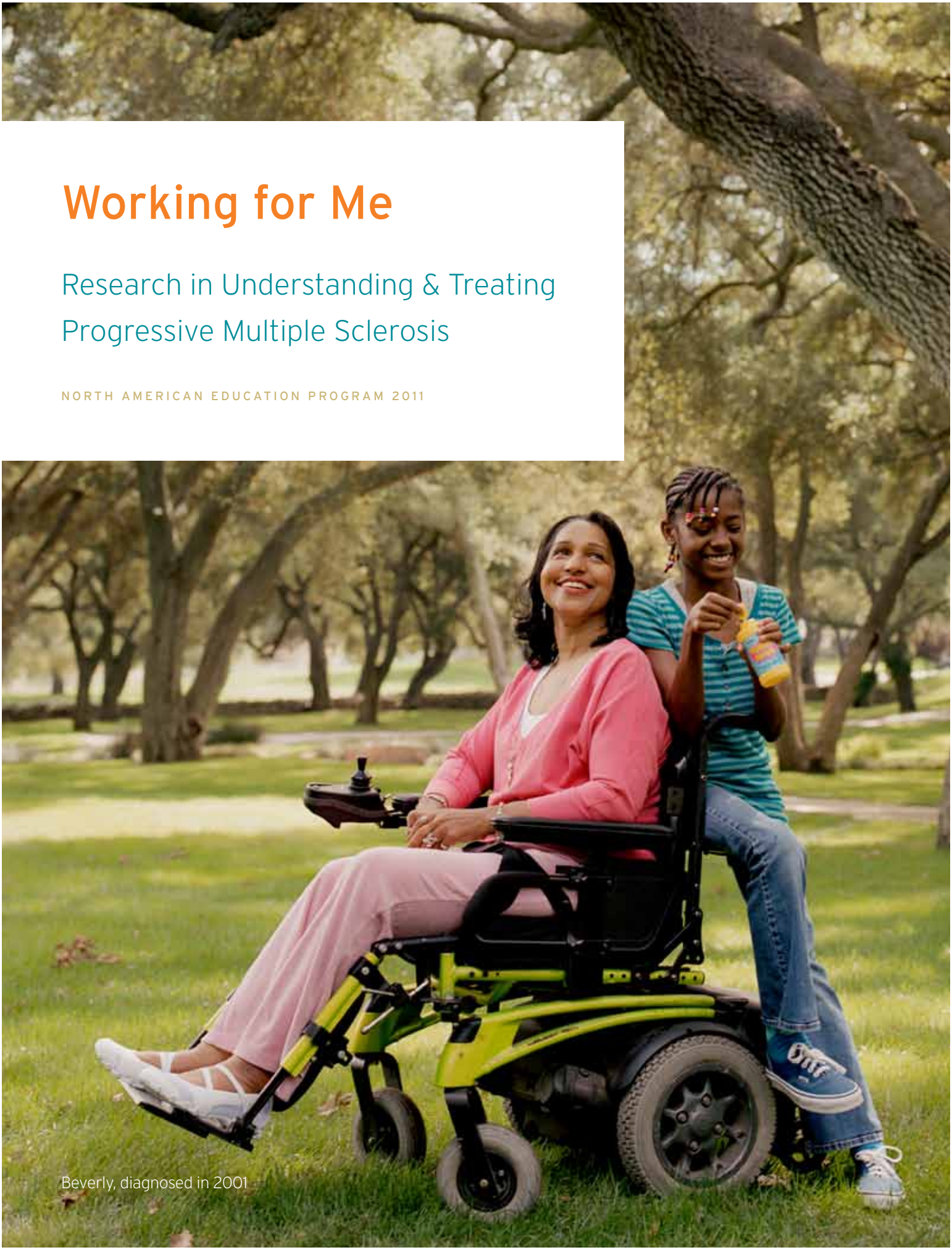
Working for Me

Research in Understanding & Treating Progressive Multiple Sclerosis

NORTH AMERICAN EDUCATION PROGRAM 2011



Beverly, diagnosed in 2001

Martha, diagnosed in 1973

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Acknowledgements

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Rick, diagnosed in 1991

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Dear Colleagues,

Welcome to the 2011 North American Education Program, **Working for Me — Research in Understanding and Treating Progressive Multiple Sclerosis,** produced by the National MS Society of the USA in collaboration with the MS Society of Canada.

Our program this year focuses on one of the most frustrating and elusive aspects of multiple sclerosis: the issue of progression. Scientists, clinicians, and those living with the disease puzzle over the same questions. What causes MS to get worse? Who is likely to have a more progressive course of the disease, and why? Why do some people experience steady progression from diagnosis, while others have a relapsing form of the disease? And what can be done to stop the progression of MS dead in its tracks?

In the video portion of the program, you will hear from those scientists and clinicians who are working on finding the answers to these and other questions about progressive MS. This program booklet provides information about studies that are completed or in process that add to the body of knowledge about the progressive nature of MS.

We want to thank of Biogen Idec, Genentech, Genzyme, Novartis, and Teva Neuroscience for providing generous educational grants to make this program possible.

We hope you will find the program informative. For further information, go to **nationalMSsociety.org** or **MSsociety.ca** or call 1-800-344-4867 (USA) or 1-800-268-7582 (Canada).

BEST REGARDS,

Nancy Law
Executive Vice President
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President & CEO
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In 2010, the National MS Society endorsed a five-year strategic roadmap, titled **A World Free of MS, National Multiple Sclerosis Society: Strategic Response to Multiple Sclerosis, 2011–2015.**

Rather than just a traditional organizational strategic plan, it strives to be a response to the challenges of living with MS and identifies what must be done, not only at the Society, but globally, to achieve a world free of MS. Progressive MS is at the center of the National MS Society's Strategic Response for 2011–2115 **(nationalMSsociety.org/about-the-society/our-strategic-response/index.aspx)** with a research focus on understanding mechanisms that lead to progression, finding ways to repair damage to the nervous system, and accelerating the development of new therapies. The Strategic Response will effectively guide priorities and work across the organization and the entire MS movement — fueling progress and moving us closer to a world free of MS.

