

Research Now is a quarterly feature of **Momentum**, the national magazine of the National MS Society, and its content is produced and vetted by the Society's Research and Clinical Programs Department.

Sara Bernstein, Editor, **Research Now**

Cathy Carlson, Senior Director, Research Information

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The National MS Society is proud to be a source of information about MS. Our comments are based on professional advice, published experience and expert opinion, but do not represent individual therapeutic recommendation or prescription. For specific information and advice, consult your personal physician.

For news and added information, visit nationalMSSociety.org/Research.

Bringing it home: MS researchers take novel ideas from the lab to clinical trials

by Sara Bernstein

A major goal of MS research—second only to finding a cure—is bringing new therapies to people with MS. It might start in the lab with the discovery that one molecule targeted under an atomic microscope can decrease immune cells or increase the cells that make nerve-sheathing myelin. Years of lab research follow, experiments in animal models, early studies in healthy subjects, and then clinical trials in people with MS.

It's an exciting time for the researchers who get there, but fraught with potential for failure. Will this compound work? Will it cause no difference, or worse, will it bring on MS relapses or progression? The Society is currently

supporting 20 researchers who are testing MS therapies. Seven of them are Sylvia Lawry Physician Fellows who are being trained to conduct clinical research. Here are just a few examples of these clinical studies.

The pregnancy payoff

Rhonda R. Voskuhl, MD (University of California at Los Angeles) published her first research on gender differences in 1996. It was a study that showed how female mice were more affected by MS-like disease than male mice. Twelve years later she is conducting a clinical trial of the sex hormone estriol in 130 women with relapsing-remitting MS. The National MS Society



Rhonda R. Voskuhl, MD

COURTESY OF UCLA DEPARTMENT OF NEUROLOGY

launched this important trial, with the help of the Southern California Chapter and the National Institutes of Health.

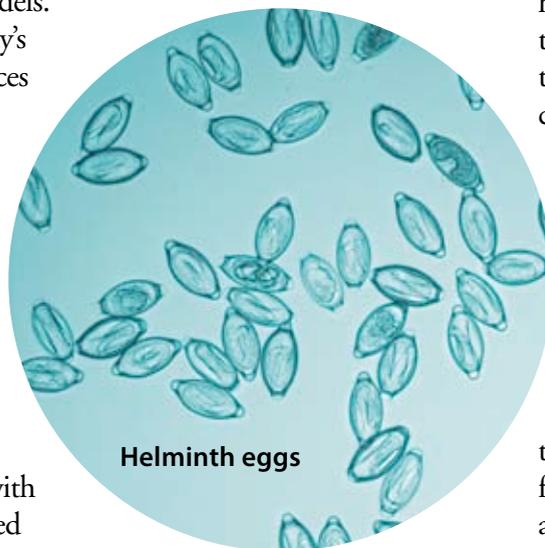
“We saw how more women were affected by MS than men, and how the disease tended to improve in late pregnancy,” Dr. Voskuhl said. “It had to be a clue into how this disease works.” Dr. Voskuhl spent years figuring out which sex hormones affected MS-like disease in animal models. With support from the Society’s initiative on Gender Differences in MS (launched with a lead gift from the Rauh family), she concluded that estriol was the safest, most effective possibility to take to clinical trials in people with MS.

The first step was a small, early-phase trial in 10 women with either relapsing-remitting or secondary-progressive MS. Only those with relapsing-remitting MS showed decreases in disease activity during estriol treatment. “The results were actually quite remarkable,” said Dr. Voskuhl. “We saw an 80% drop in inflammatory [MRI] lesions in the brain, a hallmark of the disease.” (*Annals of Neurology* 2002;52:421–8)

Now Dr. Voskuhl and collaborators are testing whether a combination of standard Copaxone (glatiramer acetate) therapy and oral estriol can slow disease course and activity. The team is evaluating effects of the combination over two years on relapse rates and several clinical and magnetic

resonance imaging measures of disability progression.

