

WHO? WHY? HOW?

Searching for the Cause of Multiple Sclerosis

NORTH AMERICAN EDUCATION PROGRAM 2010



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ACKNOWLEDGEMENTS

The National Multiple Sclerosis Society and the Multiple Sclerosis Society of Canada wish to acknowledge the generous support of Bayer HealthCare Pharmaceuticals, Biogen Idec, Genentech, Genzyme Corporation, and Teva Neuroscience, Inc. for the 2010 North American Education Program — *Who? Why? How? — Searching for the Cause of MS.*

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PREFACE

Welcome to the 2010–2011 North American Education Program. This program continues the successful collaboration between the National MS Society in the United States and the MS Society of Canada to provide the latest information about research and disease management in multiple sclerosis to thousands of people on our continent and around the world.

This year, thanks to generous sponsorship from Bayer Healthcare Pharmaceuticals, Biogen Idec, Genentech, Genzyme Corporation, and Teva Neuroscience, Inc., our program will focus on finding the cause of MS. You will learn about theories — past and present — and what the future may hold.

On behalf of our organizations and the program sponsors, we wish to express our appreciation to our researchers for taking the time to speak with us and for letting us into their labs. In addition, we want to thank the staff and volunteers of the National MS Society and MS Society of Canada chapters for

helping us to bring this program to you. We are delighted that you have chosen to participate in our program and hope that you find it interesting and exciting. Together, we will be learning about how scientists are searching for the cause of MS — research that could someday lead to a world free of MS. *We look forward to sharing this program with you.*

NANCY LAW
Executive Vice President
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PROGRAM OVERVIEW

Welcome to the 2010 North American Education Program, *Who? Why? How? — Searching for the Cause of MS*. The National MS Society began offering national education programs in 1988. The first national teleconference reached 700 participants in 60 sites. Since that time, we have utilized a range of technologies to expand our audience throughout North America.

By archiving our programs on the National MS Society website (nationalMSSociety.org), we have made it possible for people around the world to share the information as well.

In an effort to reach the broadest possible audience, and maintain the flexibility of our programming, we are again providing this year's program as a videotaped conference, thus enabling the chapters of the National MS Society and the MS Society of Canada the opportunity to offer the program to audiences at their convenience over the course of the year.

Near the end of the year the program will also be available on the National MS Society website as part of MS Learn Online (nationalMSSociety.org/MSLearnOnline) for anyone who is unable to participate in a program or would like to view or share the program more than once. In the video program, researchers discuss how understanding the causes of MS can provide hope for future MS treatments and possibly a world free of MS.

This program book provides an in-depth look at the etiology, or the study of the causes, of multiple sclerosis.

PROGRAM PRESENTERS

JEFFREY L. BENNETT, MD

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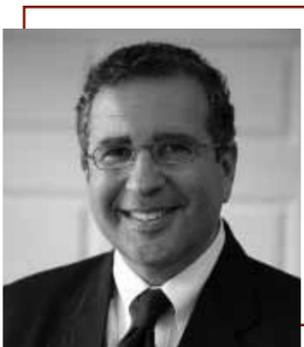
Dr. Jeffrey L. Bennett is currently Professor of Neurology and Ophthalmology at the University of Colorado Denver and is a faculty member of the Rocky Mountain MS Center at Anschutz Medical Campus. Dr. Bennett attended Case Western Reserve University, where he graduated summa cum laude with degrees in Biochemistry and Philosophy. He received his medical and doctoral degrees at Stanford University. Dr. Bennett completed his internship and residency in Neurology at the University of Colorado, fellowship in neuroophthalmology at the University of Pennsylvania, and post-doctoral research in the Department of Molecular, Cellular, and Developmental Biology at the University of Colorado, Boulder.

Dr. Bennett is internationally recognized as a leader in the fields of neuroimmunology, neuro-ophthalmology, and demyelinating disease. He directs clinical and basic research programs on optic neuritis, multiple sclerosis, and neuromyelitis optica. His research is supported by the National Institutes of Health, National Multiple Sclerosis Society, Guthy-Jackson Charitable Foundation, and private industry. In the laboratory, Dr. Bennett's research is focused on using advanced techniques in molecular immunology to identify the target of the immune response in neuro-inflammatory disorders.

Dr. Bennett maintains active specialty practices in neuro-ophthalmology and multiple sclerosis, and is regularly voted one of the Best Doctors in America. In 2006, he received the Stephen Reingold Award from the National Multiple Sclerosis Society. Dr. Bennett has written many clinical and scientific publications, been awarded numerous scholarly distinctions, serves on several scientific review committees, and serves in an editorial capacity for numerous scholarly publications in both neurology and ophthalmology.

DAVID A. HAFLER, MD

Gilbert H. Glaser
Professor of Neurology
Chairman, Department
of Neurology, Yale
School of Medicine



Dr. David A. Hafler is the Gilbert H. Glaser Professor and Chairman, Department of Neurology, Yale Schools of Medicine, and the Neurologist-in-Chief of the Yale-New Haven Hospital. He graduated magna cum laude in 1974 from Emory University with combined B.S. and M.Sc. degrees in biochemistry, and received his MD degree from the University of Miami School of Medicine in 1978. He then completed his internship in internal medicine at Johns Hopkins followed by a neurology residency at Cornell Medical Center-New York Hospital in New York. Dr. Hafler received training in immunology at the Rockefeller University, then at Harvard where he joined the faculty in 1984.

He was one of the Executive Directors of the Program in Immunology at Harvard Medical School and was on the faculty of the Harvard-MIT Health Science and Technology program where he was actively involved in the training of graduate students and post-doctoral fellows.

Dr. Hafler has been elected to membership in the American Society of Clinical Investigation, The American Neurological Association, the Alpha Omega Society, and was a Harvey Weaver Scholar of the National Multiple Sclerosis Society. He is currently a member of the editorial boards of the *Journal of Clinical Investigation* and the *Journal of Experimental Medicine*, and is co-founder of the Federation of Clinical Immunology Societies.

Dr. Hafler is a clinical scientist with a research interest in understanding the mechanism of autoimmunity, with a particular interest in inflammatory central nervous system diseases. He has more than 300 publications in the field of autoimmunity and immunology. He received the first National Multiple Sclerosis Five-Year Collaborative Center Award for work on the MS genetic effort. Dr. Hafler led the NIH Autoimmunity Prevention Center Grant at Harvard, and is a Jacob Javits Merit Award Recipient from the NIH.

His laboratory focuses on the understanding of human autoimmune diseases with the theme that investigation of naturally-occurring human diseases gives insight into the basic processes of T cell regulation, in addition to providing fundamental understanding and development of new therapies for human diseases.

Dr. Hafler is a founding member of the International MS Genetics Consortium, a group recently formed to define the genetic causes of MS, which includes scientists from University of Cambridge and the University of California, San Francisco.

**PAUL W.
O'CONNOR,
MD, MSC, FRCPC**

Director, University
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Dr. Paul O'Connor is a neurologist and Director of the Multiple Sclerosis Program at St. Michael's Hospital, University of Toronto. He is a Professor of Medicine (Neurology) at the University of Toronto and holds the Waugh Family Chair in Multiple Sclerosis Research. He directs the Clinical and Research Program at one of the largest MS Clinics in North America.

