

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.

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What causes MS? Looking for answers in people who have it

by Sara Bernstein

Epidemiology may be one of the most misunderstood fields of multiple sclerosis research. Check out this dull definition: "...the study of the causes, distribution, and control of disease in populations." Pay it no mind—this area of research features exciting, relevant findings for people with MS.

Epidemiology, after all, is literally (at least in Greek): epi (upon) + demos (the people) + ology (the study of).

It's the study of people. What puts people more at risk of getting MS—do smokers get it more than nonsmokers? What protects people from getting MS—sun exposure? What contributes to or prevents disease

progression? Epidemiologists look at all people with a disease, and the end goal is—above all—to identify a cause and cure.

As you can imagine, such studies of large groups are

What puts people at risk of getting MS?
What protects them?

expensive, time-consuming, and difficult to complete properly. Recognizing the importance of epidemiology to finding the cause of MS, the National MS Society created the Task Force on Epidemiology of Multiple Sclerosis, a panel of experts in epidemiology, health policy, and neurology. The Society charged this group with

surveying the field and recommending research priorities that have the best chance of moving this effort forward.

“Imagine the complexity of juggling numerous risk factors, including unknown genes, to determine which may contribute to MS progression,” said Nicholas LaRocca, PhD, Associate Vice President, Health Care Delivery and Policy Research for the National MS Society, who staffed the Task Force. “Just think of the decades it has taken medical science to figure out risk factors that contribute to heart disease, a disorder that is so much more common and better studied than MS.”

The Task Force met in New York in September 2007. Their discussions raise intriguing questions about MS—a few are highlighted below.

Around the globe with MS

Studying people with MS has already led to some surprising epidemiologic discoveries. Worldwide, as a general rule, MS occurs with much greater frequency in areas that are farther away from the equator. MS also occurs more frequently in people with Northern European ancestry. However, migrating from one geographic area to another can actually increase or decrease a person’s risk of developing MS! This strange clue has served as the basis for some informative studies.

Israel is a unique setting for migration studies: the population



includes immigrants from regions with more MS (Europe, North America) and less MS (North Africa, Asia Minor). Looking at people who immigrated to Israel from North Africa/Asia Minor, Milton Alter, MD, PhD, and colleagues (Lankenau Institute for Medical Research, Wynnewood, PA) have found that cases of MS increased with the length of time spent in Israel, no matter at what age migration occurred. (A few earlier migration studies had suggested that MS susceptibility peaked before age 15; more recent, larger studies suggest that there is no exact age cutoff.)

In fact, if parents born in North Africa/Asia Minor migrated to Israel **more** than five years before giving birth in Israel, the incidence of MS among those children was higher than in children of parents who migrated **less** than five years before the child was born. Dr. Alter’s team hypothesizes that lifestyle factors in Israel—such as diet—are affecting MS risk. (**Neurology**

2006;66:1061–1066).

Much earlier studies of MS in isolated populations also provided some intriguing clues to the possible cause of MS. John F. Kurtzke, MD (Georgetown University Medical Center, Washington, DC)

began studying MS in the Faroe Islands—a group of islands in the North Atlantic Ocean—in the early 1970s. The team examined every person alive in the Faroes in whom MS was suspected since 1960, and reviewed medical records available since the 1920s.

Not one case of MS was recorded in the Faroe Islands before 1943, but 21 people were diagnosed with MS between 1943 and 1944. British troops occupied the islands between 1940 and 1945, and all MS cases occurred near troop encampments. The team concluded that the British troops *brought* MS to the Faroes, and hypothesized, based on these studies, that MS



may originate with a transmittable infection. (**Annals of Neurology** 1979 Jan;5(1):6–21)

Looking for an infectious trigger

Teasing out the factor or factors— infectious or lifestyle—that may increase MS risk or protect against it is painstaking work. In a series of studies, epidemiologist Alberto Ascherio, MD, DrPH (Harvard School of Public Health, Boston) and his team have associated—or disassociated—several infectious or lifestyle factors with MS risk.