You are probably participating in this program because you or someone you care about have been diagnosed with a progressive form of MS, or you are concerned about whether your MS may take a progressive course in the future.

THIS PROGRAM HAS BEEN DEVELOPED TO:

- Educate and inform people with MS and their loved ones about the many helpful strategies, management techniques, and medications that are available now to manage progressive forms of MS, and the progress that is being made by researchers and clinicians to expand options for the future.
- Highlight areas of research for progressive MS, focusing both on what we know and what we don't know.

DOUGLAS ARNOLD, MD

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Medical Director
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Professor of Neurology, Harvard Medical School
Director, Partners MS Center, Brigham and Women's Hospital
Co-Director, Center for Neurologic Diseases, Brigham and Women's Hospital

Douglas Arnold, MD

Montreal Neurological Institute & Hospital
McGill University

Douglas L. Arnold, MD, James McGill Professor of Neurology & Neurosurgery at the Montreal Neurological Institute of McGill University, directs a research laboratory that uses advanced MRI acquisition and analysis techniques to improve the understanding of how brain injury and repair in MS evolve and how therapeutic interventions can influence this.

"Imaging can teach us a lot of things about progressive MS. And it has taught us already a lot of things."

Tanuja Chitnis, MD

Medical Director
Multiple Sclerosis Natural History Study
Brigham & Women's Hospital

Dr. Chitnis is a neurologist with a background in neuroimmunology who cares for adults and children with multiple sclerosis. She is the Director of the Partners Pediatric MS Center at the Massachusetts General Hospital in Boston, which is one of six Centers of Excellence sponsored by the National MS Society. In addition, she is the Chair of the International Pediatric MS Study Group, which has over 150 members from 40 countries. In 2008 she was selected to be the Medical Director of the MS Natural History Study (CLIMB Study) at the Brigham and Women's Hospital, which captures detailed longitudinal clinical, MRI and blood samples on 1500+ MS patients. Dr. Chitnis, with her co-investigators in the CLIMB study have begun to mine clinical data, and to apply MRI and biological markers as predictors and correlates of disease course in MS. Dr. Chitnis has published over 50 peer-reviewed articles on immune mechanisms and biomarkers on multiple sclerosis and its models, as well as the clinical course of MS in adults and children.

"I was drawn to studying progressive MS because I think it's a primary question that needs to be answered today in the MS field. Many of our patients are well treated by therapies that target relapses, but many of these patients unfortunately will still go on to have progressive disability. And we need to identify therapies to target this phase of disease as well as to prevent this phase of disease."

Tim Coetzee, PhD

Chief Research Officer, National MS Society

Dr. Coetzee is Chief Research Officer of the National Multiple Sclerosis Society and is responsible for the Society's research program, which funds more than 375 projects around the world. Most recently, he served as President of the Society's Fast Forward venture, an initiative focused on bridging the gap between innovative ideas and commercial development to bring them to the market. Dr. Coetzee helped fund and establish Fast Forward, and fuel development of strategic biotechnology and pharmaceutical company funding as well as partnerships with the financial and business communities. Prior to Fast Forward, Dr. Coetzee led the Society's translational research initiatives on nervous system repair and protection in MS as well as the Society's programs to recruit and train physicians and scientists in MS research.

Dr. Coetzee received his PhD in molecular biology from Albany Medical College in 1993 and has since been involved in the field of multiple sclerosis research. He was a research fellow in the laboratory of Society grantee Dr. Brian Popko at the University of North Carolina at Chapel Hill, where he received an Advanced Postdoctoral Fellowship Award from the Society. After completing his training with Dr. Popko, Dr. Coetzee joined the faculty of the Department of Neuroscience at the University of Connecticut School of Medicine, where he conducted research that applied new technologies to understand how myelin is formed in the nervous system. He is the author of a number of research publications on the structure and function of myelin. Dr. Coetzee joined the National MS Society's Home Office staff in the fall of 2000.

"Many of the therapies that we have on the market today and that are in the early and late stages of the pipeline focus primarily on the immune system and modulating the immune system and that is a very important aspect of treating MS. But now nerve repair is coming on the horizon as a second strategy or second arm in how we treat MS."

Robert Motl, PhD

Associate Professor, Kinesiology & Community Health
University of Illinois at Urbana-Champaign

Robert W. Motl is an Associate Professor of Kinesiology and Community Health and Director of the Exercise Neuroscience Laboratory at the University of Illinois at Urbana-Champaign. His research interests are in the areas of exercise psychology, measurement, and neuroscience for understanding physical activity and exercise in persons living with multiple sclerosis. He received a Bachelors degree from San Diego State University, a Masters degree from the University of Wyoming, and a Ph.D. from the University of Georgia. He completed a post-doctoral fellowship at the University of Georgia. He has published over 150 refereed papers, and serves as a Board Member for **International Journal of MS Care** and Study Section member for the **National Multiple Sclerosis Society.** His most recent work has been funded by the **National Multiple Sclerosis Society** and the **National Institute of Neurological Disorders and Stroke** and has embraced such topics as spasticity management, exercise programming, measurement and quantification of physical activity, and quality of life influences and outcomes among those with multiple sclerosis.

"We believe that exercise and physical activity are important for all people with MS. It can help with managing the symptoms, it can help with managing many of the functional consequences such as loss of balance or loss of ambulation. It can also affect some of the mental consequences such as depression and cognitive function. And most important it can affect the quality of life of all individuals with MS."

Helen Tremlett, PhD

Associate Professor
Department of Medicine, Division of Neurology
University of British Columbia

Currently an associate professor at the University of British Columbia in the Faculty of Medicine, Division of Neurology and the Canada Research Chair in Neuroepidemiology and Multiple Sclerosis. Also funded by the MS Society of Canada's Don Paty Career Development Award and a Michael Smith Foundation for Health Research Scholar award. Also holds operating grants from CIHR, the US National MS Society and the UK MS Trust. Trained in pharmaco-epidemiology/multiple sclerosis with a PhD from Cardiff University, UK. Heads the 'Pharmacoepidemiology in MS (PiMS) Research group.' 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 and MS; vitamin D, sunlight, infections and MS disease activity.

