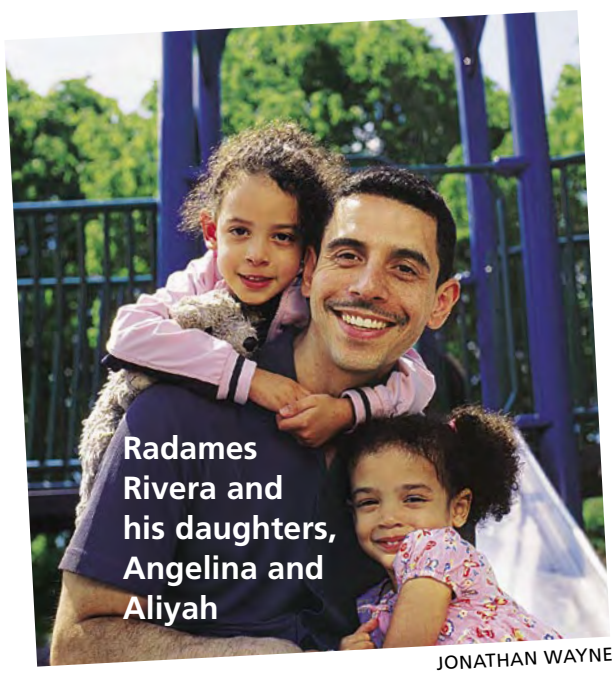
BY GARY SULLIVAN

A mere 20 years ago, physicians had little besides sympathy to offer to someone just diagnosed with multiple sclerosis. The situation was not without hope: experimental drugs were in development. But no one knew when a reliable treatment would become available.

In the 1990s, clinical trials, enhanced by developments in imaging techniques such as MRI, proved the safety and efficacy of the first disease-modifying drugs, **interferon beta-1a (Avonex)** and **-1b (Betaseron)** and **glatiramer acetate (Copaxone)**. The FDA approved them for use by people with relapsing MS. For the first time in history, at least some people with MS were empowered with options for treatment.

The 2000s brought more options. **Mitoxantrone (Novantrone)** was approved for people with some worsening forms of MS in 2000, and **Rebif**, another form of interferon beta-1a, was approved in 2002. Last

Some faces of MS from InsideMS



Radames Rivera and his daughters, Angelina and Aliyah

JONATHAN WAYNE

year **natalizumab (Tysabri)**, the first monoclonal antibody available for the treatment of MS (see **MABs**, page 18) was re-released to market for relapsing forms of MS after an earlier set-back.

As the 2010s beckon, still more treatment possibilities are being rigorously tested around the world. They range from drugs that more precisely target immune system problems to treatments that may repair some of the damage MS has already done. More than 130 clinical trials are in progress, while other experimental drugs are in earlier stages of development.

What follows are just a few of the treatments targeting the MS disease process in the pipeline. Others being tested include treatments for many MS symptoms, as well as rehabilitation techniques to help people with MS lead fuller lives.

Combinations of proven treatments

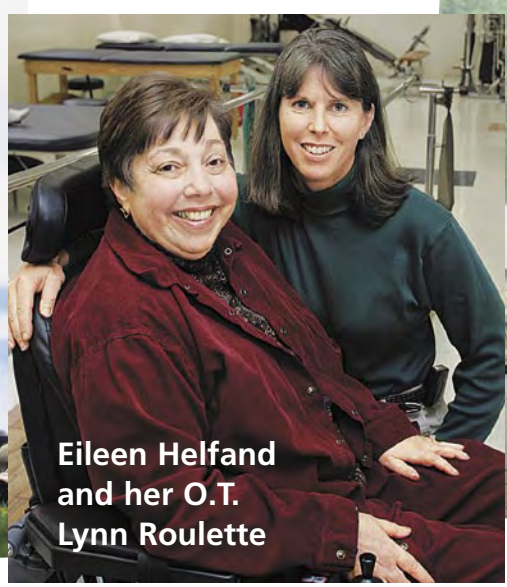
If one MS drug can reduce disease activity by 30%, will two drugs that offer 30% reduction provide more benefit if taken together? MS drug combo trials now in progress include:

Avonex and Copaxone: Dr. Fred Lublin at Mount Sinai Medical Center, New York, in collaboration with other centers in North America, launched a placebo-controlled trial—known as CombiRx—to study the use of Avonex and Copaxone in 1,000 people with relapsing MS. The trial is being funded by the National Institutes of Health and results are expected in 2009.