One infectious factor that Dr. Ascherio's team and others continue to pursue is Epstein-Barr virus (EBV), which causes several disorders including infectious mononucleosis. Most people in the U.S. show signs of having been exposed to EBV. In one Society-funded study, the team reported that individuals with signs of significant exposure to EBV were twice as likely to develop MS up to 20 years later. (**Archives of Neurology** 2006 Jun;63(6):839–44)

More recently, Francesca Aloisi, PhD, (Istituto Superiore di Sanità, Rome) and colleagues identified what could be the “smoking gun” researchers have been looking for: signs of EBV in areas of damage in brain tissue samples from people with MS. They also showed evidence of an immune attack on EBV-infected

cells in the MS brain. Such evidence of the virus's presence in MS-related damage is bound to stimulate other investigators to attempt to replicate their findings and to seek further evidence of a direct link between EBV and MS. (**Journal of Experimental Medicine**, published online



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Although these findings *associate* EBV with MS, that's a far cry from proving the virus *causes* MS. An easy way to prove a connection would be to treat EBV and see if MS improves. Unfortunately there is no known anti-viral agent that can rid the body of EBV, and no vaccine to prevent infection.

Are there protective factors?

One lifestyle factor that investigators are looking at is whether increased exposure to the sun closer to the equator plays a role in the latitude effect in MS. The body synthesizes vitamin D from the sun's ultraviolet rays.

Dr. Ascherio's team found evidence for the effects of vita-

min D in a recent Society-funded study. Comparing levels of vitamin D in a 7 million-person database of U.S. military personnel, the investigators found 257 people who had had at least two blood samples drawn before they were diagnosed with MS. Their vitamin D levels were compared with those of age- and race-matched controls without MS. In the white population in this study, there was a 41% decrease in MS risk for every 50-nmol/L (nanomoles per liter) increase in vitamin D levels. (**JAMA** 2006; 296: 2832–2838)

Society grantee Anthony J. McMichael, MBBS, PhD (Australian National University, Canberra) is looking at the effects of lifetime sun exposure and vitamin D status in hundreds of people who are at high risk for MS and who live in parts of Australia where the north-south latitude impact on MS prevalence is marked.

Such epidemiologic studies are backed up by laboratory findings. Society grantee Colleen Hayes, PhD, and colleagues (University of Wisconsin, Madison) have marshaled evidence that vitamin D can lead to the production of beneficial immune messenger chemicals, or cytokines, in mice with the MS-like disease, EAE. They recently reported that calcitriol—a hormone the body produces from vitamin D—reduced the severity of EAE within three days, causing

marked decreases in inflammatory cells and molecules. (**Journal of Neuroscience Research** 2007 Aug 15;85[11]:2480–90)

So can vitamin D supplements alter MS disease activity? Paul O'Connor, MD, and Jodie Burton, MD (St. Michael's Hospital, Toronto), and colleagues recently compared administering escalating doses of vitamin D3 (the equivalent of 4,000 to 40,000 international units per day) to 25 people with MS over 52 weeks, with 24 untreated controls. (The Institute of Medicine recommends intake levels of 200–600 IU to prevent toxic effects such as excessive calcium levels.) Reporting interim findings at the October 2007 ECTRIMS meeting, the researchers found that calcium levels remained within normal limits in this small study. The relapse rate was reduced more in the treatment group, but this finding did not reach statistical significance. The group will have information about immunological effects in the final analysis and says it is now planning a phase II study of vitamin D supplementation in 150 to 200 people with relapsing MS.

Talking to MS genes

If MS is triggered by an infectious or lifestyle factor, does this put MS geneticists out of a job? Just last July the largest genetics study to date confirmed two genetic variations as being associated with susceptibility to MS!

Actually, it's likely that the reason it is difficult to prove that

a risk factor causes MS or that a gene instructs MS is because genetics and environmental factors are working together. In fact, the Society's epidemiology task force rated gene-environment interactions as the most urgent and promising area of research in MS epidemiology.

Genes may be the determining factors in who develops MS following exposure to an environmental factor, be it infectious or lifestyle-related. Or, genes may skew the individual's immune response to a virus, resulting in autoimmune disease or in an inability to recover from the

resulting nervous system damage.

The interplay of genes and environment is evident in studies of identical twins. Generally if one twin has MS, there is a 20 to 40% chance that the other twin will develop it too. In a recent study of twins from various latitudes, Thomas Mack, MD, MPH (Keck School of Medicine, USC, Los Angeles), and colleagues studied more than 700 pairs of twins in whom at least one twin had MS. Among identical twins, concordance (both twins having MS) was almost twice as common in those born in higher latitudes than in lower

Is MS on the rise?