Dr. O'Connor's research interests include the development of new therapies for MS. He played a leading role in successful clinical trials of natalizumab for MS that resulted in the approval of this treatment in relapsing-remitting disease. His more recent research interests have focused on the development of oral therapies for MS, including teriflunomide, fingolimod and vitamin D.

Dr. O'Connor is a graduate of the University of Toronto and received his medical degree from the Royal College of Physicians and Surgeons of Canada in Neurology in 1985, with certification in Neurology

by the American Board of Psychiatry and Neurology in 1986. He received a Masters of Science degree in Clinical Epidemiology in 1991. In addition to the development of new therapies for MS, he has an ongoing interest in clinical trial design and ethics.

Dr. O'Connor also serves as the National Scientific and Clinical Advisor for the Multiple Sclerosis Society of Canada, and plays a major role in research administration and policy development on behalf of the MS Society of Canada. He is also president-elect of the Americas Committee for Treatment and Research in MS (ACTRIMS).

**PATRICIA A.
O'LOONEY, PhD**

Vice President of
Biomedical Research

National MS Society



As Vice President of Biomedical Research at the National MS Society, Dr. O'Looney directs and oversees the administration of the Society's biomedical research funding programs. Since joining the Society in 1988, she has provided leadership in directing and expanding the Society's research initiatives and encouraging collaborations across scientific disciplines in MS research. She has guided several of the Society's special research portfolios focusing on MS genetics, on gender differences in MS, on repair & protection of the damage in MS, as well as components of the Promise 2010 Campaign. In addition to coordinating the activities of the National Scientific Advisory Committees, she acts as a liaison between the medical & scientific community and those individuals suffering with MS by providing information about MS research developments to the MS community.

Dr. O'Looney holds a bachelor's degree in Molecular Biology from Regis College, Weston, MA, and a Master's Degree and a Ph.D. in Medical Biochemistry from the George Washington University Medical School in Washington, D.C. After completing her postdoctoral training, Dr. O'Looney held a dual faculty appointment in the Departments of Medicine and Biochemistry at the Medical School where she conducted research studies in lipoprotein metabolism in autoimmune diseases. She is a past recipient of the New Investigator Research Award from the National Institutes of Health and is the author of several publications in scientific/medical journals.

Memberships include the New York Academy of Sciences and the American Society for Biochemistry and Molecular Biology. She is also listed in several editions of Who's Who, including that of American Women, of Men and Women in Science, and Who's Who in Medicine & Healthcare, and Who's Who in the East.

BENJAMIN M. SEGAL, MD

Holtom-Garrett
Professor of Neurology

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Dr. Benjamin M. Segal joined the University of Michigan faculty in 2007, and directs the Multiple Sclerosis Center and the Holtom-Garrett Program in Neuroimmunology. The program's mission is to provide and support excellent diagnostic and medical management services for patients with MS. It also supports cutting-edge research in the pathophysiology of MS and protective treatments, and the education of young physicians and scientists in MS-related research.

Dr. Segal's goal is to see discoveries made in the laboratory translated into practical treatments. His multidisciplinary team is seeking to develop therapeutic vaccines and novel immune-modulating agents to improve the treatment of MS and advance nervous tissue repair.

Dr. Segal received a bachelor's degree in biochemistry in 1984 and medical degree in 1988, both from Brown University. He served an internship in Internal Medicine at the University of Chicago and a residency in Neurology at the Weill Medical College of Cornell University. He conducted research in Neuroimmunology as a Clinical Associate in the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH) from 1992–93, and as a Research Associate in the Laboratory of Immunology at the National Institute of Allergy and Infectious Diseases from 1993–99. Throughout his NIH tenure, Dr. Segal served as a Lieutenant Commander in the Public Health Service.

Dr. Segal was on faculty at the University of Rochester as an attending Neurologist, Associate Professor and Director of Neuroimmunology Research prior to coming to Michigan.

Dr. Segal's research interest is in the immunopathology of multiple sclerosis. His discoveries have contributed to the current understanding of how different types of white blood cells and the chemical messengers they secrete perpetuate inflammation and mediate tissue injury in the central nervous system during multiple sclerosis and similar diseases. His research led to three patents for immunotherapeutic agents in MS.

Dr. Segal's studies have been published in prestigious journals such as *The Journal of Experimental Medicine*, *Blood*, and the Cutting Edge section of *The Journal of Immunology*. His discoveries have been featured in *Nature Reviews Immunology* and highlighted in the "Discoveries in Neuroscience" section of *Annals of Neurology*.

His scientific contributions have been recognized by numerous awards, including a Commendation Medal for Excellence from the Public Health Service, a Harry Weaver Junior Faculty Award from the National Multiple Sclerosis Society, and the Stanley Aronson Award for Excellence in the Clinical Neurosciences.

Dr. Segal is a member of the American Association of Immunologists, the American Academy of Neurology and the American Neurological Association. He is an ad hoc reviewer for NIH study sections and numerous professional journals, including *Cellular Immunology*, *Clinical Immunology and Immunopathology*, *Immunopharmacology*, *Journal of Immunology*, *Journal of Experimental Medicine*, *Neurology*, and *Proceedings of the National Academy of Sciences*. He also serves as a volunteer on one of the National MS Society's scientific advisory committees on the scientific study section of the National MS Society.

**HELEN
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Department of Neurology
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Dr. Helen Tremlett is an associate professor on the Faculty of Medicine (Neurology) at the University of British Columbia, Vancouver, Canada, and holds an associate position within the School of Population and Public Health.

Dr. Tremlett's research is funded by a Don Paty Career Development award from the MS Society of Canada. She is a Michael Smith for Health Research Scholar and is principal investigator on grants from the Canadian Institutes of Health Research, US National MS Society, UK's MS Trust, and the BC Clinical Genome Network. Originally trained as a pharmacist from the UK, Dr. Tremlett has specialized in epidemiology and multiple sclerosis. She is research director of the British Columbia Multiple Sclerosis database, one of the largest of its kind in the world.

Dr. Tremlett also heads the Pharmacoepidemiology in MS (PIMS) research group and is the author of more than 35 peer-reviewed publications and over 50 abstracts presented at national and international conferences. Her current research interests include: the natural history of MS; prognosis and predictors of disease progression in MS; effectiveness of the immunomodulatory drugs (IMDs) in MS; adverse effects of the MS IMDs; MS epidemiology; cancer and MS; pregnancy outcomes in MS; as well as vitamin D, sunlight, infections and MS disease activity.

**JERRY S.
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Bartels Family and
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Dr. Jerry S. Wolinsky, MD, holds the Bartels Family and Opal C. Rankin Professorship of Neurology and is a member of the faculty of the Graduate School of Biomedical Sciences at The University of Texas Health Science Center at Houston, where he also serves as director of the Multiple Sclerosis Research Group and the Magnetic Resonance Imaging Analysis Center.

Dr. Wolinsky received his medical degree in 1969 from The University of Illinois. Residency training in clinical neurology, followed by a fellowship in experimental neuropathology and faculty appointment at The University of California San Francisco. While in San Francisco his research interests concentrated on the pathogenesis of viral infections of the nervous system, and his clinical efforts began to focus on experimental therapeutics of infections of the central nervous system and multiple sclerosis (MS).