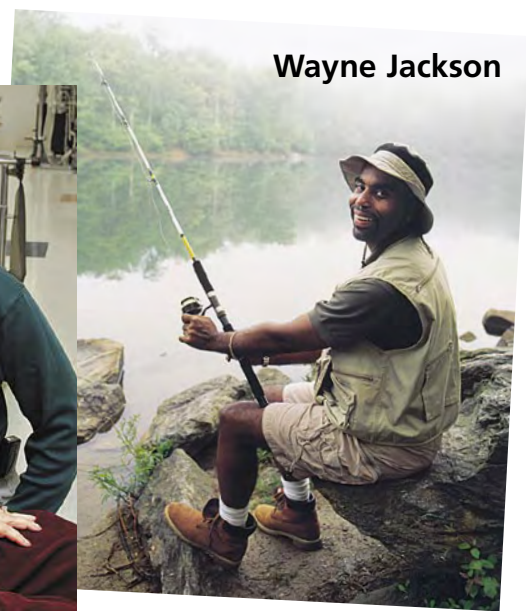
Avonex and methotrexate vs. Avonex and methylprednisolone vs. Avonex and both: Biogen Idec, which makes Avonex, is sponsoring this trial involving 313 people with relapsing-remitting MS whose disease has not responded fully to Avonex alone. Researchers at the Cleveland Clinic, in collaboration with others in the U.S., are studying the efficacy and safety of using Avonex with low-dose oral methotrexate or intravenous methylprednisolone or both. Methotrexate stops leukocytes, or white blood cells, from accumulating and methylprednisolone reduces inflammation and


Jean Griswold

DARREN MODRICKER


Eileen Helfand and her O.T. Lynn Roulette

ED KASHI


Wayne Jackson

ROBERT SEVERI

A quick and easy clinical trial glossary

Double-blind refers to a study in which neither the participants taking the drug, nor the doctors and nurses who see them, know who is taking the test drug and who is taking a placebo (see **placebo**, below). Double-blinding a trial helps to avoid bias.

Open label refers to a study in which doctors and participants know which drug is being taken.

Phase I studies are early safety trials in which all participants receive the experimental treatment. (Sometimes referred to as a **safety study**.)

Phase II (or **pilot**) studies are small-to-moderate-sized and are designed to further test a drug's safety and preliminarily evaluate its effectiveness.

Phase III studies involve hundreds, sometimes thousands, of people. These multi-center studies can last several years and may involve people in many countries. These are designed to unequivocally answer the question of effectiveness and to collect further safety data. A successful phase III study often leads to an application for FDA approval to put the drug on the market.

Placebo is an inactive, non-drug compound that is designed to look just like the test drug. It is given to some of the people in clinical trials as a way of comparing drug benefits and side-effects.

closes the blood-brain barrier, which is compromised in MS.

Copaxone and Novantrone: Teva Neuroscience, which makes Copaxone, is sponsoring this early, open-label safety study of Copaxone and Novantrone in 40 people with relapsing and progressive-relapsing MS.

Copaxone and prednisone: Teva Neuroscience is also testing Copaxone in combination with prednisone, which reduces inflammation and closes the blood-brain barrier. This phase III trial is following 500 people with relapsing-remitting MS taking either both drugs or Copaxone and an inactive placebo.

