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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.

How Dr. David Miller revolutionized our understanding of MS

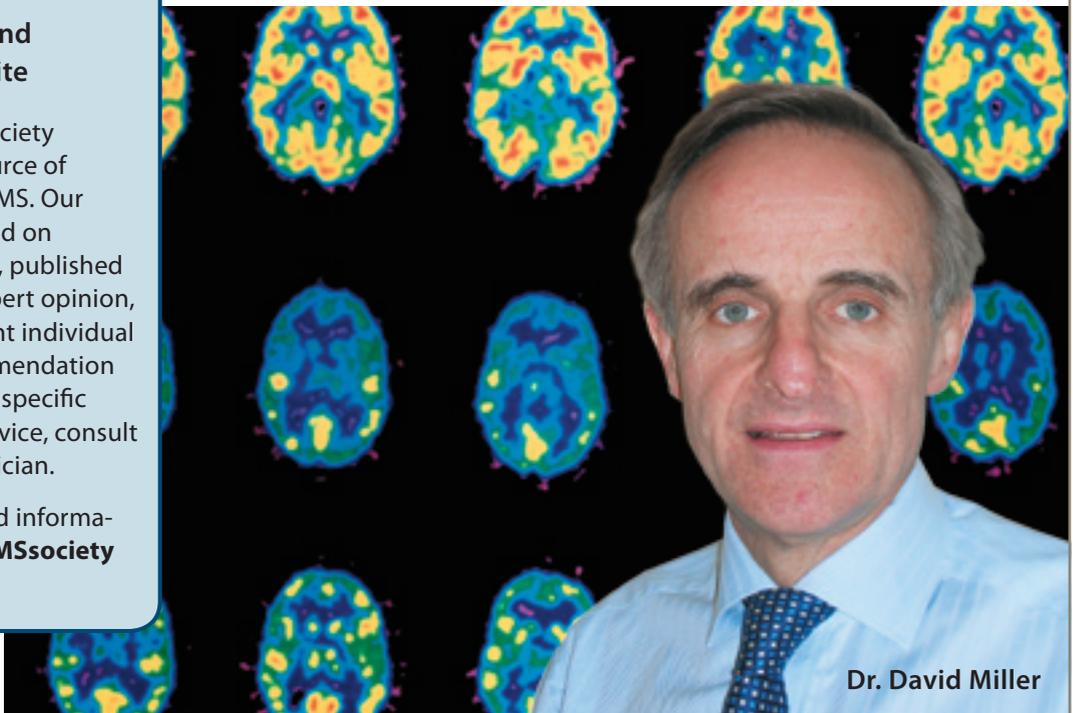
by Sara Bernstein

The John Dystel Prize for MS Research is awarded for outstanding contributions to research in understanding, treating, or preventing multiple sclerosis. Few people have affected our understanding of MS more than the 2009 winner of this prize, Professor David H. Miller, MD, FRCP (Institute of Neurology, University College London). Dr. Miller's research on the imaging of MS—creating a window to the brain and spinal cord with MRI and other techniques—substantially changed how we think about the disease, and how we study its course.