He joined the faculties of The Johns Hopkins University School of Medicine, and the School of Public Health in 1978 before settling in Houston in 1983. In Baltimore he applied more molecular tools to his basic investigations and became increasingly interested in the primary and secondary immunopathogenesis of neural disease. He currently is active in the design, implementation, conduct, and analysis of clinical trials of MS and conducts basic and applied research in quantitative MRI and MR spectroscopic imaging in demyelinating diseases.

WHAT IS THE CAUSE OF MS?

An important question that must be asked about any disease, including multiple sclerosis (MS), is “what causes it?”. This is technically known as the *etiology* of the disease. Only when we begin to understand the answers to this question does it become possible to develop better therapies to effectively treat and prevent the disease.

Dr. Wolinsky has served on review and advisory committees of the National Institutes of Health, MS International Federation, U.S. Food and Drug Administration, numerous pharmaceutical companies, the Sylvia Lawry Centre for MS Research, and as interim Dean of the University of Texas Medical School at Houston.

Dr. Wolinsky currently oversees the centralized image analysis programs for the NINDS-sponsored CombiRx Trial and the Sanofi Aventis clinical development studies of teriflunomide in MS. He is past chair of the Research Programs Advisory Committee and current chair of the National Clinical Advisory Board of the National MS Society, and current President of Americas Committee for Treatment and Research in MS (ACTRIMS). He is on the editorial board of *Multiple Sclerosis*, and recognized in Best Doctors in America and America’s Top Doctors. He has authored more than 250 publications in neurovirology and neuroimmunology, clinical trials, and the imaging of MS.

MS involves immune-system attacks against the body’s own brain and spinal cord. The disease is not directly inherited, but it is known to occur in people who have a genetic predisposition to develop it. However, a great deal of evidence suggests that most people who are genetically susceptible to MS will only develop the disease if they are exposed to some other factor or factors in their environment or life experience. Some researchers theorize that MS develops because a person is born with a genetic predisposition to react to some

environmental agent that, upon exposure, triggers an autoimmune response. Since a combination of several factors appears to be needed for MS to develop, the cause of MS is what is termed *multifactorial*, meaning that it requires more than one agent or event to occur at the right time and in the right sequence to trigger the disease.

One leading hypothesis is that MS occurs as the result of viral infection in genetically susceptible individuals, but many other possibilities have been

THE ROLE OF GENETICS IN THE DEVELOPMENT OF MULTIPLE SCLEROSIS

Although MS is not hereditary in a strict sense, having a first-degree relative such as a parent or sibling with MS does increase a person's risk of developing the disease several-fold above the risk for the general population. There is a higher prevalence of certain genes in populations with higher rates of MS. Common genetic factors have also been found in some families in which more than one person has MS. Sophisticated new techniques for identifying genes may help answer questions about their role in the development of MS.

studied, including environmental and industrial toxins, diet, trace metal exposures, and certain climatic elements such as sunlight.

As yet, none of these have been causally linked to MS, and exactly what factor(s) may be involved remains an open question.

Many investigators believe that no single infectious agent or environmental factor is “the” cause of MS. Rather, they are exploring how a susceptible person's immune system reacts to a variety of viral or other infections and environmental exposures, and how immune function is linked to hormonal and other factors.

MS is considered to be an *auto-immune* disease, in which the body misidentifies some part of itself as a foreign invader. In MS, the part of the body that is mistaken as an invader is the protective covering of nerve fibers — the myelin sheath. The cells that make myelin are also damaged, as are the underlying nerve fibers themselves. It is not known at this time whether these are direct targets of the immune attacks or simply bystanders.

It is possible that the initial cause of MS could be an overreaction to a real foreign invader, such as a virus or bacteria. This overreaction could cause the immune system to attack myelin in addition to the invading virus or bacteria.

It is important to note that, although a viral or other infection may be involved in its development, there is no evidence that MS is either infectious or contagious.

Finding a way to prevent MS will require understanding the genes that make people susceptible to developing the disease, and also identifying the environmental triggers to avoid or otherwise derail so that MS is prevented from developing.

Because genetic susceptibility appears to be the key to understanding the cause of MS, we first discuss what is known about the genetics of MS, followed by a consideration of possible triggering factors in the environment, including infectious agents. We then review what is known about the immunology of MS, where genetic and environmental factors ultimately have their effect. Lastly, we look at chronic cerebrospinal venous insufficiency (CCSVI), a newcomer to the theories about what causes MS.

Genetic inheritance appears to be only one of several factors that determine who gets MS. Most likely, an individual's genetic blueprint ultimately determines whether he or she will be susceptible to a triggering factor or factors in the environment, which in turn initiates the autoimmune process that leads to the development of MS.

GENETIC SUSCEPTIBILITY AMONG FAMILY MEMBERS OF PEOPLE WITH MS

The average person in the United States has about one chance in 750 of developing MS. First-degree relatives of people with MS — such as children, siblings or non-identical twins — have a higher chance of developing the disease. This increase is significant but still relatively low. The identical twin of someone with MS, who shares all the same genes, has a 25–30% chance of developing the disease.

If genes were *solely* responsible for determining who gets MS, an identical twin of someone with MS would always develop the disease; the fact that the risk is only one in four demonstrates that other factors — including gender, geography, ethnicity, and infections — are likely involved as well.

However, these risk estimates are oversimplifications that can easily be misinterpreted. For example, they can vary greatly depending upon the structure of a person's family. In families in which MS occurs in many relatives — called *multiplex* families — the risks for any given individual are significantly increased. Common genetic factors have been found in some of these families.

Risk for MS is also affected in part by a person's ethnic background and other factors that have not as yet been clearly identified. For example, there is a higher prevalence of certain genes in populations that have a higher rate of MS, even though they do not all develop MS. This is true in the Scandinavian countries, which have a high incidence of MS compared to other areas of Europe, and higher-than-average levels of MS are seen in those regions of North America with significant numbers of individuals of Scandinavian descent. Specific genes have been linked to MS in this population.

Sophisticated new techniques for identifying genes may help answer questions about the role of genes in the development of MS.

NEW TECHNIQUES HELP PINPOINT GENETIC FACTORS

In the past several decades, scientists have developed tools that give them the ability to pinpoint the genetic factors that make a person susceptible to MS. These tools are the methods of *molecular genetics* — techniques used to isolate and determine the chemical structure of genes.

In the 1980s, scientists began to apply these tools to human diseases caused by defects in single genes. This led to major advances in understanding diseases such as Duchenne muscular dystrophy and cystic fibrosis. The situation for a multifactorial disease such as MS is more complicated, requiring the right combination and timing of genetic and triggering factors.

Advances in molecular genetics and the identification of multiplex families facilitated scientists' efforts to uncover MS susceptibility genes. The National MS Society and others have supported projects searching for these genes. The research teams have the challenging task of finding an unknown number of genes that confer susceptibility to MS. This requires searching the 3.2 billion components of the DNA that form the code of the 30,000 to 40,000 genes in the human genome.

LOOKING FOR DNA MARKERS

In the 1990s, genetics research in MS focused on multiplex families participating in genetic studies. The researchers were looking for patterns of genetic material that are consistently inherited by people with MS. These recognizable patterns are called DNA markers. To do this, scientists probed family members' DNA, searching for identifiable patterns or markers in the DNA code inherited by the individuals with the disease but absent in their relatives who do not have MS.