Monoclonal antibodies, or MABs

Much MS research focuses on the immune system and testing new ways to modify it. Several monoclonal antibodies that **target specific immune cells** responsible for MS damage have shown promising results in clinical trials. One of those MABs, Tysabri, is now approved for relapsing forms of MS. Others are still in progress:

CNTO 1275 interferes with the triggering of the body's inflammatory response by blocking cytokines, which signal other immune cells to attack. Centocor, Inc., launched a phase II placebo-controlled trial involving 250 people with relapsing-remitting MS in 2004.

Zenapax (daclizumab), which also blocks signaling cytokines, was tested in a placebo-controlled trial of 270 people with active relapsing MS. PDL BioPharma announced in March 2007 that treatment resulted in a significant reduction of disease activity on MRI; a full report will be

submitted for presentation at an upcoming medical meeting.

Rituxan (rituximab) is FDA-approved for the treatment of B cell non-Hodgkin's lymphoma, B cell leukemia, and rheumatoid arthritis. It binds to B cells, flagging them for destruction by the immune system. It is being studied in MS in three clinical trials, including a small study funded by the Society. Genentech, Inc., which makes the drug, launched two phase II trials, one involving 435 people with primary-progressive MS, and another in 104 people with relapsing-remitting MS in the U.S. and Canada, in 2004. In the latter study, researchers reported at the American Academy of Neurology 2007 meeting that treatment with rituximab led to significantly fewer inflammatory brain lesions and relapses over a 6-month period.

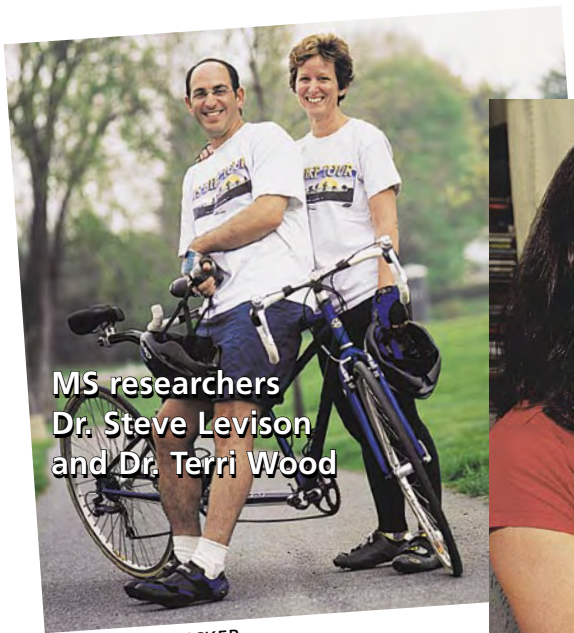
The hormones

Research into the gender differences in MS, sparked by Society initiatives, is beginning to pay off in possible treatments.

Estriol: UCLA investigators launched a Society-funded two-year phase II trial of estriol, a form of estrogen whose levels are increased in pregnancy, in 130 women with early relapsing-remitting MS. Results from the Society-funded phase I trial showed that the hormone shrank the number and size of brain lesions as seen on MRI.

Progesterone and **estradiol**: French researchers are comparing these two hormones in combination against an inactive placebo in 300 women with relapsing MS just after childbirth to see if the drug combo can prevent postpartum MS relapses.

Testosterone: In a Society-funded phase I trial at UCLA, results showed that **AndroGel** (testosterone gel applied to the skin) significantly improved cognitive function and slowed brain tissue loss in 10 men with relapsing-remitting MS. A phase II trial is in the planning stage.

