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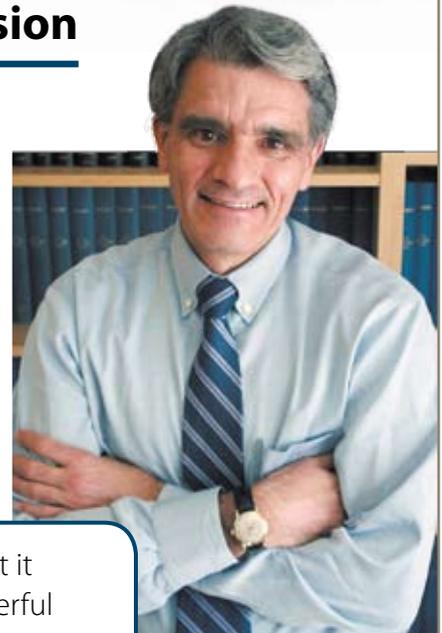
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On the cusp of a new world: MS gene pioneer Dr. Stephen Hauser shares his vision

by Sara Bernstein

This is a time of great momentum," said Stephen L. Hauser, MD. "We are at the cusp of understanding the genetic basis of MS with a resolution that we could never have imagined just two or three years ago." Dr. Hauser would know; he has received the National MS Society/American Academy of Neurology's 2008 John Dystel Prize for MS Research in recognition of two decades of pioneering studies on genetic susceptibility to MS.

Among his accomplishments is the establishment of a DNA "bank" in 1997 to carefully gather and store a large number of blood samples (from which DNA is derived) from people with MS and their family members. This vital Society-funded resource is



CASCADE WILHELM

"Wouldn't it be wonderful to prevent MS before it begins?"
—Dr. Hauser

shared with researchers around the world studying MS

susceptibility.

Although MS is not directly inherited, genetics plays an important role in who gets the disease, how they respond to therapies and possibly what course the disease will take. Most researchers believe that some additional factor determines whether a person who

has “MS genes” actually develops the disease.

Dr. Hauser’s excitement about MS genetics is due to the work of the International Multiple Sclerosis Genetics Consortium (IMSGC), a group of international MS genetic experts created with funding from the Society. Last year, Dr. Hauser and his IMSGC colleagues completed the largest replicated whole genome scan (scan of all the genes in the body) for MS to date, identifying two new genetic variations associated with MS (**The New England Journal of Medicine** 2007 Aug 30;357[9]:851–62).

The group is following up this study in a big way. “Drs. Alastair Compston and Stephen Sawcer in the United Kingdom are leading our consortium in

a very ambitious study of genetic susceptibility in more than 10,000 people with MS from across North America, Europe, Australia, and New Zealand,” said Dr. Hauser. “Most MS susceptibility genes will be identified from this study. Not only will we have a ‘dictionary’ of the genes that are important in MS, but much more significant, this information is likely to transform our understanding of just how MS begins.”

“Progressive MS needs to be a central focus of our efforts.”
—Dr. Hauser

Although Dr. Hauser surmises that there are probably 50 or so susceptibility genes for MS, he believes that identifying these genes will not complicate the MS picture, but will lead us to a much simpler view of disease pathways, better treatments, and prevention. The follow-up study is funded through the Wellcome Trust, and the Society is now raising funds to allow this team to take the imperative step of confirming its findings in a second set of 10,000 cases.

The pace of MS genetics research is increasing rapidly, thanks to tiny chips like this one—which contains data from the entire human genome.

“There’s a new spirit afoot in MS genetics—a spirit of collaboration,” said Dr. Hauser, noting that the IMSGC was formed with a Collaborative MS Research Center Award to David Hafler, MD (Harvard University, see p. 70). “And it’s safe to say that none of this progress would have hap-

pened without the support of the National MS Society. The Society is the engine that has made MS genetics on a global scale possible.”

Dr. Hauser hopes to follow up this genetics effort with a study of people who can be identified as being at increased genetic risk for MS. Investigators would seek to identify a series of changes in the immune system that occur before the damage to nerve-fiber insulating myelin—the hallmark of MS—begins. “Armed with new genetic knowledge and insight from immunology, we should be able to identify people at risk for MS and understand the very first steps,” said Dr. Hauser. “Wouldn’t it be wonderful to prevent MS before it begins?”