“The beauty of estriol is that it can be given as a pill, not a shot, and also that it’s not a new drug; it has decades of safety behind it,” said Dr. Voskuhl. This study is still recruiting volunteers in 16 sites nationwide. Please read more about recruitment at nationalMSSociety.org/trialsrecruiting.



Not your ordinary sports drink

Long-time MS researcher John Fleming, MD (University of Wisconsin, Madison) was at first skeptical when he heard about helminth therapy from researchers investigating it for Crohn’s disease (an autoimmune disease of the bowel).

Helminths are a class of small parasitic worms. “The initial idea of worm therapy might seem outrageous and off-putting, but the science behind it is serious,” said Dr. Fleming. It is based on the “hygiene hypothesis.” Both

autoimmune diseases, such as MS, and allergies are less common in the developing world, possibly because early exposure to common infectious agents—such as occurs to people in regions with poor sanitation—may stimulate immune regulation in a positive way and aid healthy immune responses.

Because MS is more prevalent in regions with high standards of hygiene, researchers have been testing the hygiene hypothesis—the idea that lack of exposure to common infectious agents at an early age may cause the immune system to overreact to a stimulus, thus increasing the risk of developing MS. Studies in an MS-like disease in lab rodents and the preliminary clinical trials in Crohn’s disease suggest that drinking a solution containing microscopic, invisible eggs from the helminth—which is an innocuous infectious agent—might alter immune attacks and improve these conditions.

Dr. Fleming’s team is conducting an exploratory clinical trial in people who have relapsing-remitting MS. In the first phase, five participants who declined to take medications approved to treat MS (and who met other study criteria) were given a kind of sports drink containing the tiny eggs of the helminth. The eggs hatch and mature inside the body, reaching about the size of an eyelash. When they reach the large intestine, the larvae interact with the immune system and

are then killed. The ingestion of the eggs is not expected to cause intestinal problems.

“We look at it like using live yeast cultures in yogurt,” said Dr. Fleming. “The idea is to use helminth eggs as a probiotic, in other words, a live agent that may provide a health benefit to patients.”

The volunteers have been followed with MRI and clinical measures to evaluate safety and effectiveness and determine how treatment affects disease activity as observed on MRI. Preliminary data are being reported at the annual meeting of the American Academy of Neurology in 2009, and based on these results—which provided evidence of safety with the probiotic treatment, among other data—the team is enrolling 15 people for a year-long study. A longer-term goal is to determine the exact mechanism of action so that people could reap the benefits using a pill.

“Although the helminth probiotic treatment is at an early, exploratory stage, it is possible in the future that a new class of therapeutic approaches will come out of this research,” said Dr. Fleming. Recruitment information for participants who can travel to the Wisconsin site is available on our Web site at nationalMSSociety.org/trialsrecruiting.



John Fleming, MD
University of
Wisconsin, Madison

Vitamin D in the spotlight

Research now supports a link between deficiency in vitamin D, which is produced in the body through the action of sunlight, and increased risk of developing MS. Since vitamin D

is available and even recommended for normal bone health, why do we need clinical trials? Actually, excessive intake of vitamin D supplements can have serious toxic effects on the body, including high blood pressure and kidney damage. So, we need studies to see if vitamin D is effective for people who already have MS, how much supplementation is necessary to see any effect, and determine what is a safe amount for people to take.

In a step toward answering some of these questions, Christopher Eckstein, MD, is embarking on a Sylvia Lawry Physician Fellowship during which he will design and conduct a clinical trial of vitamin D supplementation under the mentorship of Peter Calabresi, MD (Johns Hopkins University). “We are studying the effects of two different doses and two different forms of vitamin D in people with MS,” said Dr. Eckstein. “We are not measuring the effects of the supplements on disease activity, but we’re looking at the effects of vitamin D on a

couple of immune markers that are important in MS. We are also reviewing safety.

“I am evaluating the clinical information from people who participate in the study, and linking it to the immune system outcomes,” said Dr. Eckstein. “I will be working with a postdoctoral fellow to do the tests that Dr. Calabresi has developed to measure these markers.”