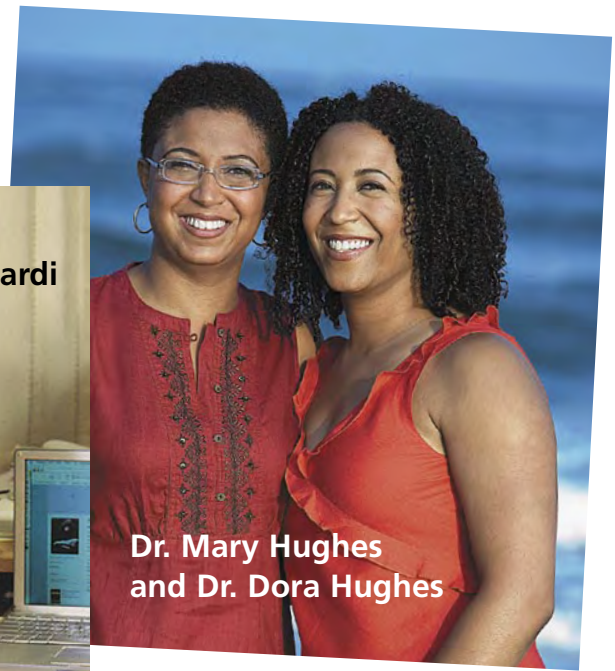


MS researchers Dr. Steve Levison and Dr. Terri Wood

DARREN MODRICKER

Chris Lombardi

PATRICK HARBRON



Dr. Mary Hughes and Dr. Dora Hughes

MILTON MORRIS

Studies in progressive MS

The majority of experimental treatments in current clinical trials are for relapsing forms of MS. As discussed in "The Road Ahead" on page 38, one reason for this is that relapses are easy to measure. While better solutions are being sought, treatments for progressive MS **are** being studied. Some are mentioned elsewhere in this article. Others include:

ABT-874: This monoclonal antibody inhibits signaling cytokines and is being studied by Abbott Laboratories in an international multi-center phase II trial in 130 people with secondary-progressive and relapsing-remitting MS.

Cyclophosphamide vs. methylprednisolone: Cyclophosphamide is currently used to treat lymphomas and some forms of leukemia and lupus. Preliminary studies of IV cyclophosphamide in people with secondary-progressive MS reported encouraging results. A phase III trial with 360 participants will compare the drug with methylprednisolone for two years.

MBP8298: A synthetic myelin basic protein fragment, or peptide, may make the immune system of people with MS tolerant of myelin. A phase II/III study involving 550 people with secondary-progressive MS is in progress.

Oral Fampridine-SR: Acorda Therapeutics announced some positive results of a phase III trial of this MS pill that compensates for lost nerve conduction. The trial involved 301 people with all forms of MS. The treatment provides symptomatic relief, but does not stop disease progress. The FDA asked for an additional study to prove its effectiveness.

Nerve protection: two different compounds are now in clinical trials in the U.K. If effective, they may specifically benefit people with progressive MS.

Lamotrigine, already in use to prevent seizures in people with epilepsy, is being tested to see if it can prevent or slow progressive shrinking of the brain (atrophy) in people with secondary-progressive MS.

THC (tetrahydrocannabinol), a cannabinoid, is being tested for its potential to slow disease progression in people with progressive forms of MS (see "Considering Cannabis," page 56).

The National MS Society also aggressively funds research to better understand progressive MS, including:

- A study at the University of Texas Southwestern Medical Center in Dallas of the immune dynamics in primary-progressive MS.
- A University of Louisville study to identify the immune cells that appear to contribute to a more severe, progressive disease course in mice.
- A study at VA Western NY Healthcare in Buffalo using novel imaging methods to track immune-cell activity in secondary-progressive MS.

MS "vaccines"

Some scientists believe they can "re-train" the immune system to leave myelin alone. They have been working to develop a vaccine that will induce immunity against T cells that attack myelin.

Tovaxin: Sponsors of a phase I "dose escalation" trial tested this T-cell vaccination—in which a person's immune cells are removed, altered in a lab, and re-injected—in 15 people with relapsing or secondary-progressive MS. Everyone in the dose 2 group had a significant reduction in their myelin-reactive T cells. Last year, Opexa Therapeutics, which makes this treatment, launched a phase II trial involving 150 people with relapsing-remitting MS or CIS (Clinically Isolated Syndrome, a single demyelinating event suggestive of MS).