A potentially important clue to MS is understanding who's getting the disease. Is MS on the rise? Are more women getting MS than ever before? Questions like these cannot be answered without having a solid base number of how many people have the disease. In the U.S., no one knows how many people are diagnosed with MS every year ("incidence") or how many have MS right now ("prevalence"), although the National MS Society estimates that about 400,000 people have the disease.

The Agency for Toxic Substances and Disease Registry (ATSDR) at the Centers for Disease Control and Prevention has attempted to help local

health departments investigate several potential MS "clusters" in various parts of the U.S. They found it impossible to determine if there actually were local "spikes" of MS since accurate estimates of the incidence and prevalence of MS in the surrounding area were not known with any accuracy.

The agency is now testing the feasibility of creating an MS national surveillance system, and is conducting small pilot studies to test possible methodologies for such an effort in New York, Minnesota, Georgia, and South Carolina.

Establishing a national surveillance system may be an important step in driving research to understand interactions between genetic and environmental factors that cause MS.

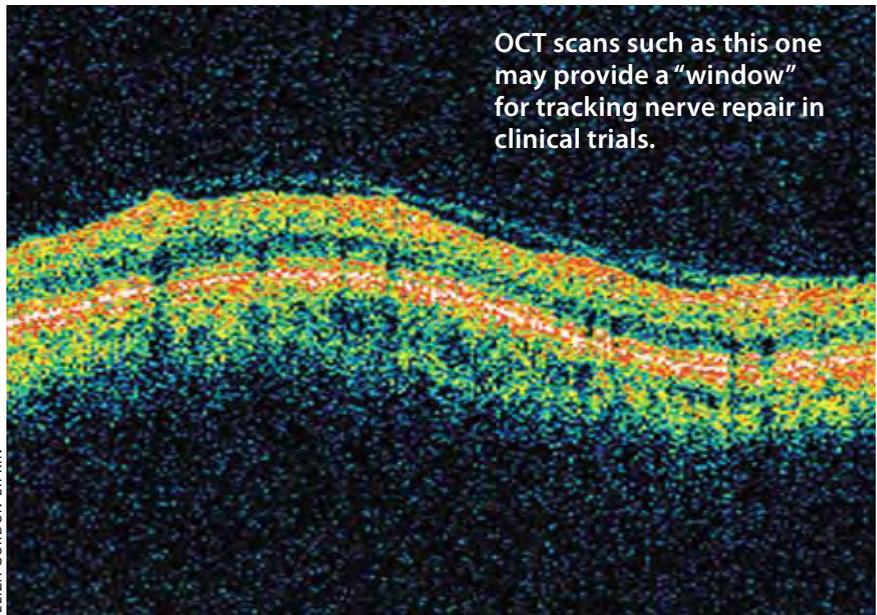
latitudes, and also nearly twice as common in those with ancestors from Northern Europe. This study provides strong evidence for genetic/environmental interaction in MS. (*Annals of Neurology* 2006 Jul;60[1]:56–64)

“Genetic and epidemiologic studies are each painstaking efforts, requiring carefully chosen groups of participants and meticulous data collection,” said Dr. LaRocca. “Put them together, and these demands grow. To get the high quality and large quantity of data that is necessary to figure out how genes and environmental factors may interact to cause MS, we need researchers worldwide to work together and share information, even unpublished findings.”

What's next?

The Society's Task Force on Epidemiology is poised to dramatically affect the field of MS epidemiologic research. A comprehensive report of the Task Force recommendations is being prepared and will be distributed to agencies—such as the National Institutes of Health and the CDC—that can implement the recommended studies. In addition, task force members are contributing chapters to a book that will provide state-of-the-art reviews of all major areas of the epidemiology of MS.

These efforts—looking carefully at the people who have MS—are key to finding the cause of MS, bringing us closer to a world free of this disease.



OCT scans such as this one may provide a “window” for tracking nerve repair in clinical trials.