Physician, scientist, mentor...

Dr. Hauser’s partner in planning this immunology study is his mentor—and last year’s Dystel prize winner—Howard L. Weiner, MD (Brigham & Women’s Hospital, Boston). “It’s especially rewarding to win the prize after Howard because he exemplifies the best traditions of the physician scientist,” said Dr. Hauser.

The importance of mentoring the next generation of physician scientists cannot be overestimated, said Dr. Hauser. “They are the future, and the ones who will find the answers,” he said. “Many of us already in the field of MS are worried that the sacrifices that young people need to make as physician



COURTESY OF AFFYMETRIX

Dr. Hauser prepares DNA samples for research.



MS, a course of MS characterized by clearly defined flare-ups followed by partial or complete recovery periods. (**The New England Journal of Medicine** 2008 Feb 14;358[7]:676–88)

A clinical trial of rituximab in 439 people with primary-progressive MS (a course of MS for which no specific treatments are currently on the market) recently reported negative results, although

“There is nothing more fun, more important, or more ethical than medical science.”
—Dr. Hauser

scientists will prevent them from entering the field. It’s 22 years, and an average of \$130,000 of debt, from the end of high school to your first day as an independent physician scientist. On the other hand, there is nothing more fun, more important, or more ethical than medical science.”

Dr. Hauser is putting his money where his concerns are—he is donating the \$15,000 Dystel prize money to create an endowment to support young physician scientists at UCSE. “We need to put in place sustainable resources for outstanding young people who want to devote their lives to MS research. Of all National MS Society awards, the junior faculty award [the Harry Weaver Neuroscience Award] is perhaps the most important. This award made it possible for me to start my career in MS research. We need to expand awards for young people—the truly dedicated ones who are creative scientists and, equally important, caring doctors.”

Taking rituximab from bench to bedside

Dr. Hauser describes his own odyssey as a clinician scientist—his path in taking a drug from the laboratory to clinical trials in people with MS. Long interested in the immune activity that underlies MS, Dr. Hauser published seminal findings associating antibodies (proteins produced by B cells) with damage to the myelin. (**Nature Medicine** 1999 Feb;5[2]:170–5) These lab findings resulted in a clinical trial of rituximab (Rituxan, from Genentech and Biogen Idec), a drug that depletes B cells.

“The development of rituximab has been thrilling,” said Dr. Hauser. “We found that treatment was effective against relapsing-remitting MS beyond what we had imagined.” Dr. Hauser and colleagues reported that one course of this intravenous drug reduced disease activity and relapses for 48 weeks in people with relapsing-remitting

there were positive trends and data analysis is ongoing.

“Although the primary endpoint was not met, as we dig deeper into the data we will likely find a component of progressive MS that is caused by inflammation and that may be helped by treatments like rituximab,” said Dr. Hauser. “It may then be possible to identify groups of people with primary-progressive MS who *will* respond to this treatment, and design a trial that will have a good chance of showing clinical effect. Progressive MS needs to be a central focus of our efforts to develop better therapy.”

Dr. Hauser looks forward to a bright future in MS research, where novel collaborations and therapeutic strategies are bringing us closer to a world free of the disease. “These exciting new developments could change the face of what is possible for people with MS,” he concluded.

Fostering teamwork: Progress from the first MS Collaborative Centers

The first Collaborative MS Research Centers launched by the National MS Society in 2003 have completed their projects, and the results vouch for the potential of this award to speed us toward a world free of MS. These \$825,000 grants create teams where seasoned MS researchers work with experts from other fields, and basic scientists join clinical investigators, addressing tough issues in MS research.

New window on MS activity

Anne Cross, MD, assembled an interdisciplinary team at Washington University in St. Louis to determine whether a novel MRI technology—“diffusion tensor imaging,” or DTI, could do a better job than conventional MRI at differentiating the extent and types of tissue damage and repair in MS. DTI reveals how many protons in water molecules are moving in tissue, and in what direction. If fatty myelin is intact, then water should be repelled, but if it is damaged, water will infiltrate the tissue.

With funding from the Center Award, Dr. Cross, Sheng-Kwei Song, PhD, and a team of neurologists, radiologists, biophysicists, biomedical engineers and pharmacologists used DTI to extensively study models of MS-like disease. Their results

show great potential for using this technology as a noninvasive method of detecting damage to nerve fibers in MS and differentiating this damage from injury to the myelin that insulates nerve fibers.