"We do have some patients who will reach secondary progressive MS within a year or two of onset of the disease and some people haven't reached it after 30 years of having MS. So there's huge variability."

Howard Weiner, MD

Professor of Neurology, Harvard Medical School
Director, Partners MS Center, Brigham & Women's Hospital
Co-Director, Center for Neurologic Diseases, Brigham and Women's Hospital

Howard L. Weiner is the Robert L. Kroc Professor of Neurology at the Harvard Medical School, Director and Founder of the Partners Multiple Sclerosis Center and Co-Director of the Center for Neurologic Diseases at the Brigham & Women's Hospital. Dr. Weiner established the Partners Multiple Sclerosis Center at Brigham & Women's Hospital in 2000 which combines clinical evaluation, MRI imaging and immune monitoring and is the first integrated MS center that brings these disciplines to the individual care of the MS patient. Dr. Weiner has pioneered the use of immunotherapy and the drug cyclophosphamide for the treatment of multiple sclerosis and has investigated immune abnormalities in the disease including the role of the innate immune system and regulatory T cells. He has also pioneered the use of the mucosal immune system for the treatment of autoimmune and other diseases. Based on his work vaccines are being tested in multiple sclerosis, diabetes, and most recently in Alzheimer's disease. Dr. Weiner is the author of "Curing MS: How Science is Solving the Mystery of Multiple Sclerosis" that chronicles the history of MS, his 30+ years in the research and clinical treatment of MS, and details his "21 point hypothesis" on the etiology and treatment of multiple sclerosis. In 2004 Harvard Medical School honored Dr. Weiner with the establishment of the Howard L. Weiner Professor of Neurology Endowed Chair.

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Dr. Weiner is the 2007 recipient of the John Dystel Prize for Multiple Sclerosis Research awarded by the American Academy of Neurology and in 2008 received the Betty and David Koetser Memorial Prize as awarded by the Betty and David Koetser Foundation for Brain Research. In 2009, Dr. Weiner was presented the Award for Outstanding Research Achievement, Nature Biotechnology SciCafé, Nature Publications.

In June, 2008 Dr. Weiner premiered his documentary film entitled, What Is Life? The Movie, a production he has been working on for three years a feature-length documentary that explores the big questions in life that everyone faces and for which there are no clear answers: God, the nature of the soul, how to attain meaning in one's life, evil, destiny.

"I remember in the '80s I would sit with someone who has MS and they'd say, 'What are the treatments?' And I would say, 'Well we don't have any treatments, but I'm sure in a number of years we will.' And that happened. Now when I sit with someone who has progressive MS they ask the same question, I give them the same answer and I'm convinced that in the future it could be five years, it could be 10 years, but not in the distant future, we will have drugs for progressive MS."

Part 1

A Look at Progressive Multiple Sclerosis

Chris, diagnosed in 1993

An Overview of Multiple Sclerosis

Multiple sclerosis (or MS) is a chronic, often disabling disease that attacks the central nervous system (CNS), which includes the brain, spinal cord, and optic nerves. Symptoms may be mild, such as numbness in the limbs, or severe, such as paralysis or loss of vision. The progress, severity, and specific symptoms of MS are unpredictable and vary from one person to another.

In MS, the body's defense system attacks myelin, the fatty substance that surrounds and protects the nerve fibers in the CNS. The damaged myelin forms scar tissue (sclerosis), which gives the disease its name. When any part of the myelin sheath or nerve fiber is damaged or destroyed, nerve impulses traveling to and from the brain and spinal cord are distorted or interrupted, producing a variety of symptoms that depend on the location of damage. It is damage to the nerve fibers, rather than damage to their myelin covering, that appears to cause progression and long-term disability in MS.

The Four Courses of MS

Multiple sclerosis is most commonly divided into four types, based on the course that the disease takes. Since no two people have exactly the same experience of MS, the disease course may look very different from one person to another. And, it may not always be clear to the physician – at least right away – which course a person is experiencing.

RELAPSING-REMITTING MULTIPLE SCLEROSIS (RRMS)

People with this type of MS experience clearly defined attacks of worsening neurologic function. These attacks – which are called relapses, flare-ups, or exacerbations–are followed by partial or complete recovery periods (remissions), during which no disease progression occurs. Approximately 85% of people are initially diagnosed with relapsing-remitting MS.

PRIMARY-PROGRESSIVE MS (PPMS)

This disease course is characterized by slowly worsening neurologic function from the beginning – with no distinct relapses or remissions. The rate of progression may vary over time, with occasional plateaus and temporary minor improvements. Approximately 10% of people are diagnosed with primary-progressive MS.

SECONDARY-PROGRESSIVE MS (SPMS)

Following an initial period of relapsing-remitting MS, many people develop a secondary-progressive disease course in which the disease worsens more steadily, with or without occasional flare-ups, minor recoveries (remissions), or plateaus. Before the disease-modifying medications became available, approximately 50% of people with relapsing-remitting MS developed this form of the disease within 10 years. Long-term data are not yet available to determine if treatment significantly delays this transition.

PROGRESSIVE-RELAPSING MS (PRMS)

In this relatively rare course of MS (5%), people experience steadily worsening disease from the beginning, but with clear attacks of worsening neurologic function along the way. They may or may not experience some recovery following these relapses, but the disease continues to progress without remissions.

What We Know and Don't Know about Progressive MS

Although four disease courses have been identified, the concept of progression is relevant to most people diagnosed with MS. Whether the disease progresses from onset or gradually becomes progressive over time, people will be working with their healthcare team to slow progression, manage their symptoms, and function optimally in the face of whatever disability they experience.

Clues to Predicting when MS is Progressive

MOTOR SYMPTOMS & GENDER

In a study of over 5,000 people with MS, researchers determined that having motor symptoms at onset (such as uncontrolled tremor or spasticity) and male gender were associated with a faster progression to SPMS and younger age when converting to SPMS. Also, younger age at disease onset was associated with a slower progression to SPMS, but also a younger age when SPMS began.