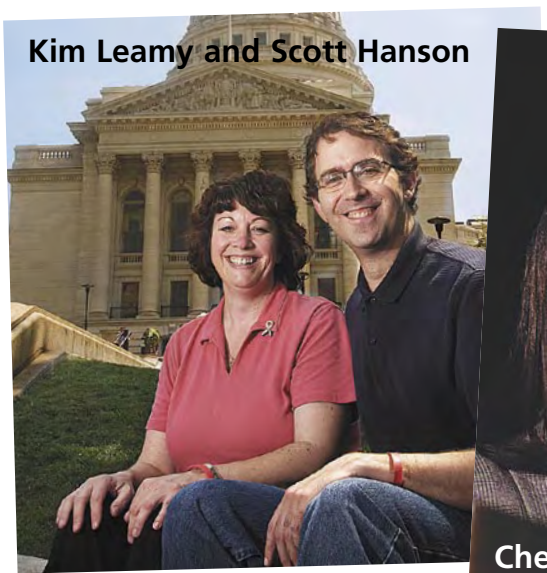
NeuroVax: Investigators at the Oregon Health Science University, Portland, recently reported on their study of NeuroVax in people with relapsing and progressive MS. NeuroVax is a vaccine made of protein fragments from a docking site on the surface of T cells. It's manufactured by the Immune Response Corporation.

By examining blood samples taken from six people before and after three monthly injections, investigators found that "Treg" cells—a type of T cell that can suppress the immune attack—were increased to a level equal to people without MS. A multi-center phase II trial of NeuroVax was just launched in Central and Eastern Europe.

RTL1000: Molecules called "recombinant TCR ligands," or RTLs, bind directly to the receptor on myelin-specific T cells. This should inhibit their ability to cause damage to myelin. Artielle ImmunoTherapeutics, Inc., is in the midst of a phase I safety study of RTL1000 in 36 people with relapsing-remitting or secondary-progressive MS.

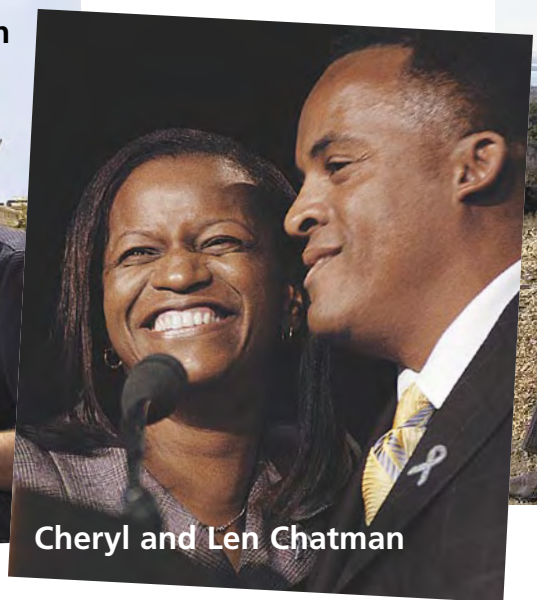
Neuroprotection and repair

Last November 50 members of four **Nervous System Repair "Dream Teams,"** funded by the National MS Society through its **Promise: 2010 c**ampaign (see page 63), met for the first time to share data and problem-solve together. These