In one study, the team showed that nerve fiber injury detected by DTI actually correlated with symptoms in mice with an MS-

Teams work! Society-funded collaborations are bringing new insights and new talents to the search for better answers.

like disease. (**NMR Biomedicine** 2007 Nov 28 [Epub ahead of print]) Such findings help to confirm the link between nerve fiber injury and the progression of disability in MS. Dr. Cross and colleagues also reported that DTI revealed abnormalities that were not apparent under a microscope. (**Magnetic Resonance Medicine** 2007 Apr;57(4):688–95)

Aside from scientific progress, Dr. Cross has used this award to establish a vibrant team of scientists dedicated to MS at her university. The group meets twice monthly to discuss progress. They have attracted new talent to the field, including Junqian Xu, PhD, who switched from cancer

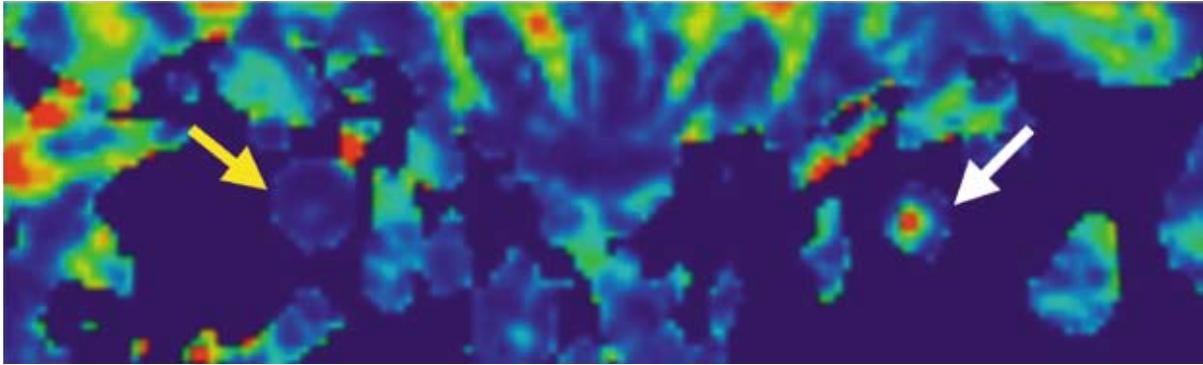
research to MS, and now has a postdoctoral fellowship from the National MS Society.

Going for genetic gold

In 2003, David A. Hafler, MD (Harvard Medical School and Brigham and Women’s Hospital) created an MS genetics “dream team” by joining with MS genetics pioneer Stephen L. Hauser, MD, (see p. 67), Eric Lander (Broad Institute of MIT and Harvard), who spearheaded the mapping of the human genome, and Alastair Compston, PhD, FRCP (University of Cambridge). The group received the Palmer Collaborative MS Research Center Award: MS Targeted Haplotype Project from the National MS Society to speed work toward discovering MS genes. (Funded by a generous gift from Barbara Palmer.)

Mission accomplished! This award propelled the formation of the IMSGC, an international group of investigators with expertise in genetics, database design/construction, and clinical assessment and immunology of MS. Members have established a shared DNA repository, which enables them to gather the large amounts of data necessary to conduct genetics studies.

In 2007, the IMSGC completed the largest replicated whole genome scan (scan of all the genes in the body) for MS to date, identifying two new genetic variations associated with MS. The findings



Collaboration among researchers at Washington University in St. Louis yielded new information on how diffusion tensor imaging (DTI) might enhance the ability to track nerve tissue damage in MS. This DTI image shows damage in the optic nerve in a person with chronic optic neuritis, an inflammation of the optic nerve that can be the first symptom of MS. Increased water content in the chronically affected eye (the yellow arrow) is seen with less organized structures (the blue color), indicating nerve tissue damage. The unaffected eye (white arrow) is seen with normal-appearing structures (red and green color).

point to potential mechanisms underlying the disease and present possible new targets for designing better therapies to stop the immune attack in MS. (*The New England Journal of Medicine* 2007 Aug 30;357[9]:851–62) The next steps for the IMSSGC are even more exciting—the consortium launched by Dr. Hafler’s Center Award is now engaged in an even larger study of over 10,000 patients in which they expect to identify all of the common MS susceptibility genes.