When one of these markers was identified, scientists focused on that area, seeking additional markers closer to that gene. Eventually, the location of the gene was identified. By 1996, many locations that might contain genes contributing to MS had been identified, but no single gene could be shown to have a major influence on MS susceptibility. It became clear that many genes are probably involved in making people susceptible to MS, and this research also made it clear that a new approach would be needed to make better headway in understanding MS genes.

In 2003, the National MS Society and the NIH brought together most of the leading researchers focusing on searching for MS genes. These included the Finnish Study of MS Genes (looking at a unique, ethnically homogenous population of families with MS in Finland); the Canadian Collaborative Project on Genetic Susceptibility in MS (utilizing a database of approximately 21,000 people with MS and relatives at 19 clinics throughout Canada); the Melbourne MS Genetics Group (a team investigating the population of Tasmania, Australia); GAMES (Genetic Analysis of MS in Europeans, a collaboration of 19 groups from 16 European countries); and the U.S. MS Genetics Group (a collaboration of researchers at Vanderbilt University, Duke University, and the University of California, San Francisco). This important meeting opened up new lines of communication and spurred consideration of several new strategies for identifying MS genes.

The field of genetics exploded in 2003 with the completion of The Human Genome Project — the map of all genetic material in humans — which essentially created a reference library for genetic studies. The follow-up to the Human Genome Project, the International HapMap Project, added even more power to the field of genetics by mapping common genetic variations in the human population. Comparing these variations in people with and without disease can help to pinpoint disease genes. These projects, and the development of gene “chip” technology that can analyze hundreds of thousands of variations at once, are the latest tools that MS gene searchers are using to shed light on the multiple genes that can make a person susceptible to MS.

In 2003, Drs. David A. Hafler (Harvard Medical School and Brigham and Women’s Hospital), Stephen Hauser (University of California, San Francisco), and Eric Lander (Broad Institute of MIT and Harvard) jointly received the Palmer Collaborative MS Research Center Award from the National MS Society for the MS Targeted Haplotype Project. The Project was designed to pool expertise and resources in an attempt to speed work toward discovering MS genes. This award propelled the formation of the International Multiple Sclerosis Genetics Consortium (IMSGC), a collaborating group of many of the major MS genetics investigator laboratories around the world.

NOVEL GENETIC VARIATIONS

These researchers used a DNA “chip,” a new technological advance that uses a grid containing multiple genetic components. This enabled the collaborators to test 500,000 individual genetic locations (sites within genes) at one time for possible involvement in MS. This, in turn, enabled them to scan blocks of the human genome for variations that were more commonly inherited by people with MS compared to those without the disease. They screened the genome in 931 “trio families,” each of which included a person with one of several different types of MS and his or her unaffected parents.

To double-check their findings, the researchers performed a second analysis of other sets of families, individual cases of MS, and a control group. Ultimately, all samples were combined for a final analysis of more than 12,000 people.

The IMSGC’s high-powered analysis resulted in the identification of two novel genetic variations that showed a highly significant association with MS. These variations are in the genes that control the function of messenger protein. Since that time, dozens of genes have been linked to MS through the use of similar genome-wide scanning techniques involving samples from thousands of people who have MS. Most of the genes identified to date are related to immune function, and several have also been identified as playing potential roles in other autoimmune diseases. Work is underway to:

- Finalize the identification of all of the common genetic variations that are linked to MS susceptibility. (The IMSGC is now conducting a genome-wide scan in 10,000 people with MS which they hope will finally identify all common gene variations linked to MS.)
- Determine the functions of these variations and how they influence immune activity.
- Explore genes that may control individual responses to therapy and others that may help protect against development of the disease.

IMPLICATIONS FOR PEOPLE WITH MS

Taken together, these studies point to potential mechanisms underlying the disease and present possible new targets for designing better therapies to stop the immune attack in MS.

Investigators agree that right now, the identification of many gene variations linked to MS susceptibility is unlikely to change current clinical practice, and that there are likely many more genes that contribute to disease susceptibility. As these additional genes are probed further for their role in MS, they may lead both to a greater understanding of the cause of MS, and also to the recognition of important new therapeutic targets.

EPIDEMIOLOGY: WHO DEVELOPS MS?

Epidemiology leads to and investigates hypotheses about the cause of a disease, and has contributed a great deal to our understanding of what causes MS. A major focus of epidemiologic studies is to determine *who* develops MS. This type of study has helped to identify factors that may be related to the risk of developing MS, including geography, genetics, environment, and infectious agents, but we still have few definitive answers. Although almost anyone may develop MS, some people appear to be at greater risk than others.

OBSERVATIONS FROM EPIDEM- IOLOGIC STUDIES

These include:

- There are an estimated 400,000 people living with MS in the United States, and at least 2.1 million people worldwide that have the disease.
- Most people are diagnosed between the ages of 20 and 50, although MS can occur in young children and older adults.
- MS is at least two to three times more common in women than in men. This type of gender bias is seen in many autoimmune diseases.
- As discussed in the previous section, genetic factors make certain individuals more susceptible than others, although there is no evidence that MS is directly inherited.
- MS occurs more frequently in relatives of people with MS, indicating that genetic factors are involved in developing MS.

- MS occurs in most ethnic groups, including African-Americans, Asians, and Hispanics/Latinos, but is more common in Caucasians of northern European ancestry.
- Some possible risk factors for MS have been identified, including cigarette smoking and previous exposure to the Epstein Barr virus.
- Some possible protective factors have been identified for MS, including vitamin D and greater exposure to sunlight (through which the body manufactures vitamin D).

The National MS Society and the MS Society of Canada sponsor many epidemiology research studies that focus on triggering or risk factors that influence whether a person develops the disease. These include disease *patterns*, such as variations in geography, demographics, socioeconomic status, genetics, environmental risk factors, and exposure to infectious agents. These studies provide vital information about relationships among these factors, so that we can better understand who gets MS and why, as well as identify and explain areas with high or low rates.

RECENT RESEARCH PROJECTS RELATED TO EPIDEMIOLOGY AND POSSIBLE INFECTIOUS TRIGGERS OF MS SPONSORED BY THE NATIONAL MS SOCIETY & THE MS SOCIETY OF CANADA

These include:

Anthony J. McMichael, MBBS, PhD (The Australian National University) is conducting a case control study of past sun exposure and first demyelinating events to investigate whether vitamin D, through sunlight exposure, reduces the risk of developing MS. Recent research indicates that ultraviolet radiation (UVR) or vitamin D synthesized via UVR exposure can dampen the immune attack. This might provide a biological mechanism for reduced MS where UVR exposure is higher.

ENVIRONMENTAL FACTORS & MULTIPLE SCLEROSIS

The team is comparing lifetime sun exposure in two groups — people at risk for developing MS (because they experienced an initial neurologic episode) and people without MS — using advanced imaging technology to examine skin, measuring vitamin D status (produced by UVR), and administering a questionnaire about sun exposure. This study may bring us new insight into non-genetic factors that may make people susceptible to the development of MS, and may suggest new avenues for treatment or prevention.

Researchers at the University of Utah are following up on evidence that colds caused by *picornoviruses* are associated with MS attacks. They are seeking to determine whether specific viruses that cause colds may be linked to MS attacks, and to compare MS attack rates in individuals whose colds are due to picornoviruses as compared to other types of virus. This study may provide important clues to the specific viral triggers of some MS attacks, as well as new leads for preventing or treating those attacks.

