NATIONAL MULTIPLE SCLEROSIS SOCIETY

Research highlights

A report of recent research progress in MS • • • • • • • • • • • • • • • • • Summer/Fall 2006

The Complex Link between Infection and MS

By Sara Bernstein

It would be simple if multiple sclerosis were caused by an infectious agent, such as a bacterium – an antibiotic might cure the disease. Although infectious triggers have been associated with MS, none has been found to cause the disease. Because evidence suggests that MS may occur years, even decades after a triggering event, the study of infectious agents in MS is actually quite complicated, necessitating several approaches.

Studying People and Infections

Studying who gets MS and their experience with infections — a specialty of epidemiologists — is one approach. Recently, Gerald N. DeLorenze, PhD (Kaiser Permanente Division of Research) and colleagues reported that individuals with significant exposure to Epstein-Barr virus (EBV), which causes infectious mononucleosis, were twice as likely to develop MS up to 20 years later (Archives of Neurology, June 2006). The study, funded by a pilot grant from the National MS Society, adds to evidence linking EBV to the risk of developing MS, but does not prove that EBV causes MS.

Alvaro Alonso, PhD and colleagues (Harvard School of Public Health) investigated a role in MS for the bacterium Chlamydophila pneumoniae. With funding from a Society pilot grant, the team identified 163 individuals with MS from a database of British patients who were followed for at least three years before MS onset. People treated with antibiotics for exposure to this bacterium did not have an increased risk of MS. Interestingly, increased risk was identified among those taking penicillin, possibly implicating another trigger (American Journal of Epidemiology, June 1, 2006).

William A. Sibley, MD (University of Arizona, Tucson) was honored for groundbreaking epidemiological efforts with the National MS Society/American Academy of Neurology's 2006 John Dystel Prize for MS Research. In 1985, Sibley and colleagues were first to report that during the weeks before and after viral infections, annual MS relapse rates in individuals were

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almost threefold greater than other times (Lancet, June 1985). This study, confirmed by others, shows that MS relapses can be triggered by infections. It does not prove, however, that MS originates with an infection.

It would take carefully controlled studies of thousands of people to confirm an agent as a cause of MS. The Society recently launched a task force to investigate the feasibility of establishing such studies.

Does the Response Trigger MS?

Because of the variety of agents with possible links to MS, some researchers suggest that the immune response to such agents (rather than the agents themselves) may trigger the attack on myelin and underlying nerve fibers in MS. In one mouse model of MS, symptoms are induced by Theiler's murine encephalomyelitis virus (TMEV). TMEV infects macrophages (a scavenger cell that ingests and destroys foreign substances such as bacteria, viruses, and cell debris), which produce messenger proteins that spur on MS-like disease. Some mice, however, resist TMEV-induced symptoms. Thomas Petro, PhD (University of Nebraska Medical Center, Omaha/Lincoln) is investigating why, with Society funding.

Petro's team has found that a "transcription factor" that activates genes, called IRF-3, is pre-activated in macrophages from mice susceptible to TMEV. This sets off a cascade of molecular events resulting in elevated production of a subunit of IL-23, an inflammatory messenger that contributes to MS. (These results are in press at the Journal of Virology.) Interestingly, studies searching for MS susceptibility genes in people have found that one MS gene may be located in the same region as the gene for IRF-3.

Stanley Perlman, MD, PhD (University of Iowa, Iowa City) is investigating a model in which MS-like damage is caused by mouse hepatitis virus (MHV), with Society funding. Perlman's team has shown that a mouse strain that lacks the necessary B and T cells to generate a rigorous immune response does not develop MS-like disease in response to MHV unless cells are "added in" from normal mice.