Closer to repairing myelin

Charles Stiles, PhD (Dana Farber Cancer Institute, Boston) and David Rowitch, MD, PhD (now at University of California, San Francisco) were investigating the foundation of brain cancer when they joined forces to identify “Olig” genes, which instruct

immature cells to become myelin-making oligodendrocytes. They showed that these genes are tremendously important in the early development of cells in the brain and spinal cord, and could hold the key to repairing myelin, the nerve insulator considered the main target in MS.

Although these scientists are experts in molecular genetics and brain development, they were relatively new to the field of MS, so they joined with an expert MS research team at Albert Einstein College of Medicine, including Cedric S. Raine, PhD, DSc, winner of the Society’s 1996 John Dystel Prize for MS Research.

It didn’t take long for this group to break new scientific ground. They studied Olig genes during development of the mouse brain and spinal cord, and in tissue samples from persons

with MS obtained by Dr. Raine’s group. The results show that Olig 1 is **required** for repairing myelin damage. (*Science* 2004 Dec 17;306[5704]:2111–5)

Based on these results, the work continues, as the group focuses on developing methods of enhancing Olig 1 activity and stimulating repair. Dr. Rowitch—who was doing mostly cancer research in 2003—is sticking with MS-related research, studying myelin-damaging diseases in children.

Fourteen Collaborative MS Research Centers are currently funded by the National MS Society to focus on many aspects of MS, including central nervous system repair, the search for MS therapies, and understanding MS damage and how to stop it. Read more about them on our Web site at nationalmssociety.org/CenterAwards.

New treatments await—if they can be tested: The challenges of clinical trials recruitment

by John R. Richert, MD

Clearly one of the most exciting aspects of MS research today is the number of experimental therapies in the late stages of clinical studies. In 2002, according to the Society's list of Clinical Trials in MS, there were only three large-scale studies recruiting more than 1000 people with MS; the 2008 list contains 11 such studies! These large, phase 3 studies are essential for gaining a better understanding of a new drug's safety and effectiveness.

Together, the 136 studies on the 2008 list have recruited, or are in the process of recruiting, more than 35,000 people to participate in clinical trials of MS agents. This is a difficult task. Investigators usually

have strict criteria by which they determine who may enroll in a study. On the patient side, participation requires a careful process of weighing the potential benefits and risks of possibly foregoing conventional therapies for the chance to try something new.

There also are aspects of MS that make patient recruitment particularly challenging. For example, some studies require that participants have never taken a disease-modifying agent. But, since the Society's National Clinical Advisory Board, among others, recommends that people diagnosed definitively with MS consider treatment as soon as possible, this is a hard group of people to find. Also, people

in the early stages of MS, whose symptoms might be mild, may not consider or desire enrolling in a clinical study.

Getting the word out

We're trying to help bring investigators and patients together through our online database of studies nationwide that are recruiting patients with MS. The database includes a section listing international studies. Thirty-six studies are currently recruiting patients and are listed with sites throughout the U.S. and in 11 other countries. The database is searchable by state and by type of MS.

Our clinical trials section also provides valuable information on what

Volunteers for clinical trials are needed! But each individual must consider possible risks and benefits before agreeing to take part.

you need to know before getting involved in a clinical study, and guidelines for making that decision. Visit this valuable resource at nationalmssociety.org/trials **recruiting**.

Seeking another gold standard

We also are making efforts to improve the process of clinical research by seeking alternatives to currently accepted trial designs and outcome measures, which are the mechanisms by which investigators determine the efficacy and safety of medications. Our International Advisory Committee on Clinical Trials in MS (IACCTMS) is greatly involved in this effort. They are working with Gary Cutter, PhD, head of the Section on Research Methods and Clinical Trials at the University of Alabama School of Public Health, to evaluate other clinical trial design strategies that might be more efficient, faster, and require fewer patients.

Furthermore, we are addressing changes in MS drug development. Our current FDA-approved disease-modifying treatments offset the immune attack on the brain and spinal cord, but none as yet directly addresses protecting nerve fibers, damage to which contributes significantly to progressive disease. Slowly, we are seeing more “neuroprotective” agents under study in MS. They include riluzole, a drug used to treat ALS (“Lou Gehrig’s disease”), and the cannabis derivative dronabinol.