The team was led by Marcus Koch, MD, at the University Medical Centre in Groningen (the Netherlands) and Helen Tremlett, PhD (University of British Columbia). They identified 5,169 people who initially presented with RRMS, from the same British Columbia database discussed. Of these, 1821 (35%) had progressed to SPMS during the observation period from 1980 to 2003. Because this study began as a "natural history" analysis – meaning that it was designed to observe the natural course of the disease, data from people who went on disease-modifying therapies were excluded starting on the first day of their therapy. Therefore, the presumed influence of disease-modifying therapies on progression to SPMS cannot be determined from this study.

EARLY RELAPSES

Another study led by Helen Tremlett, PhD, and funded by the National MS Society, reported that having more relapses early in the course of MS was associated with increased disease progression. They retrospectively reviewed the histories of 2,477 people with MS selected from a British Columbia MS database. Cases were included if MS had a relapsing onset and if the diagnosis of MS was made before 1988. The cases were followed for an average of 20.6 years.

The data showed that people who had more relapses within the first five years of disease were more likely to reach an Expanded Disability Status Scale (EDSS) of 6. Relapses during this period had the most impact on early disease progression. However the association between early relapses and progression decreased over time, so that people with early relapses who did not experience significant progression early in the course of their disease (did not require a cane to walk by year 10 or did not transition to secondary-progressive disease) were only slightly more likely to at longer-term follow-up.

They also found that relapses in people under the age of 25 had a more enduring impact on disability compared to those 35 years of age and older. This underscores the importance of early treatment to prevent relapses and hopefully, future disability.

Disease Modifying Therapies: Why They Don't Appear to Work as Well in Progressive MS

Although major advances have been made in delaying or preventing progression for the relapsing forms of MS – and these forms of MS are relatively well controlled by existing disease management therapies – people with progressive MS do not seem to benefit as much from these therapies. **Why is this so, and why has research lagged behind that for relapsing remitting MS?**

In part, this apparent lack of benefit for people with progressive forms of MS is due to the fact that existing therapies target the inflammatory process that is the primary component of relapsing forms of MS. However, the progressive forms of MS appear to primarily involve **neuronal atrophy** – a loss of neurons that may or may not result from an inflammatory process (also referred to as **neurodegeneration**) and that does not appear to respond as well to current anti-inflammatory therapies. The lack of approved treatments for progressive MS also reflects the difficulty of doing clinical trials with a disease course that does not involve easily measurable changes, such as a decline in relapse rate – which has provided an excellent way to measure effectiveness in relapsing-remitting. This means that clinical trials for progressive forms of MS may need to be designed differently, evaluate different outcomes, and take significantly longer in order to measure the impact of treatment. Scientists and clinicians are working to address this challenge. You can read about ongoing research efforts in part III. In the meantime, however, there is much that can be done today to manage progressive forms of MS

Part 2

Managing Progressive MS Today

Judy, diagnosed in 1982

Determining if You Are a Candidate for a Disease-Modifying Therapy

Accumulating evidence suggests that the best way we have of slowing disease progression is to treat MS at its earliest stages.

As discussed above, the disease-modifying therapies that are so effective in RRMS do not appear to work as well – if at all – for people with progressive forms of MS. But this situation is not always clear-cut. For example, some people with PPMS have fluctuating symptoms that resemble relapsing MS, and early symptoms may overlap with those seen in relapsing MS. People with SPMS do not suddenly convert to this pattern; instead, it is a gradual waning of relapses and remissions accompanied by a steadily developing progression. For these reasons, a doctor might decide to use one of the currently approved therapies for relapsing MS until the disease course is more clearly defined.

The currently approved disease modifying therapies include the interferon beta medications (Avonex®, Betaseron®, and Rebif®) and Copaxone®. All are approved by the FDA for use in the **relapsing forms** of MS, and these agents work primarily by reducing immune system activity as indicated by a demonstrated clinical slowing of progression and a reduced number of acute relapses and number of new lesions on MRI scans. If they are not effective or their side effects are not tolerable, a physician might recommend changing to another therapy in this group or try Tysabri® (natalizumab) or Novantrone® (mitoxantrone). In late 2010, the first oral medication was approved for the treatment of relapsing-remitting MS – Gilenya™, formerly known as fingolimod, and several additional oral medications are expected to be approved in the near future.

Managing Your Symptoms

Progressive MS can produce a wide range of symptoms, in a variety of combinations.

A brief summary is given in the table below; details about MS symptoms and their management can be found at: **nationalMSsociety.org/about-multiple-sclerosis/what-we-know-about-ms/symptoms/index.aspx.**

SYMPTOM	MANAGEMENT OPTIONS
FATIGUE	■ Energy-conservation strategies ■ Assistive technology ■ Mobility aids ■ Exercise ■ Medication ■ Treatment of any other symptoms that interrupt sleep (urinary urgency, pain, spasticity)
SPASTICITY	■ Exercise, including stretching and range-of-motion exercises ■ Medication ■ Management of any other symptoms that increase spasticity (pain, urinary tract infection, constipation)
WEAKNESS	■ Exercise ■ Mobility aids
TREMOR	■ Adaptive equipment ■ Medication
BALANCE	■ Gait training ■ Exercise ■ Mobility aids

SYMPTOM	MANAGEMENT OPTIONS
BLADDER DYSFUNCTION	■ Medication ■ Behavioral strategies ■ Intermittent self-catheterization
BOWEL DYSFUNCTION	■ High fiber diet ■ Fluid intake ■ Medication ■ Consistent bowel program
SEXUAL DIFFICULTIES	■ Medication ■ Counseling
COGNITIVE CHANGES	■ Neuropsychological evaluation ■ Cognitive rehabilitation ■ Medication
SPEECH & SWALLOWING	■ Speech/swallowing evaluation ■ Medications to relieve contributory symptoms such as spasticity ■ Safe swallowing techniques ■ Assistive technology
VISUAL PROBLEMS	■ Low vision evaluation ■ Assistive technology
DIZZINESS & VERTIGO	■ Physical therapy ■ Medication
SLEEP DISTURBANCES	■ Develop good sleep habits ■ Manage symptoms contributing to poor sleep ■ Medication
PAIN	■ Medication ■ Management of contributory factors

Enhancing Function through Rehabilitation

Even without an approved disease-modifying therapy (DMT), people with a diagnosis of SPMS or PPMS and their health care teams can do a great deal to manage the disease. This is the goal of **rehabilitation.** Rehabilitation and symptom management go hand in hand.