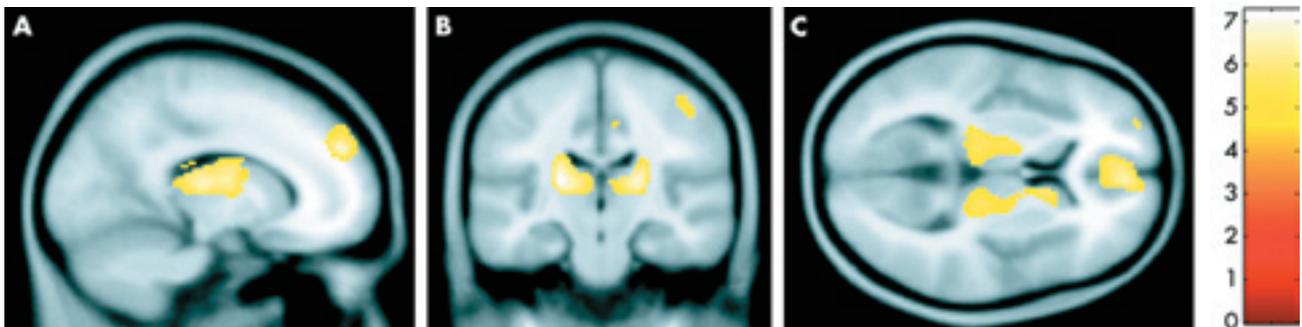
Picturing people with MS

Dr. Miller's interest in MS imaging began early in his career.

"When I was completing my clinical training in neurology in the mid 1980s, the opportunity came up to be a research fellow in the newly created Nuclear Magnetic Resonance (another name for MRI) Research Unit at the Institute of Neurology in London," he said. "I was very impressed by how sensitive MRI was at showing tissue damage in MS. I had an excellent supervisor and mentor in Professor Ian McDonald and enjoyed those two years a lot—so I have since continued in that field."



Dr. David Miller



This slide illustrates one MRI method that Dr. Miller's team has used to analyze the different courses of MS. "Continuous arterial spin labeling" detects blood flow in parts of the brain, an indicator of tissue health. The yellow areas highlight decreases in blood flow that were seen in these images taken

from people with primary-progressive MS. (The decrease was not seen in people with relapsing-remitting MS.) These decreases might pinpoint damage to nerve cells or fibers, so this method might be a way of tracking this damage, as well as its potential recovery or repair.

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The unit at the National Hospital for Neurology and Neurosurgery and Institute of Neurology at Queen Square in London was one of the first such imaging units dedicated to the study of MS. Professor Ian McDonald, its founder, won the John Dystel Prize in 1999.

Dr. Miller became the lead investigator of the unit in 1995, and now directs its talented corps. "We have a multidisciplinary team including clinicians and MR physicists, whose col-

laboration is essential in developing new imaging methods and applying them in studies of people with MS," he said.

Grant support for the unit is provided by the MS Society of Great Britain and Northern Ireland. "This funding has underpinned our research; it means that we can dedicate one scanner entirely to research in MS. Our proximity to the National Hospital has been crucial in facilitating the clinical aspects of our research."

Moving imaging research forward

Many of today's headlines in MS research and treatment would not be possible without the work of Dr. Miller's team; he has authored nearly 450 original research articles, largely focusing on imaging.

Dr. Miller's visionary contributions include his efforts to track the development of MS from even before diagnosis. He pioneered the use of serial imaging studies—in which people with MS undergo MRI scans at various time points. "Our longest study was for 20 years," he said. "We started by recruiting people with a first episode suspicious for MS, called a Clinically Isolated Syndrome [CIS]. The long period of follow up has helped us to understand the imaging features that are associated with different long-term courses of MS.

"For example, we have found that people with secondary-

The **John Dystel Prize for Multiple Sclerosis Research** is given to a scientist who has made significant contributions to the understanding, treatment, or prevention of MS. The \$15,000 award, given jointly by the National MS Society and the American Academy of Neurology, is funded by the Society's John Dystel Multiple Sclerosis Research Fund. Oscar Dystel, National Board of Directors honorary life member, and his late wife, Marion, established the fund to honor their late son, John, a lawyer whose promising career was cut short by progressive MS. The prize has been given every year since 1995. To learn more, visit nationalmssociety.org/dystelprizewinners.

progressive MS generally accumulate more lesions on their earlier brain scans than people who have a milder long-term course,” Dr. Miller continued. “We have also found that people with secondary-progressive MS lose more tissue in their grey matter [nerve cell bodies] and spinal cord, and that the involvement of these regions is an important cause of long-term disability in MS. This means that it may be necessary to develop treatments that are effective in preventing damage in all of these regions in order to prevent disease progression.” **Annals of Neurology** 2008;64:247–254