ELIZA GORDON-LIPKIN

Nervous system repair: The next frontier in MS research

by John R. Richert, MD

People often ask me what's coming down the pipeline for MS—what's the next breakthrough. I tend to point out that within a few years we'll likely have more effective and more convenient weapons to fight the immune activity that underlies multiple sclerosis. The next frontier is to find ways to repair the damage that MS does to brain and spinal cord tissues, ultimately to restore function.

Myelin—the insulating material that is wrapped around the nerve fibers (axons)—protects the axons and also helps nurture

them. When myelin is stripped away by the immune system, the axons and their cell bodies become vulnerable. Damage to both the myelin and the nerve

fibers leads to the progressive disability experienced by many people with MS. That's why it's so important that we find ways to protect and repair

these vital tissues.

One of two 2008 North American Education Programs focuses on nervous system repair. The program, being released this month, is a collaboration between our own Society and the MS Society of Canada. Some

The next frontier: find ways to repair MS damage and restore function.

of the repair strategies covered by the program are outlined briefly below.

Stimulating the brain's repair capacity

The body attempts to repair myelin damage and often succeeds, especially early in the MS disease process. Work is underway to understand why some lesions are repaired and others are not, and on deciphering the molecular signals that are sent out at sites of injury to recruit the body's own repair cells.

The hope is to find ways to mimic these signals to stimulate repair. Also under investigation are a host of proteins known as "growth factors" for their roles in turning on different stages of myelin formation and nerve growth. Investigators have developed high-speed screening systems to identify molecules that may stimulate tissue repair.

Another approach is to identify and block natural processes that may actually **inhibit** the body's ability to repair nervous system damage.

Prospects for cell therapy

What about supplying new cells to do the repair work? Right now this work is going on largely in rodents and other animals to work out safety issues and to figure out the optimal source of cells to transplant, how to obtain enough cells for transplant, the best mode of delivery, and other issues. There are also concerns

that certain types of transplanted cells could multiply uncontrollably and give rise to tumors.

Many readers will have heard of bone marrow stem cell transplantation to treat some forms of cancer. Over the years, there have also been efforts to determine whether this procedure (called autologous hematopoietic stem cell transplantation) can stop MS by "rebooting" a person's immune system. There have been mixed results, and further trials are ongoing to determine whether this invasive procedure can stop disease activity or even restore some functions.

But now researchers at the University of Bristol in the UK have announced the beginning of a study involving a handful of people with MS who would receive infusions of a different type of their own bone marrow-derived stem cells, called "mes-

enchymal stem cells," with the aim of repairing nervous system damage.

There has been some debate as to whether there is enough information on mesenchymal stem cells to warrant proceeding with a clinical trial at this time. The scientific world will be watching to see what can be learned about the safety of this type of cell therapy. Some fear that if this trial is not successful from the safety standpoint, it would set nervous system repair research back a number of years. It will be important to interpret the results in the context of what we know and don't know about the basic biology of mesenchymal stem cells.

Tracking repair

One thing that's missing is a "window" into the brain to see whether any repair or protection interventions will work, and to track how well they enhance repair. New imaging methods to assess the health of nerve tissue and to quantify damage and responses to therapy are under development.

One new tool is a high-resolution imaging technique called optical coherence tomography, or OCT (see picture, page 71). A recent report suggested that OCT-detected thinning of the nerve layer at the back of the eye echoes evidence of brain shrinkage in MS, suggesting it may be a useful tool for tracking repair in clinical trials.



Dr. Richard

“Today we are making progress in virtually every field that impacts MS.”

—Caroline Whitacre, PhD

This study involved a team of investigators from Baltimore, Philadelphia, Dallas and Birmingham who were formerly working individually on this problem. This kind of collaboration, on an even larger scale, is what it will take to properly tackle questions surrounding nervous system repair for people with MS.

Big science + wide collaboration = progress

Achieving nervous system repair requires lots of money and many collaborations between researchers across disciplines. The National MS Society alone is investing \$38 million for multi-year projects focusing on virtually every aspect of myelin formation, nerve function in MS, and repair of the brain and spinal cord. This includes our flagship Nervous System Repair and Protection initiative being funded through the Promise: 2010 campaign. The four international repair teams are becoming a catalyst pushing this field forward.