When combined with effective symptom management, rehabilitation will allow you to reach and then maintain the best physical, emotional, and functional level possible, whatever your level of disability. **(nationalMSsociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/rehabilitation/index.aspx)**

The Goals of Rehabilitation

Rehabilitation encompasses a wide variety of strategies and therapies designed to help restore function, promote independence regardless of the severity of your MS, and help you maintain a high quality of life.

A REHABILITATION PROGRAM IS DESIGNED TO:

- Maximize symptom management, as discussed in the previous section
- Enhance mobility and promote safety, independence, and productivity
- Provide you with any assistive devices you need to conserve energy and carry out your daily activities effectively, safely, and comfortably
- Promote overall health and wellness

- Promote emotional well-being and quality of life
- Prevent complications, such as bladder infections and skin breakdown
- Help you reach and maintain the highest possible level of function and comfort possible, given the limitations that result from progressive MS

How Rehabilitation Maintains & Improves Function

Rehabilitation will help you relearn skills and find new ways of doing things that may have become difficult. A rehabilitation program often involves physical therapy (PT) to help your strength, mobility, and fitness; occupational therapy (OT) to help with your daily activities; speech-language therapy to help with speaking, understanding, reading, writing, and swallowing; and specialists in pain management. It should be individually designed to deal with your specific symptoms, problems, and life circumstances

The Rehabilitation Team

Optimally, rehabilitation is provided by a team of specialists, with you and your needs as its focus. At a comprehensive MS center or clinic, many or most of these team members will be affiliated with the center. Neurologists or other specialist physicians who practice independently or with a group of specialists will create the team through referrals.

The rehabilitation team includes, but is not limited to, the following specialists:

NEUROLOGISTS

Neurologists normally diagnose MS, prescribe and manage disease modifying therapies, and manage MS symptoms. Your neurologist must be seen on a regular basis – usually several times a year. He or she will evaluate your MS, review your medications, recommend any new management strategies that might be helpful, and make referrals to other medical specialists when necessary.

OTHER PHYSICIANS

Other physicians will treat specific issues associated with MS, as well as all general medical and surgical care that might or might not be related to MS. Your internist, family practitioner, or other general medical specialist will continue to oversee general medical care and regular screening tests – such as colonoscopies and mammograms – designed to detect other diseases at the earliest possible time.

NURSES, NURSE PRACTITIONERS (NPs), & PHYSICIANS ASSISTANTS (PAs)

Nurses, nurse practitioners, and physicians assistants are often the "managers" who coordinate overall care and wellness-related issues. A primary goal of nursing care in progressive MS is to help with learning effective, preventive self-care, in order to manage minor problems before they become major ones. Some nurses, NPs, and PAs provide follow-up care and help coordinate clinical trials.

PHYSICAL THERAPISTS (PTs)

Physical therapists treat problems that involve mobility and ambulation, balance, coordination, strength, pain, and fatigue. The goal of physical therapy is to help manage the mobility challenges and physical demands of your family, work, and social life that are caused by progressive MS. A PT can suggest an appropriate exercise program, and should be consulted regarding the proper use of rehabilitation equipment and mobility devices.

OCCUPATIONAL THERAPISTS (OTs)

Occupational therapists can help you maintain the everyday skills you need to function as independently as possible. They focus on four major areas:

- Upper body strength, movement, and coordination
- Aids to independent living, such as the use of technology and environmental modifications
- Compensatory strategies for symptoms, including sensation problems, weakness, or vision loss
- Energy conservation

OTs can also assist you with activities such as dressing, bathing, grooming, meal preparation, and writing, as well as managing a job, going to school, driving, and participating in leisure activities.

SPEECH & LANGUAGE PATHOLOGISTS

Speech and language pathologists evaluate and treat problems that might result from damage to the nerves controlling muscles used in speech and swallowing. They also evaluate and treat communication issues related to cognitive deficits, such as problems with attention, memory, and finding the words to express ideas while speaking or writing.

MENTAL HEALTH PROFESSIONALS

Mental health professionals include psychiatrists, psychologists, neuropsychologists, and licensed professional counselors such as social workers. They can help you deal with the many emotional issues that can affect your overall ability to adjust to living with progressive MS.