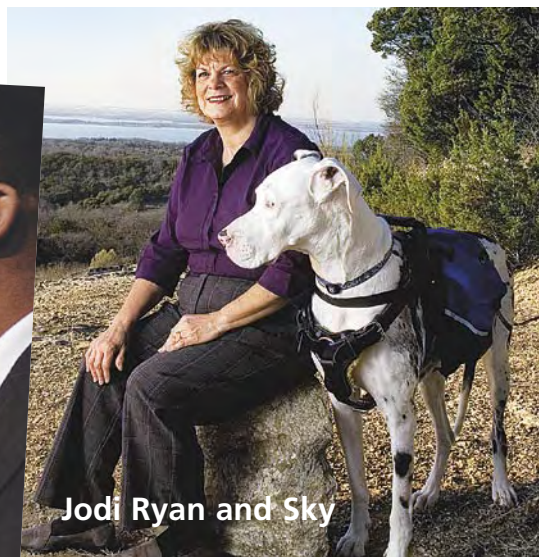
Kim Leamy and Scott Hanson

DAVID ORNDORF



Cheryl and Len Chatman

PHYLLIS REDMAN



Jodi Ryan and Sky

DAN BRYANT

teams are paving the way for clinical trials of therapy to protect nervous system tissue and restore function. People with both relapsing and progressive forms of MS stand to benefit from these new directions.

Early studies have identified a molecule called **glutamate**, which helps excite nerve cells, in MS brain lesions. Some research suggests that too much glutamate may contribute to tissue damage. Scientists at the University of California, San Francisco are testing the ability of an oral drug currently approved for ALS (Lou Gehrig's disease) called **riluzole** to prevent the release of glutamate. The team is conducting a Society-supported phase I trial in 40 people recently diagnosed with relapsing-remitting MS. Participants are taking either Avonex plus riluzole, or Avonex plus inactive placebo, over two years. This trial is funded through the Society's regular research grant program.

The race for an MS pill

Several oral MS therapies made news last year, bringing hope to the needle-weary.

Oral cladribine: Results from a phase II trial of this immunosuppressive drug by Serono encouraged the FDA to designate this drug as a "fast track product." This should expedite the review of an international phase III trial now in progress, as soon as the trial is completed. More than 1,200 people are participating in this multi-center trial.

Oral fingolimod (FTY720): A phase II controlled clinical trial in 255 people with active, relapsing MS found that up to 77% of those taking fingolimod remained free of relapses over two years. International phase III trials sponsored by Novartis and involving more than 2,000 people are now underway.

Oral BG00012: A multi-center phase II controlled clinical trial of this immune system modulator, sponsored by Biogen Idec, and Fumapharm AG, led to a 69% reduction in MS inflammation as seen on MRI scans in people with relapsing-remitting MS.

Oral MN-166: In 2005, MediciNova, Inc., launched a phase II multi-center trial in Eastern Europe of an oral drug that may inhibit MS inflammation. Results are expected later this year or in 2008.

Oral SB-683699: A phase II study of 350 people with relapsing-remitting MS was recently launched by manufacturer GlaxoSmithKline. The drug is thought to reduce the number of active white blood cells that breach the blood-brain barrier and enter the brain.

Oral teriflunomide: An open-label, 180-participant, 144-week extension study of this agent, which is believed to modulate T cells, showed that those on placebo during the original trial who switched to the active drug experienced up to an 85% decrease in new, active areas of disease activity as seen on MRI by the final week of the study. A larger study in more than 1,000 people, sponsored by Sanofi-Aventis, is underway.

A role for statins in MS?

Statins are drugs used to lower high cholesterol. They have also been shown to modulate immune responses. Lab research suggests that statins can reduce the severity of an MS-like disease in mice,

and early trials in people suggest that they may indeed reduce disease activity.

Lipitor (atorvastatin calcium): U.S. and Canadian researchers are studying Lipitor in 152 people with CIS (one attack, but not diagnosed with MS) to see if Pfizer's drug will decrease or delay disease activity as shown on MRI.

Lipitor is also being studied in combination with the myelin basic protein **BHT-3009-01**. Results from this trial showed a decrease in the immune response to myelin and a reduction of inflammatory cytokines.