This project is promising on several levels. “By determining how vitamin D affects the immune system, we may move one step closer to using supplementation to help people with MS,” said Dr. Eckstein. This fellowship also brings him one step closer to his goal of a career in clinical research. “I want to continue investigating new therapies for people with MS. That is where I see my future role.”

This is just one of several studies of vitamin D in MS, which are needed to determine whether vitamin supplements could reduce the risk of MS or affect the course of MS once it has begun.

The landscape of clinical trials is complicated, but these researchers are helping promising therapeutic strategies to make their way through the pipeline. Only time will tell whether they achieve the status of safe and effective new therapies for people with MS.

Sara Bernstein is the editor of **Research Now**.

Research shows the way to healthy living with MS

by John R. Richert, MD

In my former life as director of the Georgetown MS Center, I tried to help people with MS navigate the maze that includes trying disease-modifying therapies, addressing both the numerous symptoms of MS and conditions unrelated to MS, and normal preventive health-care. We often tend to focus on immunomodulatory therapies when discussing MS treatment, but it's also tremendously important to aggressively tackle troubling **symptoms** in order to enhance quality of life.

Research plays an important role in this effort, believe it or not. For example, it might have been a natural inclination to think that exercise might

increase fatigue in people with MS. This was indeed the thinking in the medical community for decades. In fact, a landmark Society-funded study showed that aerobic exercise could actually fight fatigue (**Annals of Neurology** 1996;39:432–41), and since then many studies support the benefits of many types of exercise in MS.

Here are some recent studies that are helping to move us toward healthy living with MS.

When is a headache just a headache?

Although headache is not a common symptom of MS, some reports suggest that people with MS have an increased incidence of certain types of headache.

Norman Putzki, MD (University of Duisburg-Essen, Germany) and colleagues studied 491 people with MS and 447 people without MS who had participated in the German Headache Study—a massive study of 16,000 people. Dr. Putzki's team wanted to determine if migraines and tension headaches were more prevalent in people with MS.

In fact, the rates for these headaches were no higher in

the MS group than in controls and were not associated with MS disability or treatment. This study is an important reminder that not every symptom you experience will be related to MS. Headaches, regardless of why you are having them, are uncomfortable, so it's important to communicate this symptom to your doctor and get it treated. Prevent pain from taking over your life, whenever possible.

(**European Journal of Neurology** 2009;16:262–7)

Breathe easier

Just as a person with MS can experience muscle weakness in the arms or legs, weakness can occur in the muscles of the chest and abdomen that are involved in breathing. Most studies that examine respiratory problems in people with MS tend to evaluate them in people with significant disability, and studies have even shown that



TIMOTHY TADDER/JUPITER IMAGES

respiratory problems are a major cause of illness and death in people with advanced MS.

Toni Chiara, PhD, PT, and colleagues (Malcom Randall VA Medical Center, Gainesville, FL) assessed respiratory function in 17 people with MS who had mild to moderate disability and 14 controls without MS. The team found that maximal expiratory pressure, pulmonary function and voluntary cough were all reduced in people with MS. They administered a technique to improve breathing muscle strength and found that it improved respiratory function. (*Archives of Physical Medicine and Rehabilitation* 2006;87:468–73) This study shows us how crucial it is for your doctor to evaluate respiratory function from the start of your MS—examining not only your muscle strength but also any history of smoking or pulmonary problems. Rehabilitation interventions can help you to breathe more easily—and just like disease-modifying meds, the earlier you seek them out, the better.

Falling: fear vs. risk

We know that the risk of falling is increased if you have mobility issues, but what about how nervous you are about it? Fear of falling is common in people with disabilities, and the fear itself can limit activity and even cause falls, possibly leading to further disability.