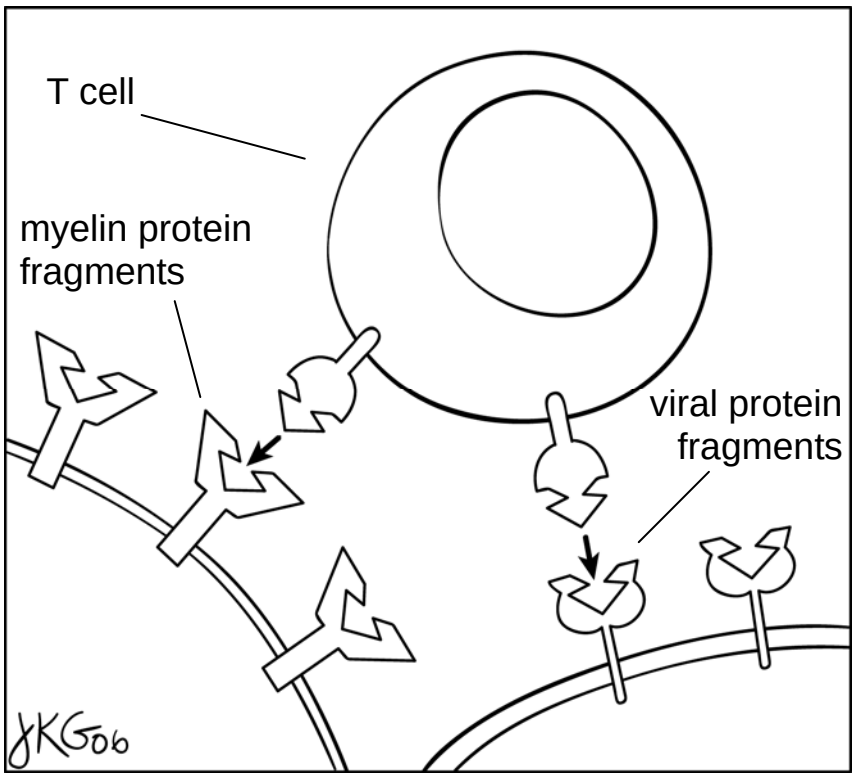
Perlman is now investigating how these immune cells induce damage. Results indicate the importance of the immune messenger interferon gamma, and, in some instances, a molecule on T cells called NKG2D; disabling these molecules decreased MHV damage (Journal of Virology, August 2005).

These studies suggest that genetic or immune factors may enhance susceptibility to a variety of infectious triggers.

Sleeping Triggers

Other researchers suspect that the immune attack in MS may be triggered by a virus that lies dormant in the nervous system until reactivated years after infection. Ralph Feuer, PhD (The Scripps Research Institute, La Jolla, CA) is investigating coxsackievirus (CV), which causes myelin damage after infection in children. Dr. Feuer's studies suggest

that CV may lie dormant within mouse cells after infection and can be reactivated if the cells change. Feuer, a Society-funded fellow, is applying CV to samples of brain cells in laboratory dishes, to identify which cells are damaged by the infection. He recently showed that CV targets immature nerve cells; infected cells lose the ability to multiply (The Journal of Neuroscience, March 2, 2005). Whether or not CV is eventually linked to MS, these experiments demonstrate how a common, dormant infection may play a role in MS.



In "molecular mimicry," because of similarities between segments of myelin and viral/bacterial proteins, T cells generated against the invader also attack myelin. Here, T cells are presented with protein fragments (possibly by immune or brain cells).

Myelin Mimics

Still another hypothesis is that an infection may trigger MS or MS relapses through "molecular mimicry." In this scenario, because of structural similarities between myelin and viral/bacterial proteins, immune cells generated against the invader also attack the body's own myelin. Stephen D. Miller, PhD (Northwestern University, Chicago) and colleagues have developed a model of MS-like disease induced by molecular mimicry, with funding from the Society (Journal of Clinical Investigation, July 2001). They injected mice with a virus that was fused to part of a bacterial gene that is similar to a myelin gene. The mice quickly developed myelin damage and paralysis, caused by a T-cell attack on myelin.

Miller's team recently showed that injecting mice with a myelin protein segment resembling a virus worsened previously existing disease (Journal of Virology, July 2005). His studies shed light on how molecular mimicry may contribute to MS and MS relapses.

Curing MS may not be as simple as administering one antiviral or antibacterial medicine, but the study of infectious triggers offers insight into MS development, and new avenues for therapeutic strategies.❑

Small Molecules, Big Payoff: High-Throughput Screening in MS

New technology is revolutionizing the field of research into disease diagnosis and treatment: High-throughput screening (HTS) allows researchers to test millions of small molecules in a brief period of time. Small molecules are organic chemicals that have proven to be extremely important to researchers in exploring cell function, or even treating disease. It is difficult to predict which compounds will be most effective, so HTS allows researchers to screen "libraries" containing thousands of small molecules. HTS is made feasible because of advances in robotics, high-speed computer technology, and the biologic information made available through the Human Genome Project.