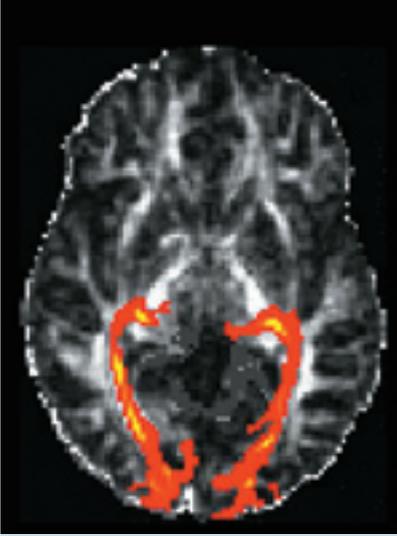
Dr. Miller also is responsible for the concept of applying imaging to the study of the optic nerve, which connects the eye to the brain, beginning these studies early in his career, with a published study focusing on areas of tissue damage in the optic nerve of people with MS. **Lancet** 1986;1:1492

He has continued studying the optic nerve, now using novel techniques such as optical coherence tomography (OCT), an easy-to-use scanner that researchers are using to track the health of nerve fibers in MS.

Scanning progressive MS

Dr. Miller lists several other technologies that show promise for helping us understand the damage that occurs to nerve fibers that underlies MS progression.

KOLAPPAN M, J NEUROL. 2009 MAR;256(3):305-19, WITH KIND PERMISSION OF SPRINGER SCIENCE+BUSINESS MEDIA



An image taken using diffusion tensor imaging shows—in color—the flow of water particles along nerve tissue; applying this method in MS can show where damage is occurring to nerve fiber pathways.

“High-field MRI scanners (3 Tesla or higher) are becoming more available for research and these have great potential to better monitor and understand the effects of MS in the brain, spinal cord and optic nerves,” he said. “Methods such as diffusion tensor imaging (DTI, which measures the flow of water particles) can investigate the integrity of nerve fiber pathways, and magnetization transfer imaging (MTI, a technique that improves image contrast) may be able to detect myelin repair.”

Dr. Miller believes these technologies are crucial to the development of better therapies. “These measures are promising tools in the search for therapies that will prevent or even reverse the effects of progressive MS,” he said. “I would like to see more standardization of scanner technology so that multicenter trials using them are feasible.”

Dr. Miller is now working shoulder-to-shoulder with other members of MAGNIMS, a collaborating group of European imaging investigators, to find even better methods of diagnosing MS, along with speedier clinical trials.

Tracking MS treatment

Dr. Miller’s research played a crucial role in the development of the currently approved therapies and continues to play that role in experimental drugs in the pipeline. He co-chaired an international workshop exploring the use of MRI in clinical trials in MS, and its recommendations have since become the accepted standard worldwide. His group has used MRI measures to study the effect of numerous MS treatments and shown beneficial effects of drugs including beta interferon, mitoxantrone and natalizumab. In one such study—the phase II clinical trial of natalizumab—Dr. Miller’s team demonstrated the drug’s inhibition of new disease activity on MRI scans, providing the basis for larger studies which ultimately led to the drug’s approval to treat people with MS. **New England Journal of Medicine** 2003;348:15–23

Multiple sclerosis is notorious for its unpredictable nature. Dr. David Miller’s work is helping to reduce some of that unpredictability to move us closer to a world free of MS.

Clinically isolated syndrome: Improving the future for people at high risk for MS

by John R. Richert, MD

When Professor David Miller was honored with the 2009 John Dystel Prize (see page 67), I thought about how his imaging research, along with other advances, has helped change the landscape immeasurably for people in the earliest stages of their experience with MS—those who haven't even been diagnosed yet.

I'm referring to people with "Clinically Isolated Syndrome" (CIS)—those who experience a first neurologic episode that lasts at least 24 hours,

and is caused by inflammation/demyelination in one or more sites in the central nervous system (the brain, spinal cord and optic nerve). When CIS is accompanied by MRI-detected tissue damage that is similar to that seen in MS, the person has a high risk of a second neurologic event, and therefore a diagnosis of clinically definite MS, within several years.