SOCIAL WORKERS

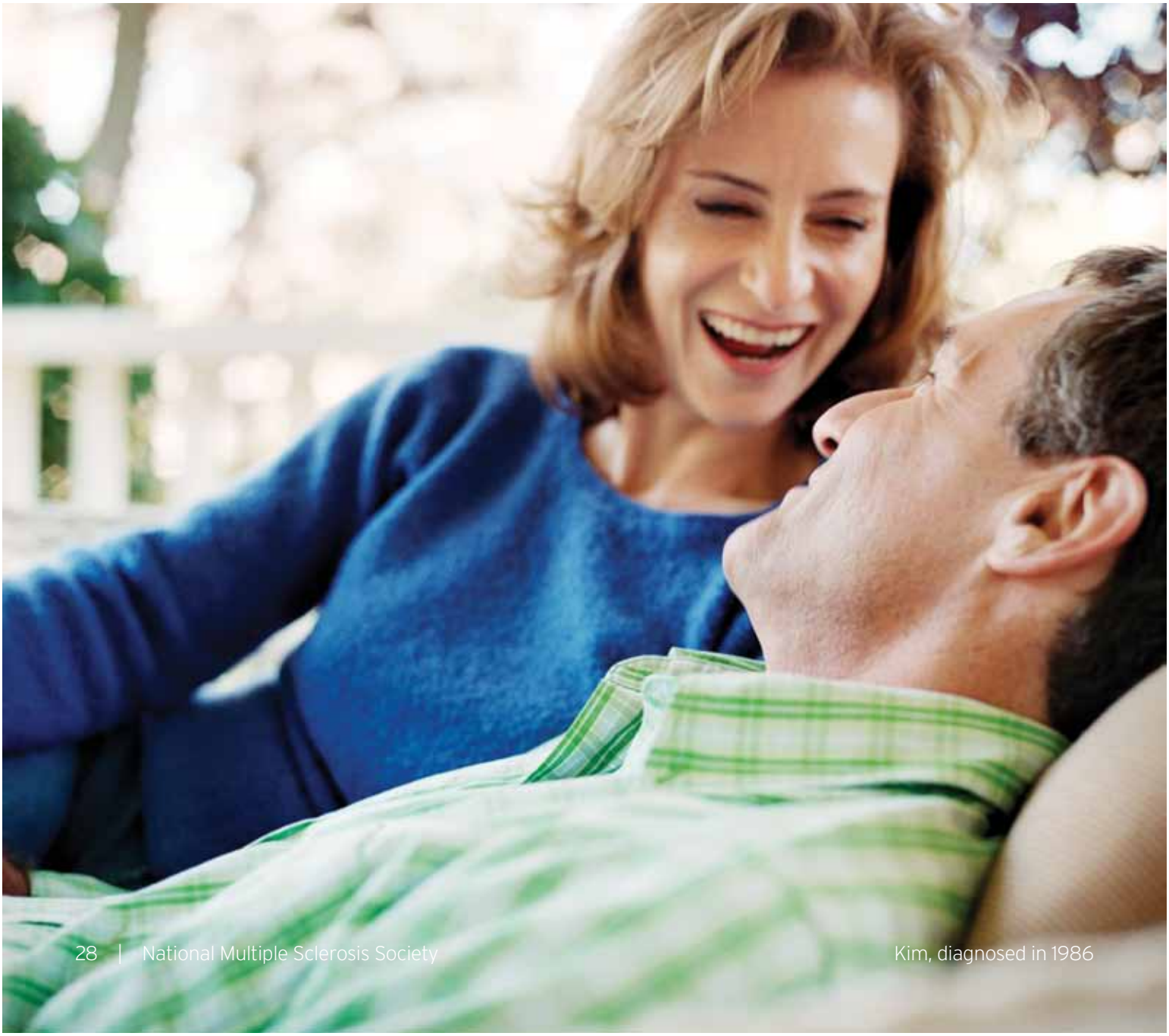
Social workers also can help you deal with any changes and adjustments that need to be made in coping with MS on a daily basis. They can assess social and family needs, and refer you to community service organizations that can assist you with income maintenance, insurance, housing, long-term care options, counseling, and many other issues.

OTHER TEAM MEMBERS

Other team members might include vocational rehabilitation specialists, recreational therapists, spiritual counselors, attorneys for legal assistance, nutritionists, and many others.

Part 3

Research in Progressive MS



Kim, diagnosed in 1986

When most people think of "research," they envision scientists in laboratories working with chemicals, test tubes, and the like. However, the term also has a much broader interpretation.

Research on any disease has two components: basic and clinical. Basic research is the first step of many before a new therapy can be tested in people. It often begins in a laboratory and involves exploring how cells function outside the body **(in vitro).** This is followed by a series of human clinical trials. All of these steps must occur before any new treatment becomes available for general use.

The Broad Scope of Current Research

Solutions for MS include not just stopping the disease, repairing damage and restoring lost function, but also protecting future generations by ending it forever. Although these areas continue to be aggressively pursued, the **good** news is that research strategies in progressive MS are now broader than in the past.

The National MS Society's Promise: 2010 initiative on Nervous System Repair and Protection provided the largest single grant in Society history to launch an international effort to address the need for ways to stop progression and restore function.

More than 70 leading researchers in four teams in the U.S. and Europe have:

- Made progress developing cell transplantation techniques, which may ultimately enable nervous system repair
- Developed better imaging methods to track the success of attempts at repair and protection in clinical trials
- Successfully induced "stalled" myelin-making cells in lab dishes to begin producing myelin with molecules that have potential as future therapies
- Advanced knowledge for further research into repair and protection by publishing more than 150 research papers on nervous system repair in MS.

Because of this targeted progress, clinical trials of nerve-protecting therapies are underway, as are advanced studies of cell transplantation and other strategies for stimulating repair in MS. And now, progressive MS is the centerpiece of the National MS Society's **Strategic Response for 2011-2115.** Research is focused on what causes progression, how brain cells may be protected from being damaged (neuroprotection), and how lost function may be restored, as well as on managing the symptoms of progressive MS and its effect on quality of life. In addition, a number of new treatments for progressive MS are actively being researched or in clinical trials.

The Society and its commercial development entity, Fast Forward **(fastforward.org)** sponsored a "think tank" meeting in Boston in late 2010 that was critical in developing the next steps that need to be taken to implement this program. It brought together MS investigators, research funding agencies, and industry representatives, to map out next steps to move the field toward a better understanding of factors underlying MS progression and to increase the number and quality of clinical trials in progressive MS. Areas targeted for development include finding answers to the following questions:

- What factors influence the transition from a largely relapsing-remitting course with distinct immune attacks to a largely progressive (steadily worsening) course (secondary-progressive MS)?
- What are the underlying mechanisms that influence why some people have very slow progression while others worsen quickly? Knowing these should point to new therapeutic targets.
- What causes primary-progressive MS, and is it the same (currently unknown) thing that causes more common forms of MS?
- How similar or different are progressive forms of MS? The differences and similarities will help inform future research and clinical trials.
- Can the existing disease-modifying therapies prevent, delay, or slow long-term MS progression?
- What new therapies will help people with progressive MS?
- What causes degeneration of nerve fibers – thought to be the cause of long-term disability experienced by many with MS–and how can that be stopped or reversed?

A More Detailed Look at Ongoing Research Efforts

The Disease Process (Pathology) in Progressive MS

The better we understand the process by which progression occurs during the course of MS, the better researchers will be able to develop more effective techniques to stop it. A growing body of research is leading to a better understanding of both what causes progression and what factors may either inhibit it or promote restoration of normal function.