Multiple sclerosis researchers are using HTS to screen for small molecules to help predict, track or treat MS. Not every scientist has access to HTS equipment, however, so novel funding mechanisms are helping scientists accomplish these advanced technological feats.

How does it work?

To prepare for a screen, a researcher takes a "plate," a small plastic container that features a grid of small, open wells containing a chemical compound. The biological entity to be studied – for example, a protein or some cells – is added to each well. After some time has passed, the wells are evaluated either manually or by a machine to determine if the entity reacted, or failed to react with the compound. A high-capacity machine can analyze the results of dozens of plates in a few minutes. An HTS robot can prepare and analyze many plates simultaneously, testing possibly 100,000 compounds per day. The researcher can perform follow-up screens on wells that gave positive results (also known as "hits").

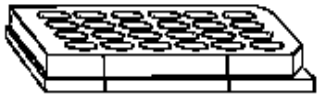
Applying HTS to MS Repair

Bruce D. Trapp, PhD, and colleagues (Cleveland Clinic Foundation) are using HTS to identify molecules that stimulate the repair of nerve fiber-insulating myelin damaged by MS. Their focus is to find molecules that promote maturation of oligodendrocyte progenitors — immature myelin-making cells that mature into replacement oligodendrocytes, and travel to sites of damage to promote repair.

Trapp is funded by a National MS Society Collaborative MS Research Center award, which teams up researchers from diverse fields. The Center award has allowed Trapp to collaborate with Andrei Gudkov, PhD, an expert in identifying molecular targets for cancer treatment. Together they are screening a library of 200,000 small molecules, provided by Chem-

bridge Corporation. In the first stage of this project they have screened around 10,000, to fine-tune the protocol; this pilot phase has already led to several hits, and the group is continuing to screen the rest of the library. The identified molecules are being tested in cell cultures and rodent models, to determine their effectiveness in promoting repair.

Bruce Appel, PhD (Vanderbilt University, Nashville) is adding a twist to a similar project. Appel is studying the maturation of oligodendrocytes using zebrafish, since their embryos develop outside the mother and are transparent, and therefore can be observed during all stages of development.



Plates used in high-throughput screening can be just 3" by 5", yet allow researchers to test thousands of small molecules.

With funding from a Society research grant, Appel's team has developed zebrafish that have fluorescent proteins in their oligodendrocyte progenitors. They've created "movies" of these progenitors from the time they are produced until they wrap myelin around nerve fibers.

They are now using this unique model to perform a high-throughput screen for compounds and are observing how these compounds alter formation of oligodendrocytes in zebrafish. This effort may yield new drugs that promote myelin repair in MS.

To complete this screen, Appel is funded with a pilot research award from the Society, a short-term award that allows researchers to generate data on high-risk ideas. Appel also received a grant from the National Institute of Health's Molecular Libraries Screening Center Network. This consortium provides researchers nationwide with access to HTS. Results from NIH-funded screens are entered into a public database called PubChem.

Tracking MS

Gavin Giovannoni, PhD (University College, London) is using HTS for prognostic purposes – to investigate specific markers that will identify people with MS who are more likely to progress, with funding from the Society's Promise: 2010 initiative. Giovannoni has considerable expertise in MS markers; he recently reported that high spinal fluid levels of a protein found in nerve cells (neurofilament heavy chain) was predictive of poorer clinical outcome and of post-relapse progression in people with MS (Multiple Sclerosis, October 2005). By selecting patients more likely to progress, researchers can improve the success of trials testing therapies to protect nerve tissue.

It is difficult to confirm MS markers, however, because of the number of samples necessary. Giovannoni's grant will help to resolve this issue – his team is one of four to receive a total of

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Meet Ari Green, MD: Bringing Science to the Clinic

The number of physicians – MDs – engaged in MS and other fields of research has steadily declined in recent years; these scientists are the ideal people to translate basic laboratory findings into clinical applications. To address this issue, the National MS Society and the American Academy of Neurology (AAN) Foundation joined forces to launch a new training program to recruit more physicians to MS research. The NMSS-AAN MS Clinician Scientist Development Award is a two-year, post-residency training grant designed for young clinician-scientists who have demonstrated potential to make significant contributions to MS clinical research. Here, we meet the first recipient of this award, Ari Green, MD, of the University of California at San Francisco.