The development of CIS can be a tremendous challenge for people who have it and for the physicians they consult. Will they get MS? If so, what course will the disease take? Should

they be treated? In the past decade, research and treatment breakthroughs have helped to clarify this picture.

Tracking CIS

Dr. Miller and other researchers have taught us a lot about CIS by tracking people with this syndrome with serial imaging studies. Dr. Miller's team

initially followed people presenting with CIS for five years to determine how well their first MRI scan could predict future outcomes. Abnormalities on MRI served

as powerful predictors of the development of definite MS.

Brain 1993;116:135–146

This study was crucial to distinguishing people with CIS who are at high risk of developing MS from those whose risk is low. Since then, Dr. Miller and his colleagues have extended this study to 20 years to shed further light on early predictive factors. **Annals of Neurology** 2008;64:247–254

Process of elimination

Just last year, an effort spearheaded by the National MS Society shed enormous light on

a dim area of MS diagnosis. The diagnostic criteria for MS specify that other possible disorders must be ruled out before MS is diagnosed. A tall task! To clarify this criterion, in 2006 the Society's International Advisory Committee on Clinical Trials convened an International Task Force on Differential Diagnosis in MS.

Using available literature, and achieving a consensus through conference calls and meetings, the group developed and published guidelines that can serve as a practical tool to help physicians diagnose MS more speedily, or to rule it out. The task force identified 79 "red flags" that would point away from an MS diagnosis in individuals with some neurological involvement. The paper also offers more precise descriptions of CIS and diseases commonly mistaken for MS.

These guidelines are likely to evolve as they are used in the clinic, but they represent a valuable tool for all clinicians. The National MS Society provided funds to make this paper available to all at no charge. It is in the November 2008 issue of the journal **Multiple Sclerosis** (<http://msj.sagepub.com/>). I encourage physicians who are faced with diagnosing MS to check it out.

Delaying development of clinically definite MS

Should people at high risk for MS start treatment in hopes

Will they get MS? If so, what course will the disease take? Should they be treated?

of delaying the disease? Growing research indicates that in many cases the answer is yes. It's a big decision, and one that deserves thoughtful discussion between doctor and patient. But now there are three MS treatments whose labeling has been extended to treat CIS because studies have shown their merit for delaying the development of clinically definite MS.

Here are those treatment options, and the large-scale trials that made them possible:

- The U.S. FDA extended the labeling of Avonex to include individuals with CIS and MRI-detected brain lesions consistent with MS based on the "CHAMPS" study, involving 383 participants. The Avonex-treated group demonstrated a 44% reduction in the probability of developing clinically definite MS. **New England Journal of Medicine** 2000;343:898–904

- Betaseron is FDA approved for treating individuals at high risk for MS based on results of the "BENEFIT" study in 468 people. Those on treatment experienced a 50% reduction in risk for developing definite MS, and that development was delayed by 363 days. In addition, treatment helped delay progression of disability. **Neurology** 2006;67:1242–1249

- The FDA extended the labeling of Copaxone to include people with CIS and MRI fea-

Treatments for People with CIS

There are now three MS treatments whose labeling has been extended to treat CIS because studies have shown their merit for delaying the development of clinically definite MS. Also listed below are several drugs currently under study for delaying MS in people with CIS, including several experimental oral drugs. Please visit nationalmssociety.org/trialsrecruiting and type "CIS" into the keyword search to view clinical trials recruiting people with CIS.