Few scientific fields are changing as quickly as the landscape of nervous system tissue repair. There are hundreds of scientists around the world who stay awake at night thinking their way through these issues. This exciting area may ultimately lead to ways to reverse the damage and restore nerve function in people with MS.

Dr. John Richert is executive vice president for our Research and Clinical Programs.

SHERYL TAYLOR



We've come a long way: Research featured at National Conference

At the 2007 National Conference of the National MS Society in Dallas, Caroline C. Whitacre, PhD (The Ohio State University, Columbus) delivered the keynote address on multiple sclerosis research.

“When I began my research career in the 1970s, there were no approved therapies for MS and knowledge of the immune system was limited,” said Dr. Whitacre, whose career was launched with a postdoctoral fellowship award from the Society. “Today, we are making progress in virtually every field that impacts MS.”

Dr. Whitacre cited the following strides:

- Finding genes that make people susceptible to whatever triggers MS—a recent genome-wide study identified two new genetic variations.
- Discovering possible trig-

gers, such as smoking or viral infection, and possible protective factors, such as sun exposure.

- Understanding the potential of cell transplants for stimulating repair—studies show that immature nerve cells can repair damage in mice with MS-like disease.

- Translating knowledge of gender differences to clinical trials—the nationwide study of oral estriol in 130 women with MS.

Dr. Whitacre has been at the forefront of research into gender differences, and presented new findings on the widespread immune suppression which occurs during pregnancy.

“Pregnancy is the best treatment for multiple sclerosis,” Dr. Whitacre said. “We need to take advantage of this naturally-occurring suppression. The best is yet to come!”

In the news and on our Web site

● Study suggests MS drugs significantly delay progression of disability in relapsing MS

A large-scale analysis suggested that disease-modifying drugs for MS (specifically, interferon beta-1a, interferon beta-1b or glatiramer acetate) are effective in delaying disability progression in people whose MS started with relapses. Researchers from Dalhousie University in Halifax developed estimates of drug effectiveness based on data from 590 people with MS treated with the drugs. Compared to estimated rates of progression before treatment, therapy was estimated to significantly reduce progression—as determined by the EDSS scale of disease impact—in people with relapsing MS, although more effectively for relapsing-remitting than secondary-progressive MS. Although this study was based on clinical observations and not on a well-controlled clinical trial, it provides much-needed evidence of the longer-term benefit of therapy.

● Clinical trials of oral fumarate under way

Enrollment has begun for two large-scale clinical trials testing the safety and effectiveness of the experimental oral drug BG00012 (dimethyl fumarate, Biogen Idec, Inc.) in people with relapsing-remitting MS. Although its

exact mechanism of action is not known, BG00012 is thought to inhibit immune cells and molecules and may protect against damage to the central nervous system. Both studies are being sponsored by Biogen Idec, Inc.

Read more news and details of these stories on our Web site: www.nationalmssociety.org/Bulletins.



BLEND IMAGES/PUNCHSTOCK

● Early daclizumab study reports positive results

Researchers from the University of Utah report that daclizumab (PDL Biopharma, Inc. and Biogen Idec) alone or in combination with interferon beta reduced disease activity seen on MRI and improved symptoms in nine people with relapsing-remitting MS. This laboratory-created monoclonal antibody blocks the activity of a key immune activator in MS. Active lesions and the number of relapses were reduced

significantly during the study, and symptoms improved. Larger studies of daclizumab already are underway.

● Myelin repair strategies investigated

Two studies presented novel strategies for the repair of myelin, the insulating coating on nerve fibers that is attacked and damaged during the course of MS. One by Mayo Clinic researchers, funded in part by the National MS Society, found that an antibody can stimulate repair of myelin in mice with MS-like disease. It remained effective when combined with methylprednisolone, a corticosteroid used to treat relapses in people with MS. The second study, by Biogen Idec investigators, found that blocking or removing a myelin molecule called “LINGO-1” promoted myelin repair and enhanced nerve fiber integrity in the spinal cords of mice with the MS-like disease EAE.

●ECTRIMS highlights MS drug trials, disease pathology

Multiple sclerosis research took center stage at the 23rd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held October 10–14, 2007, in Prague. Results were presented from numerous clinical trials, indicating the potential within the MS pipeline. Key findings also were reported on the development of disease. ■