Helen Tremlett, PhD (University of British Columbia) is asking: *Do relapses affect disease progression in MS?* by evaluating the long-term relationship between MS attacks and disability. The majority of people with MS experience disabling relapses that can last weeks to months before a full or partial recovery occurs. However, the progression to permanent disability is not necessarily associated with a relapse.

The team is focusing on patients enrolled in a database of 6,000 people with MS in British Columbia. They are examining relapse rates in over 2,500 people who have not taken disease-modifying drugs and have been followed for up to 23 years. They are investigating the effect of MS relapses occurring at different stages of the disease on disability progression, using measures such as the Expanded Disability Status Scale (EDSS). This study may provide much needed information on the progression of MS, and on how to tailor treatments for individuals with the disease.

Lauren Krupp, MD (State University of New York at Stony Brook) has been identifying cases and characteristics of pediatric MS (in children under 18) in a region of New York, to lay the groundwork for future studies of this condition.

Since this study began, thanks to its Promise: 2010 campaign, the National MS Society established the first-of-its-kind network of six Pediatric MS Centers of Excellence, including a Center led by Dr. Krupp. The Centers provide comprehensive evaluation and care to children with MS and related central nervous system demyelinating disorders. Now the way is clear for deeper research into the triggers of MS in young children, which may clarify the cause of MS in adults as well.

MS occurs more frequently in areas that are farther from the equator. Epidemiologists are looking at many factors in an effort to understand why, including variations in geography, demographics (age, gender, and ethnic background), genetics, infectious causes, and migration patterns. Migration patterns show that people born in an area of the world with a high risk of MS who move to an area with a lower risk often acquire the risk of their new area. This suggests that exposure to some environmental agent may predispose a person to develop MS.

GEOGRAPHY & MIGRATION PATTERNS

The incidence of a disease whose cause is *entirely* genetic will be unaffected by migration. On the other hand, an alteration in the risk of disease after migration is compelling evidence that one or more environmental factors must be involved in its development. The extensive data on migration and its impact on the risk of developing MS clearly support the existence of an interaction between environment and genetics.

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 of 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 his colleagues at the Lankenau Institute for Medical Research, Wynnewood, PA have found that cases of MS increased with the length of time spent in Israel, no matter 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.)

MS clusters — higher-than-expected numbers of cases of MS that have occurred over a specific time period and/or in a certain area — may provide clues to environmental factors that might cause or trigger the disease.

The study of environmental factors that affect MS is closely linked to epidemiology. A wide variety of possible environmental factors have been looked at over past decades. Although none has been determined as *the* cause of MS, some appear promising as contributing to the multifactorial nature of MS.

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.

VITAMIN D & SUNLIGHT

Migration patterns and other epidemiologic data show that people who live nearer to the equator have a lower chance of developing MS than those who live farther from it. Some scientists think the reason may have something to do with vitamin D.

The human body produces vitamin D naturally when the skin is exposed to sunlight, and people who live closer to the equator are exposed to greater amounts of sunlight year-round. As a result, they tend to have higher levels of naturally-produced vitamin D, which is thought to have a beneficial impact on immune function and may help protect against autoimmune diseases such as MS. The possible relationship between MS and sunlight exposure is currently being looked at in a Society-funded epidemiologic study in Australia.

Another study indicated that women whose intake of vitamin D is greater than or equal to about 400 IU/day from supplements and food, or from supplements alone, had a 40% lower risk of developing MS than women who did not take vitamin D supplements.

Additionally, preliminary research indicates that vitamin D can alter immune attacks in mice with MS-like disease.

A team of researchers at Oxford University led by Dr. George Ebers has found what may be the link between vitamin D and genetics; he demonstrated that vitamin D affects the ability of a genetic variant previously linked to the development of MS to function normally.

So, can vitamin D supplements alter MS disease activity? Dr. Paul O'Connor, (St. Michael's Hospital, Toronto) and colleagues compared 25 people with MS over 52 weeks, with 24 untreated controls.

Reporting early findings at the October 2007 ECTRIMS meeting, the researchers found that calcium levels did not reach abnormally high levels in this small study. The relapse rate was reduced more in the treatment group, but this finding did not reach statistical significance. The group says it is now planning a phase II study of vitamin D supplementation in 150 to 200 people with MS.

SMOKING

Evidence from several studies suggests a statistically significant association between smoking and the risk of developing MS. A recent study funded by the National MS Society reported that smoking is associated with a moderate increase in the risk of developing MS, and also found an association between smoking and the risk of MS progression in people already diagnosed with the disease.

It is not clear how smoking may contribute to MS risks, but there are plenty of reasons not to smoke. It is known to produce shortness of breath, susceptibility to lung infections, and heartbeat irregularities in many people. These might transform a mild or moderate neurologic limitation into a severe disability.

In a study published in spring 2010, Harvard researchers, with collaborators in Australia and Sweden, found that two individual factors that had been previously identified as increasing the likelihood of developing MS — exposure to Epstein-Barr virus and tobacco smoking — may interact and multiply to substantially increase the risk of developing MS in those with both risk factors. Further research is needed to understand how these factors may interact.

TOXIC SUBSTANCES

People living near hazardous waste sites in the US have expressed concern to public health officials about a perceived high prevalence of MS in their communities and its possible link to exposure to chemical agents from the waste sites. Preliminary studies have collected prevalence data for some of these areas, but much additional work is needed to fully investigate even a fraction of these proposed sites.

A potentially important clue to MS is to understand who gets the disease. Is MS on the rise? Are more women getting MS than ever before? These and other questions 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 (CDC) 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 National MS Society is advocating for a national surveillance system that could be an important step in driving research to understand interactions between genetic and environmental factors that cause MS.

Radon exposure is being investigated in a case-controlled study of 100 people with MS and 100 non-MS neurology patients in the Kansas City area. All participants are being asked to complete questionnaires that include questions on occupation, exposure to chemicals, family history of MS, smoking, and other factors. Part of this group will be asked to allow their homes to be measured for radon gas. The results of this study have not yet been published.

HORMONES

MS is approximately two to three times more common in women than in men, and attacks are less likely during pregnancy — findings that have led to a number of studies on the possible influence of sex hormones on the disease. This research has also led to hypotheses about a possible association between oral contraceptives, which may include the sex hormones estrogen or progesterone, and a reduced risk of MS.

Previous studies of oral contraceptives and MS have shown mixed results. Harvard researchers have published a study suggesting that women who use oral contraceptives during the three years prior to diagnosis had a 40% reduction in the risk of developing MS compared to nonusers.

This study provides further support for the concept of hormonal influences in MS, but does not provide direct evidence that oral contraceptives can prevent the onset of this disease. Currently, a form of estrogen is being tested in a multi-center clinical trial in women with relapsing MS to determine whether this hormone can enhance the benefits of interferon beta therapy.

TETANUS VACCINE

A recently published study by Harvard researchers reported that people who had received tetanus vaccine were one-third less likely to develop MS than those who had not been vaccinated. The investigators used sophisticated analytic techniques to pool the results of nine previous studies to compare 963 individuals with MS to 3,126 “controls” who were friends or relatives, who had other neurologic disorders, or who were from the general population. The controls were more likely to have had a history of tetanus vaccine than those in the MS group.