Approved to treat CIS, as well as MS

Avonex (interferon beta-1a)

Betaseron (interferon beta-1b)

Copaxone (glatiramer acetate)

HMR1726 (teriflunomide, an oral agent that may modulate T cells)

Lipitor (atorvastatin, an oral cholesterol-lowering agent)

Minocycline (an oral antibiotic)

In the pipeline for CIS

Atacicept (a drug injected under the skin that affects B cells)

Cladribine (an oral drug that interferes with immune cell activity)

Rebif (interferon beta-1a, a disease-modifying drug approved for MS)

Rilutek (riluzole, an oral drug that may protect nerve fibers)

Tovaxin (T cell vaccination, injected under the skin)

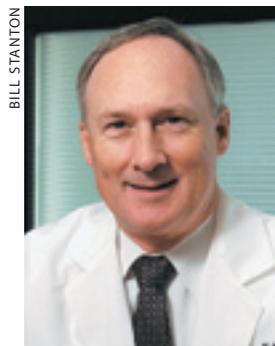
tures consistent with MS based on the "PreCISe" study. In this study of 481 people with CIS, the risk of developing clinically definite MS was reduced by 45% versus placebo, and the development of definite MS was delayed by 386 days. Abstract #LBS.003, **American Academy of Neurology Annual Meeting**, 2008

We have a long way to go before we

can give people a clear, early picture of the path that CIS, or even MS, will take. But the advances of the last couple of decades have seen great strides toward that goal.

Read more about CIS and MS diagnosis at nationalmssociety.org/diagnosis.

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



BILL STANTON

Dangerous foe or tiny protector? Understanding microglia

Microglia are unique immune cells; they actually live in the brain. For some time, researchers have studied how these cells welcome the immune attack on the brain and spinal cord of people with MS, and even spur it on. But microglia might have another face to show—one that actually **protects** nerve cells. National MS Society grantees are teasing out the roles of these two-faced cells.

Researchers investigating these paradoxical powerhouses are already finding the potential for novel strategies to treat people with MS.

Keeping the home fires burning

In a healthy immune system, microglia help to keep the brain and spinal cord safe from infectious agents. The immune system proteins that protect the rest of the body are too large to cross the blood-brain barrier (BBB, the lining of cells that protects the brain) so it is microglia that must recognize invaders and initiate the immune defense. They have to move quickly, so they are structured to detect even the smallest sign of danger.

Unfortunately, many immune system defenders switch to the offense in the immune attack

in MS. In MS lab models, it is believed that microglia get involved early, acting as “antigen-presenting cells”—the cells that serve up triggering molecules to immune T cells and spur on the attack. In fact, Eugene D. Ponomarev, PhD, and colleagues (Blood Center of Wisconsin, Milwaukee) showed that microglia were activated even before disease symptoms appeared in mice with the MS-like disease EAE. **The Journal of Neuroscience Research** 2005;81(3):374–89

The role of microglia becomes further clarified when they are deactivated. Frank Heppner, MD (University Hospital Zurich) and colleagues including National MS Society Harry Weaver Neuroscience Scholar Burkard Becher, PhD, designed a mouse model in which they could paralyze microglia to determine their impact on EAE. When microglia were unable to act, symptoms improved and inflammation was reduced in the brain and spinal cord. **Nature Medicine** 2005;11(2):146–52

Some researchers are investigating how microglia might be drawn into the destructive process in MS by focusing on blood proteins that leak into the brain when the BBB breaks down. Katerina Akassoglou, PhD (University of California, San Diego),

and colleagues have uncovered evidence that one such molecule called fibrinogen, known as a blood clotting factor, directly activates microglia. They have developed a method of inhibiting fibrinogen in mice without compromising its clotting capabilities.