Complementary and alternative therapies—or CAM

Trials of CAM remedies are also on the MS agenda. Ongoing and recently completed studies include:

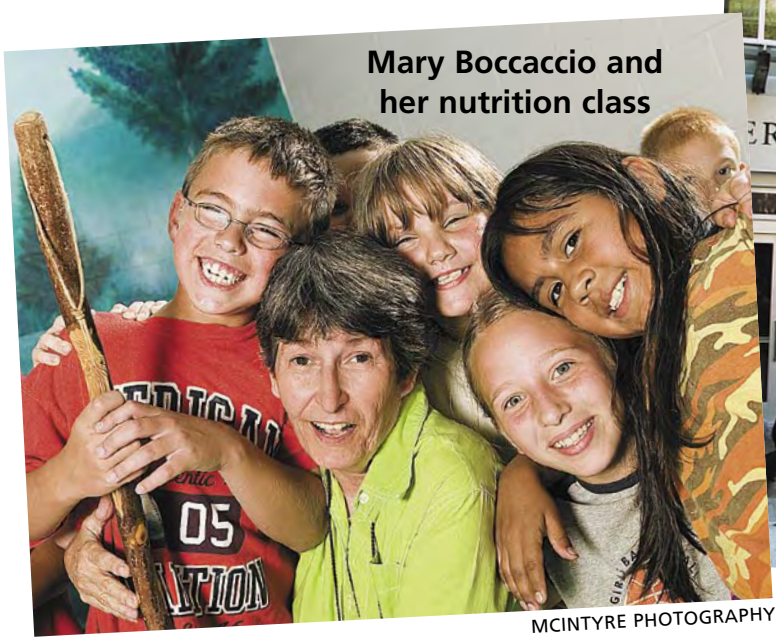
Ginkgo biloba: Results from a small Society-supported study at the MS Center of Oregon in Portland showed that ginkgo biloba measurably improved attention span on one test as compared with inactive placebo.

Ginseng: Also in Oregon, researchers are testing, with Society funding, ginseng versus an inactive placebo in 108 people with all types of MS to see if this traditional medicinal root can improve mental alertness and reduce fatigue.

Omega-3 fatty acid: An open-label study of this popular supplement in 10 people with MS showed a 52% reduction in "matrix metalloproteinase-9," which is associated with MS inflammation. A two-year study of 100 people with relapsing-remitting MS is now underway in Norway to further examine omega-3's effect on disease activity as seen on MRI.

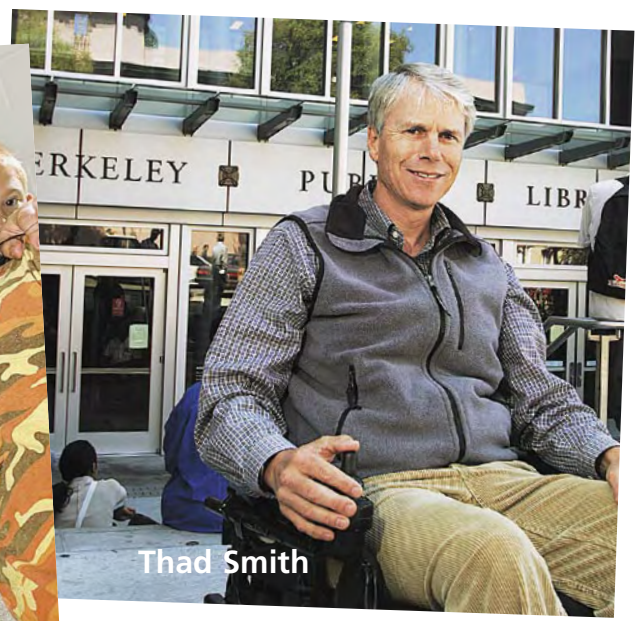
Fish oil (omega-6 fatty acid): The MS Center of Oregon is also studying fish oil in 60 people with all types of MS to see if it improves depression. Fish oil may decrease cytokine levels. The study is funded by the National Institutes of Health. ■

Gary Sullivan is managing editor of this magazine.



Mary Boccaccio and her nutrition class

MCINTYRE PHOTOGRAPHY



Thad Smith

ED KASHI