The National MS Society funded Marcia Finlayson, PhD, OTR/L (University of Illinois at Chicago) and colleagues to look at this issue specifically



ALTREND/GETTY IMAGES

in people with MS. Her team's findings are highly instructive. They did telephone interviews with 1064 people with MS living in the Midwest, and found that 63.5% reported experiencing fear of falling. Of these, 82.6% were curtailing their activity. Curtailing activity was associated

with, among other things, more mental health issues. (*Multiple Sclerosis* 2007;13:1168–1175)

This important study shows us that fear of falling is something to be reckoned with: If you've done what you can to minimize the risk of falling, like working with a physical therapist to learn how to move more safely; wearing safe, low-heeled shoes; being careful of where you walk and keeping floor areas clear—and you still have heightened anxiety, talk to your doctor about interventions that can help you to prevent that fear from getting in your way and bringing you down. It may also help to determine the safest ways to get up from a fall.

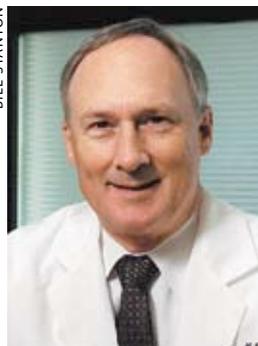
Research continues to expand the world for people with MS. We often talk about this expansion in terms of advances that will lead us to a cure, but it's important to remember that research also tells us more about the daily life of a person with MS so that we can help support the quality of that life until we eliminate this disease for good.

For more information about healthy living with MS, go to

the **Living with MS** section of our Web site—nationalMSSociety.org.

Dr. John Richert is executive vice president for the Society's Research & Clinical Programs.

BILL STANTON



Trimming the fat: Are lipids contributing to MS?

What triggers the immune attack on the brain and spinal cord in MS? We talk a lot about proteins, but myelin—the substance that ensheathes nerve fibers and is a main target of the attack—is primarily composed of lipids. These fatlike molecules are harder to work with than proteins because they do not dissolve in water and, until recently, technology to facilitate their study did not exist. But now researchers are breaking through. Studying these fatty molecules may lead to a lean, mean strategy for tackling MS.

Myelin lipids and proteins have a complex relationship. Slow electrical charges that pass between them are crucial to keeping myelin stuck on nerve fibers, which in turn helps nerve cells conduct impulses. Even small changes in this interaction might

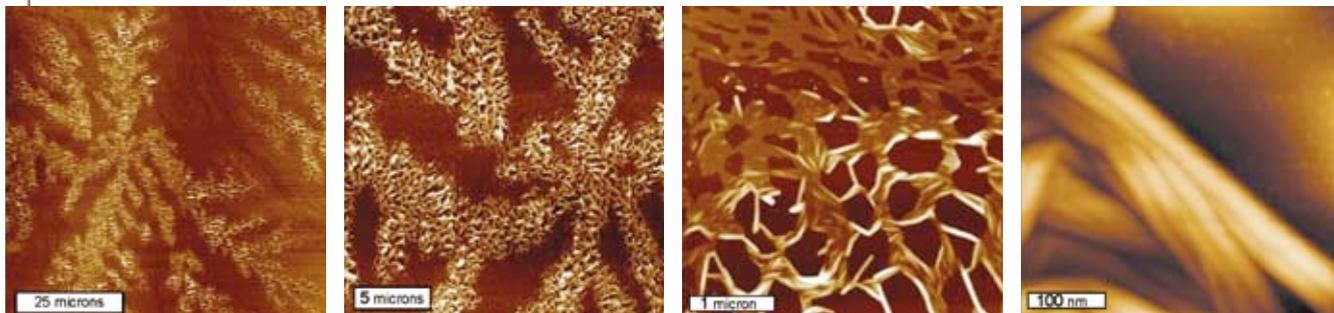
cause myelin to deteriorate. (*Proceedings of the National Academy of Sciences USA* 2004;101:13466–71)

Jennifer Kanter, PhD, made great strides in understanding MS lipids while studying with Bill Robinson, MD, PhD, and Larry Steinman, MD (Stanford University; she now is the National MS Society's Paul, Hastings, Janofsky & Walker Research Fellow at Harvard Medical School, Boston). Dr. Kanter created a "microarray" of lipids which she used to test blood or spinal fluid samples from people with MS. Microarrays are glass slides dotted with hundreds or thousands of molecules; in this case those molecules were lipids that are found in the myelin sheath and are potential targets of the immune system in MS. When a blood or spinal

fluid sample from a person is placed on the slide, if antibodies that react against these lipids are present, they will latch on to their target molecules.