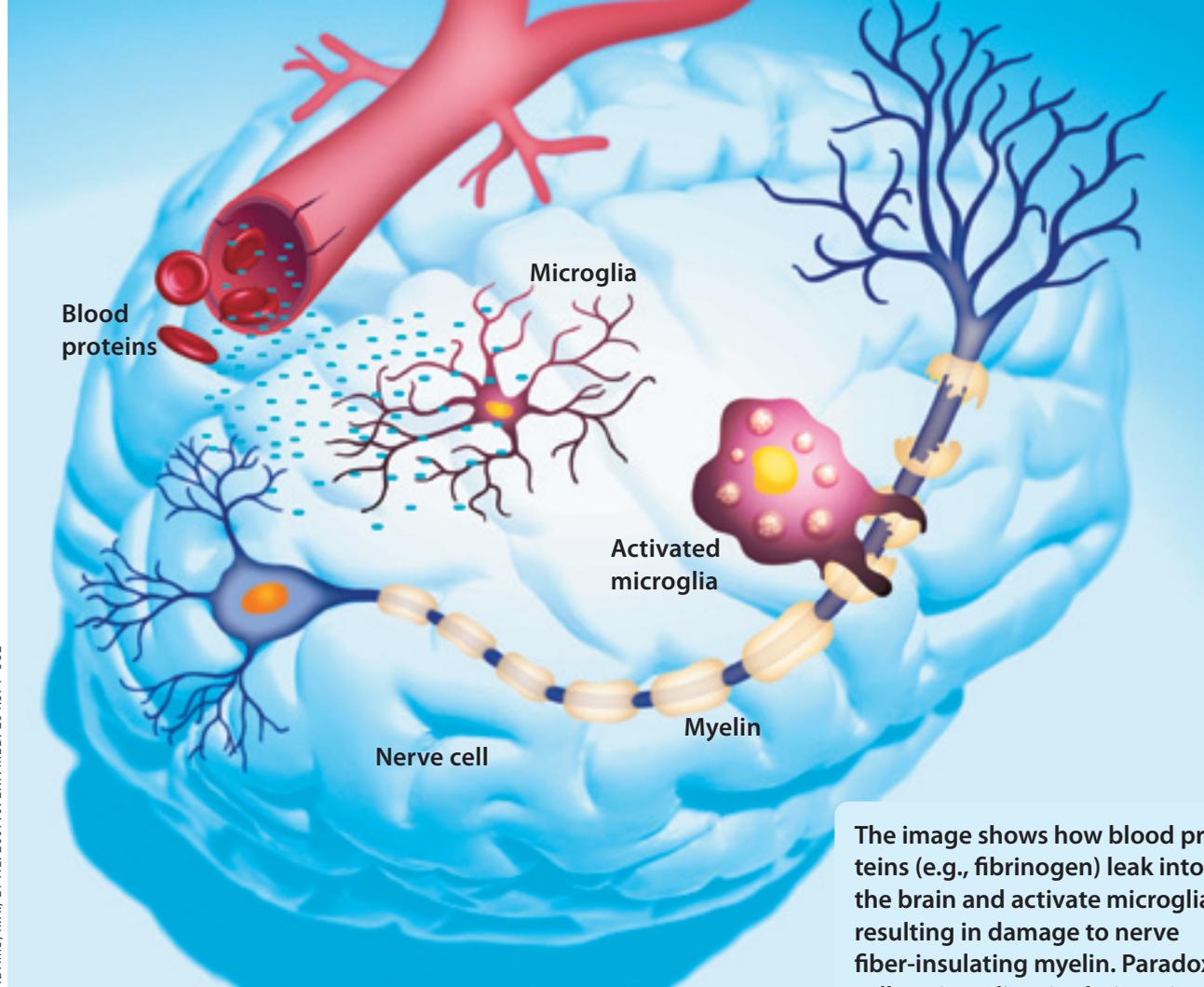
By inhibiting fibrinogen in mice with EAE after the first attack, they were able to decrease the activation of microglia, and subsequent damage to nerve fiber-ensheathing myelin (a main target of the MS attack) diminished dramatically. The treated mice recovered faster as well, and didn't experience further relapses. Further study is necessary to translate these findings into a potential treatment strategy for people with MS.

The Journal of Experimental Medicine 2007;204(3):571–82

Keeping an eye on neurons too?