One problem that makes it difficult to detect progressive MS in its early stages is that conventional MRI brain scans cannot distinguish between different types of tissue damage in people with MS. Also, while MRI can detect myelin injury and inflammation in the white matter areas where nerve fibers are coated with myelin, it cannot detect damage in the gray matter of the brain—that portion of brain tissue that contains cell bodies and not myelinated axons, which appears to be related to the extent of progressive disability.

Another issue that needs to be better understood is that one type of disease activity in the progressive stages of MS is what has been termed "diffuse" or "smoldering" inflammation, rather than the acute immune attacks that are seen in relapsing-remitting MS. This diffuse inflammation appears to be driven by cells called **microglia,** which are the only immune cells that reside in the brain. Microglia have not only been implicated in MS damage, but they may also play a key role in tissue repair. That being the case, more work is needed to understand their dual role.

A good example of the type of work being done to study this type of problem is that by David Baker, PhD, at the London School of Medicine and Dentistry. He and other researchers have been developing animal models that mimic various aspects of progressive MS. Although no one model mimics all aspects of progressive MS, some are already being used to screen potential therapies that target progression, and to test ideas about factors that may influence progression. Having good disease models will help speed the identification and preclinical testing of new therapies for progressive MS.

Risk Factors (Triggers) that Lead to Progression

One of the first steps to being able to control or manage any disease process is to understand the factors that contribute to its development. MS progression is no exception to this principle. At this time, although we have some clues, we don't yet fully understand what triggers relapses or what causes MS to progress. Research is ongoing to find risk factors that might contribute to MS progression and markers that will help predict the course of MS, which would help greatly in making treatment decisions.

LOOKING FOR BIOMARKERS & RISK FACTORS

A major goal of new research is to find ways to more quickly identify or diagnose progressive disease based on biological markers – or **biomarkers** – rather than waiting for symptoms to appear. This would make it possible to test therapies earlier in the course of disease in hopes of protecting the nervous system from MS injury.

A team led by Tanuja Chitnis, MD of the Harvard Institute of Medicine and Brigham and Women's Hospital is working to identify biomarkers and risk factors that may influence whether, and how rapidly, MS may develop and progress. The team will begin to address many of these unknowns by evaluating a group of people with MS for whom there is detailed clinical information, serial MRIs, longitudinal immunologic blood studies, and stored serum samples.

The researchers hope to identify clinical risk factors that may affect the rate of disease progression, including those that are potentially modifiable such as hormones and vitamin D levels. They also will develop statistical models to predict an individual's risk of disease progression, with the hope of identifying people who are at high risk for rapid progression and to treat them more aggressively.

A special National MS Society initiative, funded through its Greater Delaware Valley Chapter, has launched two feasibility studies to investigate how to best detect and track factors that influence MS progression. One of these studies is by a consortium of investigators at four major academic MS Centers organized by Howard L. Weiner, MD, at Brigham and Women's Hospital and the Harvard Institutes of Medicine. The study will develop methodology to be used in later studies and test hypotheses that link blood and MRI biomarkers with clinical disease parameters and the rate of disease progression. The group will participate in a prospective pilot study that collects uniform clinical, MRI, blood, and genetics data on 1,500 people with MS over the two-year period of the pilot grant. In addition, they will collect five types of epidemiologic data: background and family history, vaccination and infectious diseases history, smoking history, diet and sun exposure, and gender hormones and pregnancy.

The second study of this initiative involves the New York State Multiple Sclerosis Consortium, which was created in 1996 to develop a unique demographic and clinical long-term follow-up database of people with MS to provide a durable resource for longitudinal, interdisciplinary research; it currently has approximately 9,000 registrants. A team led by Bianca Weinstock-Guttman, MD, at the State University of New York at Buffalo, will study the clinical, MRI, neuropsychological, and gene-environmental risk factors for progression using this database.

The team hopes to develop and maintain a group of 500 people in which they will investigate risk factor roles and interactions related to MS disease progression.

VITAMIN D, EPSTEIN-BARR VIRUS, & SMOKING: EXAMPLES OF THE SEARCH FOR POTENTIAL RISK FACTORS

Research into triggering or risk factors that influence whether a person develops MS is key to finding the cause of and cure for the disease. A team led by Alberto Ascherio, MD, DrPH, Professor of Medicine at Harvard Medical School, have found that higher vitamin D intake and high blood levels of vitamin D are associated with a significantly lower risk of developing MS. They also found that smoking and elevated levels of antibodies to Epstein-Barr virus (EBV, a herpes virus known to cause infectious mononucleosis), are associated with an increased risk of MS. Separate studies have also pointed to smoking as a contributor to MS progression. In a current study, this team is studying more than 1,600 people, measuring progression from a first neurologic episode (CIS, a first demyelinating event that indicates a high risk for developing MS) to MS, as defined by clinical and MRI exams. They are examining the influence of some of these risk factors in early progression in MS.

Strategies to Reverse or Prevent Tissue Injury

One of the most exciting areas of current research is to develop ways to repair cells damaged by MS, possibly by replacing them through regeneration and cell transplantation techniques. This holds the promise of showing us how to stop disease progression, thereby improving the quality of life for people living with MS. Eventually, we hope to restore function in people who have already experienced significant damage to the nervous system. Another strategy, called **neuroprotection,** attempts to find ways to keep vulnerable tissues from harm.

Researchers are trying to identify the molecular signals used by the body to activate young **oligodendrocytes –** myelin-producing cells – so that those signals can be mimicked in a controlled fashion to stimulate additional repair. A large group of proteins – known as "growth factors" because of their roles in "turning on" different stages of myelin formation and nerve growth – are the focus of extensive research.

Another approach is to identify and block natural processes that might inhibit the body's ability to repair nervous system damage. Scientists are working to identify potential sources of replacement cells for those damaged by MS; this takes us into the field of stem cell research. The usefulness of these possible replacement cells will depend on many factors, including finding or creating the signals needed to stimulate their transformation and growth into healthy new cells. Many challenges await these efforts.