A panel convened by the IACCTMS has recommended that neuroprotective studies include people with actively progressive disease and that the studies evaluate clinical signs and symptoms as well as MRI outcomes. They also recommended boosting the number of neuroprotective agents under study by using “weeding” studies, in which multiple treatments are tested simultaneously in smaller trials to determine which might succeed in larger efforts. (**Multiple Sclerosis** 2005;11:669–676)

Taking a balanced approach

Making it easier to study drugs should not come at the cost of patient safety. The IACCTMS led a task force on the ethics of placebo-controlled trials in MS which recently updated its recommendations. (**Neurology** 2008;70:1134) The use of placebos—“dummy” medications—as a control group for experimental therapies when there are multiple agents available to treat relapsing forms of MS has been of growing concern.

The task force recommended the use of placebo only in carefully chosen and conducted studies. In these clinical trials it is important that participants understand that other treatment options are available but that they are refusing these established, effective therapies in order to

take part in the new placebo-controlled clinical trial.

The task force’s recommendations highlight the great importance of the process of “informed consent.” This is usually thought of as the long, technical document that people sign when enrolling in a study, but actually it’s a process that continues throughout the study. The task force suggests using, when possible, a health professional or informed lay person who is not a member of the research team or affiliated with the sponsor to help the patient volunteers make autonomous decisions and to maintain his or her understanding of that decision throughout the study. They also recommend counseling and re-consenting during a placebo-controlled trial if there is a disease relapse or if an individual’s disease otherwise worsens during the study. We require that placebo-controlled studies listed on our Web site adhere to the recommendations of this task force.

As clinical research in MS heats up, we need to ensure that this long, complicated process gets easier for all of those involved, and yet remains safe and productive. We are proud to be guiding and facilitating this exciting era, as it will surely help us to stamp out MS.

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



BILL STANTON

In the news and on our Web site

● Compound protects nerves in mice with progressive MS

Harvard researchers reported that an experimental compound (a derivative of fullerene, a form of carbon molecule) reduced disease progression, as well as damage to nerve fibers and their myelin insulation, when administered to mice with a progressive MS-like disease. This novel study, partly funded by a National MS Society research grant, represents a different approach to preventing the progressive stages of MS. More work is needed to determine whether this new approach would be effective and safe in people.

● AAN highlights MS drug trials

MS was the focus of a record 338 presentations at the annual American Academy of Neurology meeting held in April in Chicago. National MS Society grantees were among those presenting novel findings on many different aspects of MS. New data analyzed from ongoing or completed clinical trials of drugs were presented, including promising results from a phase 2 study of daclizumab (PDL Biopharma and Biogen Idec) in people with relapsing MS who were taking interferons; preliminary results from two studies of low-dose naltrexone; and evidence that

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



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Copaxone (glatiramer acetate, Teva Pharmaceutical Industries Ltd.) reduced the risk of MS and delayed its development in individuals with CIS, clinically isolated syndrome, a first event suggestive of MS.

● New projects launched to propel MS research

The Society committed \$24 million to support 61 new MS research projects as part of its international effort to spur cutting-edge MS research. These include nearly \$2 million to investigators and trainees at the University of California, San Francisco who are searching for genes that make people susceptible to MS; a study in Italy on the potential of cell transplantation to repair the nervous system; and three new Collaborative MS Research Centers fostering innovative approaches to prevention, treatment and a cure.

● Study: Fampridine-SR speeds walking in all types of MS

Walking speed improved significantly in a clinical trial of 240 people with all types of MS taking Fampridine-SR (Acorda Therapeutics, Inc.) compared with those taking inactive placebo. This is a sustained-release formula of 4-aminopyridine, which temporarily enhances nerve signaling. The phase 3 results were reported by Acorda in a press release that also stated the company's intention to file for marketing approval to treat mobility issues in MS in 2009.

Researchers need your help:

MS Trial Alerts were posted on new clinical trials recruiting participants across the country and in Europe to test the next generation of MS therapies, including ones taken by mouth. Go to nationalmssociety.org/trials recruiting to find ongoing studies in your area. ■