The authors suggest that something about tetanus vaccination may be protective against MS, and that further research is warranted to determine the possible role of the timing of the immunization and the number of doses. As this was a retrospective study, based on retrievable reports in the literature, no firm conclusions as to cause and effect can be drawn.

CLUSTERS & EPIDEMICS

A *cluster* of MS can be defined as higher-than-expected numbers of cases of MS that have occurred over a specific time period and/or in a certain area, and may provide clues to environmental or genetic risk factors that might cause or trigger the disease. However, although certain “clusters” of MS have been suggested, to date they have not produced clear evidence for a causative or triggering factor in MS.

Clusters are difficult to investigate because it is difficult to determine what constitutes an “excess” of cases of MS. Surprising as it sometimes seems, an apparently extraordinary number of MS cases in a neighborhood or county may turn out to be the “expected” number.

In addition, MS clusters are difficult to investigate due to the uncertainty of the MS diagnosis, the lag time between clinical onset and diagnosis, and the possibility of simple coincidence.

Perhaps the best-known clusters are a series of alleged epidemics that occurred in the Faroe Islands, a Danish possession in the Atlantic between Norway and Iceland. Although the inhabitants are Nordic and considered a high-risk group for the disease, there were no known reports of MS prior to 1943 among native-born residents. In the early 1960s, Dr. John Kurtzke became intrigued with a report by a Danish investigator, K. Hyllsted, about 25 cases of MS in the Faroes that had occurred starting in 1943.

It appeared that the disease had been brought into the Faroes since it hadn’t been reported there before.

The most significant event that had taken place on the Faroes was the British occupation during World War II. Many of the occupation soldiers were from the Scottish Highlands, where the MS prevalence is quite high: 90 cases per 100,000. If MS is triggered by a virus, the disease might have been brought to the Faroes by the soldiers. However, despite years of intensive investigation, no factor has yet been identified that can definitively account for the alleged epidemic.

EVIDENCE FOR AN INFECTIOUS CAUSE OF MS

Since initial exposure to numerous viruses, bacteria, and other microbes occurs during childhood, and since viruses are well recognized as causes of demyelination and inflammation, it is possible that a virus or other infectious agent is the triggering factor in MS. More than a dozen viruses and bacteria have been or are being investigated to determine if they are involved in the development of MS, but none have been definitively proven to trigger MS. Most MS experts believe that some infectious agent, most probably a virus, is involved in initiating the disease process. Researchers have long searched for a specific, identifiable virus related to MS, with the hope that this will result in a relatively simple explanation for the disease, and that combating such a virus with a specific vaccination will result in a safe and effective prevention strategy (as was the case in the control of poliomyelitis beginning in the 1950s) or a specific virus-focused treatment.

The possible involvement of a virus or viruses in the development of MS is suggested by several observations:

- Virus infections can cause human diseases that have characteristics similar to those of MS.
- Certain viral diseases in laboratory animals result in myelin damage similar to that seen in MS.
- Some viral infections, particularly those that affect the upper respiratory tract, may trigger acute exacerbations in people who already have MS.
- As discussed above, data from epidemiologic studies suggest that exposure to an infectious agent may be involved in causing MS.
- Some viruses are known to have a long latency period between time of infection and appearance of clinical symptoms, as is thought to be the case in MS.
- Increased antibodies to many different viruses have been found in the blood and cerebrospinal fluid of people with MS.

Although many different viruses have been studied as possible causes of MS, there has not yet been definitive proof linking any one virus to the autoimmune reaction that is believed to be responsible for the demyelination seen in MS. At one time or another, canine distemper virus, measles virus, herpes virus (HHV-6), rubella (German measles) virus, HTLV-1 virus, and others have been reported to be associated with MS. Measles, mumps, rubella, and varicella are common childhood infections, and all have been considered as potential causal agents.

At least 30 case control studies have investigated the association between measles and MS, with mixed results. With the exception of HHV-6, later studies have not substantiated these reports, and there is no proof that any of them causes MS. To date, an association with the Epstein-Barr virus (EBV) appears to be the most promising line of investigation.

In recent years, most of the focus has been on viruses that are very common in the general population — not necessarily isolated only in individuals with MS — such as EBV, the cause of infectious mononucleosis. The possible involvement of one or more of these viruses in the development of MS is based on epidemiologic studies, the presence of higher levels of antibodies against a given virus in individuals with MS, or — more recently — evidence from very sophisticated polymerase chain reaction (PCR) analysis that can detect the “footprint” of a viral protein in body fluids and tissues even if the virus has been long eliminated by the immune system.

THE EPSTEIN-BARR VIRUS (EBV)

Since virtually everyone in the population has been exposed to these viruses, but not everyone has MS, the question arises as to how common infectious agents might be involved with MS when relatively few people have the disease. Are these false leads and not really causes of MS? Are such agents simply associated with MS or are they “co-factors” that are required, but not in themselves sufficient, to cause the disease? If so, what else might be required for the disease to appear?

This is where *genetic susceptibility* may have its impact: while a common infectious agent may be a trigger for MS, perhaps the disease will only occur in people who carry a genetic susceptibility to it. Is it possible that both — a triggering agent and the “right” genetic background — are required, and that neither alone is sufficient for MS to develop?

EBV is a very common virus that causes infectious mononucleosis and other disorders. Several studies have suggested that it may be involved in the development of MS, and it is a good example of the promise and problems associated with the study of viruses and MS:

- A study published in 2003 suggested that increased levels of immune antibodies to EBV might be associated with an increased risk of developing MS, although no specific causal relationship was established. The researchers found that, although virtually all of the study participants — with and without MS — had been exposed to this virus, levels of antibodies to EBV were consistently higher in those individuals who subsequently developed MS than in those who did not. Furthermore, the risk of developing MS increased with increasing levels of antibodies.
- In 2006, investigators reported that individuals who showed signs of significant exposure to EBV were twice as likely to develop MS up to 20 years later. More recent studies have added evidence to the link between EBV and MS, but they still do not prove that EBV actually causes MS.
- In 2007, investigators reported finding traces of EBV in brains examined after death from people with different forms of MS. They found traces of EBV infection in immune cells that were present in 21 out of 22 brains from people with MS, but not in the brains of people who had other neurologic diseases that, like MS, involve inflammation. Thus far, these findings have not been confirmed by other laboratories.

THE ROLE OF IMMUNOLOGY IN MULTIPLE SCLEROSIS

NON-SPECIFIC IMMUNE REACTIONS IN MS

Many investigators believe that no specific virus, bacterium, or other infectious agent will be found to be a cause of MS. Rather, they are concentrating on research that explores how a susceptible person's immune system reacts to a variety of viral or other infections, or how immune function is tied to hormonal and other factors that might explain the initiation of the MS process.

Studies in the last 15 years or so, largely in laboratory animals, have helped to explain how an immune system that has lost its ability to distinguish “self” from “non-self” tissue can be tricked by certain infectious agents into mounting an attack against a person's own myelin. The “trick” might be a very close similarity of molecular structure between some viruses, bacteria, and myelin itself — called molecular mimicry to reflect the similarity of molecular structure between some parts of myelin and some infectious agents.

If the molecular structure of the infectious agent mimics part of the molecular structure of myelin, an effective and natural immune response mounted against a common infectious agent might result in a damaging “cross-reaction” with myelin. This scenario of “mistaken identity” may explain much of the origin of MS and help to determine how the disease can be prevented from occurring in susceptible people.