SB: What is the goal of your project?

AG: It is difficult to evaluate how experimental therapies affect disability. The measures currently used are not universally accepted, or are limited because it takes too long to demonstrate a definite reduction in the progression of disability. We need new, highly sensitive measures that do not merely rely on traditional clinical findings. We are looking at ways of following MS disease progression by studying the eye – specifically, the retina and optic nerve. We are using new, non-invasive techniques called "optical coherence tomography" and "multifocal visual evoked potentials." We would like to learn whether we can use studies of the optic nerve and retina to predict a patient's prognosis and to follow whether or not they are responding to treatment.

SB: What progress have you made so far?

AG: We have learned that these techniques are relatively easy to perform, and that they are completely safe. We have seen that many people with MS have changes in their retina (thinning of the nerve) even if they don't have many symptoms in their eyes and have never had optic neuritis [inflammation of the optic nerve]. We need to complete our study before we can analyze our data fully. For now, we are enthusiastic that these noninvasive methods might be widely used for following MS patients in the future.

SB: How does this award help you toward your career goals?

AG: Learning traditional and novel techniques in neuro-ophthalmology, along with intensive training in clinical neurology, will enable me to make a unique contribution to the field of MS research. This award also allows me time to teach and treat patients. I thrive on teaching medical students; with my training and by advancing our understanding of MS and improving the available treatments, hopefully we will be able to attract some of them to MS research. I look forward to a career dedicated to managing and treating people with MS.

Shedding Light on Employment Discrimination in MS

Research indicates that most people with multiple sclerosis are unemployed, even though they have a strong desire to work. What issues are keeping these individuals from the workplace? Answering this question is crucial to improving quality of life for people with MS, and is the subject of a research grant funded by the National MS Society to Richard T. Roessler, PhD (University of Arkansas, Fayetteville).

For the first time, researchers led by Roessler were given access to detailed data about discrimination complaints filed with the U.S. Equal Employment Opportunity Commission (EEOC) between 1992 and 2003. The team gathered information on the types of allegations, the industries and regions in which they occurred, and the resolutions that resulted. They also compared experiences of people with MS with groups of individuals with other disabilities.

Roessler reports that 3,663 allegations of discrimination were filed by 2,167 adults with MS during this time period, most often related to discharge and reasonable accommodations. In comparison to people with other disabilities filing discrimination claims, people with MS were more likely to be white, female and younger, and were more likely to be working in larger organizations (of 501 employees or more).

Women with MS more frequently filed charges of discrimination regarding harassment and intimidation, while men were more likely to file regarding unlawful discharge. Workers in the smallest companies were less likely than workers in the largest companies to allege discrimination related to reasonable accommodations, working conditions or employment benefits, and more likely to allege discrimination related to discharge. Roessler's results were published in the Journal of Vocational Rehabilitation (Volume 23, Number 3, 2005).

Finding Solutions

What can be done to resolve these difficult employment issues? Roessler emphasizes the importance of increasing awareness. "Employees with MS need assistance in developing strategies for identifying and responding to perceived discrimination," he says. Specifically, women with MS would benefit from training materials and support groups that would assist them in coping with harassment and intimidation, and men would benefit from assistance in dealing with unlawful treatment in hiring and firing. Employers also need to be informed, says Roessler, of the protections entitled to employees with MS through the Americans with Disabilities Act.

Roessler plans to investigate such

claims further to understand more about how employers behave toward people with MS, and how the employees respond. This will further inform efforts to develop ways of helping people with MS to negotiate employment issues and to stay employed.

The National MS Society provides comprehensive materials about employment, including guidance on employment decisions, a video designed to help individuals with MS remain in the workforce, and a brochure for employers of people with MS. These materials are available through our Web site (http://www.nationalmssociety.org/employment.asp), or by contacting your local chapter at 1-800-FIGHT-MS.❑

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$15.6 million for the Society's bold initiative on nervous system repair and protection in MS. This grant is allowing Giovannoni to launch the vigorous process for establishing an MS marker using HTS. His team is performing large-scale analyses of known and novel candidate markers in spinal fluid from people with MS to identify those that are associated with disease course and severity. Such markers of myelin or nerve fiber damage could then be used to monitor people with MS via a simple blood test.

As HTS opens up the field for MS researchers, novel funding mechanisms are enabling them to use this technology to speed MS research exponentially.❑

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.

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