As is typical for our intricate immune system, microglia may not be all bad. Recent studies showed that microglia actually protected nerve cells after stroke in mice. Bruce Trapp, PhD (Cleveland Clinic Foundation) and colleagues, including Society-funded postdoctoral fellow Wadid Jalabi, PhD, observed that when stimulated by an immune response, microglia in mice become activated and physically surrounded the nerve cell body. **Glia** 2007;55(4):360–8

Dr. Trapp's team has since reported evidence of nerve cell regeneration in chronic lesions



The image shows how blood proteins (e.g., fibrinogen) leak into the brain and activate microglia, resulting in damage to nerve fiber-insulating myelin. Paradoxically, microglia—in their activated form, in which they surround nerve cells—may somehow **protect** these cells.

(areas of tissue damage) in brain tissue samples from people with MS. In 15 chronic lesions, nerve cells were increased by 72% compared with neighboring brain regions. Interestingly, one of the things that was different about these chronic lesions was evidence of an increase in activated microglia. **Brain** 2008;131(Pt 9):2366–75

So what does this mean for MS treatment? How can we stop microglia from over-reacting in terms of their immune system function, without causing them to under-react in terms of protecting nerve cells?

Radmilla Filipovic, PhD, and Nada Zecevic, MD, PhD (University of Connecticut

Health Center, Farmington) were funded to look at a unique approach to this question. The antibiotic minocycline has been shown to inhibit the activation of microglia and yet protect nerve cells from loss in animal models of MS. Small clinical trials in people with relapsing-remitting MS suggested decreased tissue damage, but the data were limited on the effects of minocycline on human nerve cells.

Drs. Filipovic and Zecevic studied whether minocycline would protect human nerve cells grown in lab dishes. They reported that the drug inhibited the activation and proliferation of microglia, but spared nerve cells. In particular, these neuro-

protective effects were noted when a specific enzyme—ERK 1/2—was blocked from signaling. Further studies are needed to confirm these findings, and to determine if they hold true in the current, larger-scale clinical trial of minocycline in people with MS. **Experimental Neurology** 2008 May;211(1):41–51

The two faces of microglia might seem confusing, but researchers investigating these paradoxical powerhouses are already finding the potential for novel strategies to treat people with MS.

In the news and on our Web site

● MS drug news and risk factors featured at 2009 American Academy of Neurology Meeting

More than 11,000 neurologists, investigators and trainees gathered in Seattle in late April for the 2009 annual meeting of the American Academy of Neurology, one of this country's top venues for sharing clinical

Read current news and details of these stories on our Web site: nationalMSSociety.org/bulletins.

research progress related to multiple sclerosis and other neurological disorders. This year, there were over 400 platform and poster presentations focusing on progress in MS.

Presented in abundance at the meeting were short and long-term studies of the currently approved, disease-modifying therapies for MS. These drugs generally continue to show benefits and sometimes reveal unsuspected mechanisms of action. But taking center stage at this year's meeting were the first public presentations of positive results from two phase 3 clinical trials of experimental oral therapies for relapsing

MS: cladribine and fingolimod. Read a complete wrap-up at nationalMSSociety.org/research/research-news/index.aspx.

● Is it MS or a look-alike? International Society task force offers guidelines

An international task force convened by the National MS Society has published a land-

mark paper to guide neurologists through the complex process of distinguishing MS from other disorders. The consensus-based guidelines should greatly enhance the accuracy of diagnosing MS and its look-alikes, and speed the delivery of appropriate therapies. These guidelines appear in the November 2008 issue of **Multiple Sclerosis** (<http://msj.sagepub.com/>).

Because of its potential impact, the Society provided funds to make this paper available to all at no charge.

● New study reports reduced overall cancer risk in people with MS

Swedish researchers report that risk for several types of cancers was reduced in people with MS, but that the risk for brain tumors and urinary cancer was increased. The study compared more than 20,000 people with MS with more than 200,000 people without MS. The reasons for these findings are unclear, but the study serves as a reminder to both people with MS and their health care providers of the need to keep careful watch on overall health.

● Keeping up with clinical trials:

The list of **Clinical Trials in MS 2009** includes 129 ongoing, planned or recently completed studies, and is now available at nationalMSSociety.org/clinicaltrials.

MS Trial Alerts were 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/trialsrecruiting to find ongoing studies in your area. ■