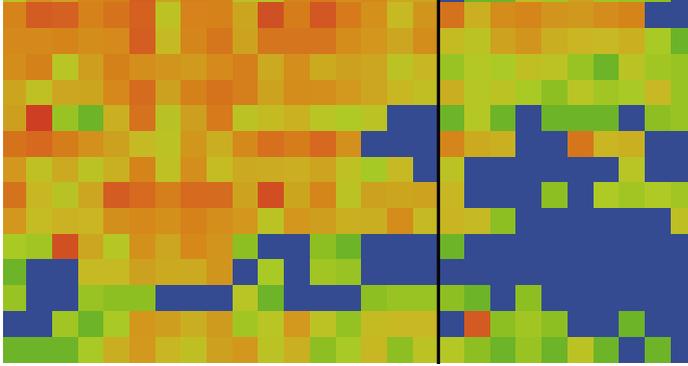
For the first time, Dr. Kanter's team showed reactivity to certain brain lipids in spinal fluid from people with MS. To follow up on their study, they induced an MS-like disease in mice by injecting a combination of myelin proteins and lipids. They found that more severe disease occurred by using the combination than by using proteins alone. (*Nature Medicine* 2006;12:138–43)

So now we have some strong evidence that lipids play a part in the MS picture. But the immune responses to lipids may differ in people with different forms of the disease, according to a recent study that used brain tissue samples obtained from the MS Lesion Project, funded through the Society's Promise: 2010 campaign. Project investigators have found four distinct types of



These images were produced by Cynthia Husted, PhD, and colleagues (University of California, Santa Barbara) using an atomic force microscope. These views of lipids called "galactocerebroside" in nerve-sheathing myelin increase in magnification from left to right. The fact that these lipids form tube-like structures indicates that they are important in the stacked structure of myelin. (See the most magnified image, far right.) Galactocerebroside is decreased in areas of disease activity in MS, even in those regions that appear normal. *Journal of Structural Biology* 2001;133(1):1–9

This image is the result of a microarray study of how people's immune systems react to lipids. Microarrays are glass slides dotted with hundreds or thousands of molecules.



When a blood or spinal fluid sample from a person is placed on the slide, if antibodies reacting to the molecules are present, they will latch on to their targets. On the left, the orange spots show strong reactivity to lipids in blood samples from people with MS. On the right, control samples from people with other neurologic diseases show a much weaker reaction. *Nature Medicine* 2006;12(1):138–43

lesions (patches of disease activity and damage) that differ in the pattern of myelin damage and in the immune molecules present.

Examining samples from 62 people and comparing the results with microarrays, an international team found that unique antibody patterns were associated with different lesion patterns. One pattern was characterized by the presence of antibodies against seven lipids, including three cholesterol derivatives. The group then administered these derivatives to mice with MS-like disease, making the disease worse. (*Proceedings of the National Academy of Sciences USA* 2008;105:18889–94)

What this means for MS therapy

If cholesterol plays some role in triggering the immune attack, perhaps drugs that reduce cholesterol can help MS. Clinical trials of such drugs—statins—have been underway for several years in people with MS, not necessarily because of the role of lipids, but because these drugs have been shown to modulate the immune system. The studies have shown mixed results, though,

perhaps because statins can also reduce immune system cells and proteins that **protect** people during the attack in MS.