It is now generally accepted that MS involves an autoimmune process — an abnormal response of the body's immune system that is directed against the myelin (the fatty sheath that surrounds and insulates the nerve fibers) in the central nervous system (CNS — the brain, spinal cord and optic nerves). Ongoing efforts to learn more about the autoimmune process in MS — what sets it in motion, how it works, and how to slow, stop, or repair it — are bringing us closer to understanding the cause of MS. Alterations in the way the immune system responds is essentially the “final common denominator” of genetic and environmental factors that predispose an individual to develop the disease.

However, as is also the case with other viruses studied as a possible “cause” of MS, it is still not possible to determine whether EBV causes MS, or whether its presence is a consequence of MS, because the follow-up studies needed to confirm a relationship to MS have been unsuccessful. Most such claims have been a result of inadequate experimental sampling or laboratory contamination. Nonetheless, there remains the possibility that specific infections may be related to MS, and virologists who focus on this disease remain at the forefront of ongoing searches.

The prefix “auto” means “self.” An autoimmune disease occurs when the immune system reacts against normally occurring *antigens* — proteins that trigger an immune response in the body — as if they were foreign.

Other diseases thought to have an autoimmune basis include myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, and insulin-dependent (Type 1) diabetes. Ongoing efforts to learn more about the auto-immune process in MS — what sets it in motion, how it works, and how to slow or stop it — are bringing us closer to understanding the cause of MS.

In MS, it is believed that the abnormal response of the body’s immune system is directed against myelin in the CNS. The exact antigen that the immune cells are sensitized to attack remains unknown. Researchers have identified which cells of the immune system are responsible for an MS attack, some of the factors that cause them to attack, and some of the sites, or receptors, on the attacking cells that appear to be attracted to the myelin to begin the destructive process.

Immune function is helped by two kinds of white blood cells. The “B cells” (called such because they develop in bone marrow) produce antibodies. The “T-cells” (which develop in the thymus gland) are responsible for a variety of other immune responses. These include: 1) attacking foreign substances such as bacteria, viruses, or foreign tissues; 2) augmenting the B-cell response; and 3) producing substances called cytokines that direct responses and activities in other immune cells.

In people with MS, T-cells become sensitized to myelin and cross the blood-brain barrier into the CNS. Once there, these cells not only injure myelin, but also secrete chemicals that damage nerve fibers (axons) and recruit more damaging immune cells to the site of inflammation.

It is not known what causes T-cells in people with MS to become activated but — as discussed earlier — both genetic and environmental factors appear to be important. Recently, it has been shown that B cells play a more active role in MS than was previously known, and research continues to explore their role.

RESEARCH DIRECTED AT THE ROLE OF THE IMMUNE SYSTEM IN MS

Scientists have begun to identify the sites or “receptors” on the T-cells that bind to the myelin. The precise identification of these receptor sites may help lead to the development of more specific immunosuppressant therapies that destroy these sensitized T-cells while leaving other cells intact. Much of the ongoing research in MS is directed toward finding answers to questions about the role of the immune system in the development of MS.

Individual T-cells are able to recognize only certain antigens. Their ability to discriminate between antigens is conferred by protein molecules on the cell surface called *receptors*. The receptor and the antigen fit together like a lock and key, but only when their shapes match perfectly. The number and specificity of T-cell receptors appear to be determined by the cell’s genes.

There are three broad categories of T-cells:

- *Helper T-cells* augment the immune response by recognizing the presence of a foreign antigen and then stimulating antibody production and producing cytokines that “turn on” or activate other T-cells.
- *Regulatory T-cells* function in an opposite manner; they dampen or turn off the immune response.
- *Cytotoxic or “killer” T-cells* directly attack and destroy cells bearing antigenic material.

As noted earlier, there is now information linking vitamin D’s apparent protective effect against MS to specific genes that code for receptors that bind to *cytokines* and affect the ability of regulatory T-cells to turn off the immune attack.

THE ROLES OF T-CELLS IN MULTIPLE SCLEROSIS

Over the last 15 years, much knowledge has been gained about the specific roles of T-cells. Among the activities that have been observed are:

- Decreased regulatory T-cell function in the peripheral blood of MS patients during an acute exacerbation (also known as an attack, relapse, or flare);
- Increased numbers of helper T-cells in the spinal fluid;

- Increased numbers of activated T-cells passing into the brain from peripheral blood, which then attract other immune cells into the brain;
- The presence of T-cells in MS plaques; and,
- Increased frequency of activated T-cells against the myelin seen in MS patients compared to healthy controls.

While much more information is needed before the exact nature of the autoimmune response in MS is explained, it appears that T-cells and their cytokines are the keys to this process. Ongoing research in these areas may provide new, specific immunotherapies that will stop the progression of MS without harming any immune cells that are not involved in the process of myelin destruction.

CHRONIC CEREBRO-SPINAL VENOUS INSUFFICIENCY (CCSVI): A POSSIBLE FACTOR IN THE DEVELOPMENT OF MS?

Recent preliminary studies have suggested that a phenomenon called chronic cerebrospinal venous insufficiency (CCSVI), a reported abnormality in blood drainage from the brain and spinal cord, may contribute to nervous system damage in MS. This hypothesis has been put forth by Dr. Paolo Zamboni from the University of Ferrara in Italy. Now, the MS Societies in the U.S. and Canada have launched seven new studies to investigate CCSVI and its possible role in the disease process.

Based on the results of his initial preliminary findings published in June 2009 from a study of approximately 65 patients, Dr. Zamboni and colleagues state that this pilot study warrants a subsequent larger and better controlled study to definitively evaluate the possible impact of CCSVI on the MS disease process.

It is not yet known how many people with MS have CCSVI, but preliminary evidence from a prevalence study at the University at Buffalo suggests that a proportion of people without MS also show signs of this condition. Further studies are now taking place at other centers, including the University at Buffalo, where researchers are collaborating with Dr. Zamboni's team.

The National MS Society and the MS Society of Canada are pursuing this new and potentially promising research direction by funding seven new studies to investigate CCSVI and its possible role in MS. New projects stemming from the Society's request for applications began July 1, 2010. Go to nationalMSSociety.org/ccsvi for the latest information about these projects and for other information about CCSVI.

To date, surgical procedures to correct CCSVI in people with MS have been "open label" rather than done in the context of controlled trials. Several private, mostly for-profit groups are advertising procedures to improve blood flow by inserting a tiny balloon or stent into blocked veins. It is prudent that such surgical procedures be undertaken in conjunction with formal clinical trials in order to assure that rigorous safety protocols and long-term monitoring standards are followed.

Dr. Zamboni and others emphasize the need for more research on his hypothesis, noting that it is still not proven whether CCSVI is a cause of MS or is related to MS in some other manner. He recommends that people with MS remain on their immunomodulatory therapies.

SUMMARY

Multiple sclerosis appears to result from a complex interaction of genetic susceptibility, environmental factors, and an infectious agent that may be a virus. Advances in the past several decades have resulted in the identification of many of these factors, and have begun to suggest the ways in which they interact. This knowledge will hopefully lead to new and better ways to manage MS.

GLOSSARY

ANTIBODY

Protein produced by certain cells of the immune system in response to bacteria, viruses, and other types of foreign antigens.

See Antigen.

ANTIGEN

Any substance that triggers the immune system to produce an antibody; generally refers to infectious or toxic substances.

See Antibody.

AUTOIMMUNE DISEASE

A process in which the body's immune system causes illness by mistakenly attacking healthy cells, organs, or tissues in the body that are essential for good health. Multiple sclerosis is believed to be an autoimmune disease, along with systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and many others. The precise origin and pathophysiologic processes of these diseases are unknown.

AXON

The extension or prolongation of a nerve cell (neuron) that conducts impulses to other nerve cells or muscles. Axons are generally smaller than 1 micron (1 micron = 1/1,000,000 of a meter) in diameter, but can be as much as a half meter in length. Many axons in the central nervous system are covered with myelin.

B-CELL

A type of lymphocyte (white blood cell) manufactured in the bone marrow that makes antibodies.

BLOOD-BRAIN BARRIER

A semipermeable cell layer around blood vessels in the brain and spinal cord that prevents large molecules, immune cells, and potentially damaging substances and disease-causing organisms (e.g., viruses) from passing out of the blood stream into the central nervous system (brain, spinal cord and optic nerves). A break in the blood-brain barrier may underlie the disease process in MS.

CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY (CCSVI)

A reported abnormality in blood drainage from the brain and spinal cord that may contribute to nervous system damage in MS.

CENTRAL NERVOUS SYSTEM

The part of the nervous system that includes the brain, optic nerves, and spinal cord.

CYTOKINES

Messenger chemicals produced by various cells, particularly those of the immune system, to influence the activity of other cells.

DNA

Short for deoxyribonucleic acid, DNA constitutes the chemical basis for genes, the basic units of heredity.

EPIDEMIC

The occurrence of a group of illnesses of a similar nature, clearly in excess of normal expectancy, deriving from a common or propagated source.

EPIDEMIOLOGY

The branch of medical science that deals with the study of incidence, distribution, and control of a disease in a population.

ETIOLOGY

The study of all factors that may be involved in the development of a disease, including the patient's susceptibility, the nature of the disease-causing agent, and the way in which the person's body is invaded by the agent.

GENE

A basic unit of heredity containing coded instructions for manufacturing a protein. Genes are sub-units of chromosomes, which are strands of DNA contained within most cells.

HELPER T-LYMPHOCYTES

White blood cells that are a major contributor to the immune system's inflammatory response against myelin.

HUMAN GENOME

The total set of genes (approximately 90,000 to 100,000) arranged on two sets of 23 chromosomes in most cells of the human body.

HYGIENE HYPOTHESIS

Scientists have noted that autoimmune diseases and allergies are less common in underdeveloped regions. Some researchers have noted that early exposure to common infectious agents, such as what occurs to people in less developed regions, may stimulate the immune regulation in a positive way and aid healthy immune responses.

Because MS is more prevalent in regions with high standards of hygiene, researchers are testing the idea that lack of exposure to common innocuous agents may lead the immune system to over-react and cause MS. Early clinical trials are now underway testing whether introducing harmless parasitic worms, which interact with the immune system when they reach the intestine, might alter immune attacks in MS.

IMMUNE SYSTEM

A complex network of glands, tissues, circulating cells, and processes that protect the body by identifying abnormal or foreign substances and neutralizing them.

IMMUNE-MEDIATED DISEASE

A disease in which components of the immune system — T-cells, antibodies, and others — are responsible for the disease either *directly* (as occurs in autoimmunity) or *indirectly* (for example, when damage to the body occurs secondary to an immune assault on a foreign antigen such as a bacteria or virus).

IMMUNO-COMPETENT CELLS

White blood cells (B- and T-lymphocytes and others) that defend against invading agents in the body.

IMMUNOGLOBULIN

See Antibody.

IMMUNOLOGY

The science that concerns the body's mechanisms for protecting itself from abnormal or foreign substances.

IMMUNO-SUPPRESSION

In MS, a form of treatment that slows or inhibits the body's natural immune responses, including those directed against the body's own tissues. Examples of immuno-suppressive treatments in MS include mitoxantrone, cyclosporine, methotrexate, and azathioprine.

INCIDENCE

The number of new cases of a disease in a specified population over a defined period of time. The incidence of MS in the United States is approximately 10,000 newly diagnosed people per year.

INFLAMMATION

A tissue's immunologic response to injury, characterized by mobilization of white blood cells and antibodies, swelling, and fluid accumulation.

LYMPHOCYTE

A type of white blood cell that is part of the immune system. Lymphocytes can be subdivided into two main groups: B-lymphocytes, which originate in the bone marrow and produce antibodies; T-lymphocytes, which are produced in the bone marrow and mature in the thymus. Helper T-lymphocytes heighten the production of antibodies by B-lymphocytes; suppressor T-lymphocytes suppress B-lymphocyte activity and seem to be in short supply during an MS exacerbation.

MACROPHAGE

A white blood cell with scavenger characteristics that has the ability to ingest and destroy foreign substances such as bacteria and cell debris.

MYELIN

A soft, white coating of nerve fibers in the central nervous system, composed of lipids (fats) and protein. Myelin serves as insulation and as an aid to efficient nerve fiber conduction. When myelin is damaged in

MS, nerve fiber conduction is faulty or absent. Impaired bodily functions or altered sensations associated with those demyelinated nerve fibers are identified as symptoms of MS in various parts of the body.

MYELIN BASIC PROTEIN

One of several proteins associated with the myelin of the central nervous system, which may be found in higher than normal concentrations in the cerebrospinal fluid of individuals with MS and other diseases that damage myelin.

NERVE

A bundle of nerve fibers (axons). The fibers are either *afferent* (leading toward the brain and serving in the perception of sensory stimuli of the skin, joints, muscles, and inner organs) or *efferent* (leading away from the brain and mediating contractions of muscles or organs).

NERVOUS SYSTEM

Includes all of the neural structures in the body: the *central nervous system* consists of the brain, spinal cord, and optic nerves; the *peripheral nervous system* consists of the nerve roots, nerve plexi, and nerves throughout the body.

PREVALENCE

The number of all new and old cases of a disease in a defined population at a particular point in time. The prevalence of MS in the United States at any given time is about 1/750 — approximately 400,000 people.

SUPPRESSOR T-LYMPHOCYTES

White blood cells that act as part of the immune system and may be in short supply during an MS exacerbation.

T-CELL

A lymphocyte (white blood cell) that develops in the bone marrow, matures in the thymus, and works as part of the immune system in the body.

TWINS — DIZYGOTIC

Also known as fraternal twins, two babies that come from separate, simultaneously fertilized eggs. If one dizygotic twin develops MS, the other has the same genetic risk for MS (approximately 2–5/100 as any other sibling or first-degree relative).

TWINS — MONOZYGOTIC

Also known as identical twins, two babies that come from single fertilized egg and share identical genetic makeup. If one monozygotic twin develops MS, the other has a 25–30/100 risk of developing the disease, indicating that factors other than genetic makeup contribute to the etiology of MS.

WHITE MATTER

The part of the brain that contains myelinated nerve fibers and appears white, in contrast to the cortex of the brain, which contains nerve cell bodies and appears gray.



**National
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The National Multiple Sclerosis Society is a collective of passionate individuals, moving together to create a world free of MS.

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