Atif Awad, PhD (University of Buffalo) and colleagues are now studying phytosterols—chemicals found in plants—that have been shown to reduce cholesterol. They collected blood samples from 11 untreated people with MS and seven controls without MS. The team manipulated blood cells to release immune messenger proteins that either increased inflammation (pro-inflammatory) or decreased inflammation (anti-inflammatory). Then they “treated” them in lab dishes by adding simvastatin (a statin) or beta-sitosterol (a phytosterol). The phytosterol decreased pro-inflammatory proteins (in some cases less effectively than simvastatin) but, unlike the statin, did so without decreasing the important anti-inflammatory protein interleukin-10. More research is needed to determine the safety and effectiveness of these plant compounds for treating MS. (*International Immunopharmacology* 2009;9:153–7)

Fingolimod, a once-a-day pill in phase III clinical trials for MS, is another

example of a strategy that might take on lipids in MS. Fingolimod binds to a docking site on immune cells (sphingosine-1-phosphate receptor, or S1P receptor), preventing these cells from migrating into the brain and spinal cord. The S1P molecule is actually a signaling sphingolipid.

Targeting sphingolipid pathways may be key, according to a team funded through the Society's Promise: 2010 Nervous System Repair and Protection Initiative. Peter Calabresi, MD, Norman Haughey, PhD, and colleagues (Johns Hopkins University, Baltimore) compared brain tissue samples from people with active MS, inactive MS, and no MS. In active MS, sphingolipid content was reduced and phospholipid content increased. The researchers commented that fingolimod may restore S1P-receptor signaling that is lost in MS due to a hyperactive metabolism of S1P. Fingolimod, by restoring S1P signaling, may resolve this imbalance. (*Brain* 2008;131:3092–102).

The team is working on developing therapeutics that target other sphingolipid signaling pathways that may be dysfunctional in MS.

Lipids are a promising target. Some are already crossing from the lab to the clinic, where the study of these fatty molecules might bring new treatment options for people with MS.

In the news and on our Web site

● Oral cladribine reduces MS relapses in phase 3 clinical trial

Oral cladribine (EMD Serono) reduced the relapse rate significantly more than inactive placebo in the phase III “CLARITY” study of 1,326 people with relapsing-remitting MS. These initial results—the first from any phase III study of oral therapy for MS—were reported in a press release from Merck Serono. Additional study results will be submitted for presentation at an upcoming scientific meeting. Cladribine can interfere with the activity of white blood cells that underlie the immune attacks that cause the unpredictable symptoms of MS. Oral cladribine has been designated by the FDA as a “Fast Track Product,” which should expedite its future review. At press time the company plans to file for FDA approval of oral cladribine in mid-2009. Check our Web site, nationalMSSociety.org, for updates.

● Results from small study of stem cell therapy to “reboot” immune system

Northwestern University researchers reported on the safety and benefits from an early phase study of experimental transplantation of individuals’ own

blood stem cells to turn off the immune attacks in MS. Unlike some of the previous studies of this procedure, this one involved people with relapsing-remitting disease, rather than people with later stage, progressive disease. In this uncontrolled trial, they found that the procedure was

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relatively safe, and after an average of 37 months, none of the 21 participants had progressed. A significant portion experienced a reversal of at least 1 point on their disability (EDSS) scores, and 76% remained free from relapses. It will take larger-scale, controlled trials to determine whether this expensive, potentially risky procedure is superior to other approved treatment options. Controlled trials of this procedure are now recruiting

participants. Go to clinicaltrials.gov and search for “stem cells” and “multiple sclerosis.”

● FDA expands labeling for Copaxone

The FDA has extended the labeling of Copaxone (glatiramer acetate) to include people with MS who have experienced a first clinical episode and have MRI features consistent with MS. The FDA based its decision on the findings of the “PreCISE” study, in which Copaxone reduced the risk of developing clinically definite MS by 45% versus placebo. Research suggests that damage to brain and spinal cord tissues can occur early in MS, and that early use of disease-modifying therapies can delay onset and forestall to some extent future disability. This expanded labeling for Copaxone adds another option for early treatment, and sends a signal to physicians and third-party insurers that this is an appropriate therapy for individuals with this condition.

● **Researchers need your help:** MS Trial Alerts have been posted on new clinical trials recruiting volunteers across the country and in Europe to test the next generation of MS therapies, including some taken by mouth. Go to nationalMSSociety.org/trials **recruiting** to find ongoing studies in your area. ■