Recent scientific advances in many different fields are now coming together to bring these possibilities within our grasp. People with PPMS will be candidates for future CNS repair and protection strategies. (For a detailed overview of research in MS, visit the National MS Society's website at **nationalMSsociety.org**.)

IMAGING & OTHER WAYS TO DETECT DAMAGE & REPAIR/PROTECTION

Having ways to detect nervous system injury, protection, and repair—without having to wait possibly years to observe a person's disease progression—would greatly improve our ability to conduct clinical trials in progressive MS. Steady progress is being made in finding noninvasive ways of detecting nervous system damage, protection, and repair. More work is needed to determine the best methods to use in different settings, and to further validate their use as markers of therapeutic success in clinical trials involving people with progressive MS.

Research proceeds on conventional and unconventional MRI techniques that are offering new windows to see the nervous system injury that occurs during the course of MS. These techniques, such as DTI (diffusion tensor imaging), MTR (magnetization transfer ration), and measures of atrophy or brain shrinkage, may be helpful for detecting whether the nervous system is being repaired or protected by therapies to be tested in future clinical trials.

Another approach being tested is OCT (optical coherence tomography), to measure the thickness and integrity of the inner layer of nerve fibers at the back of the eye. This appears to be a useful barometer of nerve health that is ready to be used in clinical trials of agents designed to protect against nervous system damage.

BLOCKING MOLECULES THAT INHIBIT REMYELINATION

A team led by Dr. L. Lau of the Hotchkiss Brain Institute in Calgary has uncovered a group of molecules that reside in brain tissues and that may be among several that block the ability of the myelin-making oligodendrocytes to repair damage caused by MS. The molecules, CSPGs (chondroitin sulfate proteoglycans) contribute to scarring, and in laboratory studies they reduce the number of oligodendrocyte progenitor cells that mature into myelinating cells. By selectively turning off CSPGs in laboratory mice with myelin damage, the researchers were able to increase myelin repair. More research by these and many other investigators looking into this question should determine whether this approach might be useful for encouraging myelin repair in people with MS.

STIMULATING MYELIN-MAKING CELLS IN MS

Another approach to understanding the mechanisms that underlay progression is to study the cells involved in making myelin, with the goal of determining how they are affected when progression occurs; this may lead to ways to prevent these changes and/or restore them to their pre-progression status.

Myelin damage is repaired during the early phase of MS, but fails during the chronic phase. This occurs despite the continued presence of immature myelin-making cells—oligodendrocyte precursor cells, or OPCs – within chronic lesions. This suggests that specific factors limit the ability of OPCs to promote repair once the progressive stage begins.

Many teams, including one led by Joel M. Levine, PhD, at the State University of New York Stony Brook University, are working to characterize those cells that reside in the brain and are capable of repairing myelin, as well as to develop techniques and molecules that will induce them to rebuild damaged tissues in MS and restore function. They are combining their extensive expertise to better understand the complex interactions that prevent spontaneous repair in MS. This understanding is needed before it will be possible to develop cell transplantation strategies that will promote repair in people with MS.

A group of international researchers co-funded by the National MS Society's Promise: 2010 Nervous System Repair and Protection Initiative identified a molecule in rodents, called retinoid acid receptor (RXR)-gamma, that appears to stimulate the brain's natural ability to repair myelin. The finding resulted from a massive hi-tech screening system to identify new strategies to repair nervous system damage in MS. This study points to a possible target for the development of repair strategies in MS, and will need additional research to determine its translation to human disease. It also introduces a new, valuable resource for the neuroscience and regenerative medicine community to better understand the signaling networks and factors required to repair the injured brain.

In 2009, Fast Forward partnered with EMD Serono, Inc. to support innovative early-stage projects directed towards the development of therapies to prevent, treat, or reverse nervous system damage in MS. One project being done is directed by Dr. Larry Sherman in the Program in Molecular and Cellular Biology at the Oregon Health & Science University School of Medicine. It is examining the possibility that a group of molecules called hyaluronidase inhibitors may have potential to aid in the promotion of remyelination in MS.

The researchers found that a form of a complex sugar molecule, called hyaluronan, accumulates in myelin-damaged areas in the brains of people with MS. In models of MS-like disease, hyaluronan prevented myelin repair by inhibiting OPCs from developing into mature cells capable of making myelin. The researchers postulate that by-products of hyaluronan inhibit myelin repair, and they are testing whether blocking the enzymes that produce these by-products, known as hyaluronidases, will overcome the myelin repair blockage. If successful, this project could lead to a new therapeutic strategy to stimulate repair and restore function in people with MS.

DISCOVERING THE POTENTIAL OF CELL THERAPY

The concept of cell-replacement strategies to treat MS includes such promising strategies as being able to infuse people with cells that could make new myelin or transform into healthy nerve cells. However, introducing new cells into humans also involves great risk, and developing safe and effective cellular therapies demands great care and extensive research.

In 2010, international consensus on the future of stem cell transplantation research for people with MS was published, paving the way for more coordinated global research efforts and potentially better, and quicker, patient access to stem cell clinical trials. The guidelines, developed by an international panel of MS experts with input from MS Societies around the world, spell out hope for the future of MS stem cell research and debunk myths about overseas stem cell clinics claiming to cure the condition. A public information booklet on stem cells, "Stem Cell Therapies in MS," produced in partnership by many MS Societies and the MS International Federation, summarizes the current status of stem cell research in MS and frequently asked questions, and is available to download (.pdf) at **mssociety.org.uk/document.rm?id=7495.**

Animal studies are now being done to work out safety issues relating to the use of new cells to repair MS-related damage, to find the optimal source of cells to transplant, to determine how to obtain enough cells for transplant, and to find the best mode of delivery.

Thomas E. Lane, Ph.D., and a team of collaborators at the University of California, Irvine, and many other investigators around the world, have mounted multifaceted efforts to explore strategies for cell replacement in MS. Dr. Lane's team is investigating how to combine the surgical implantation of immature cells while at the same time modulating the immune attack, thus simultaneously promoting myelin repair while muting myelin damage.

A number of studies have attempted to stop MS progression using infusions of an individual's own bone marrow or blood stem cells, called mesenchymal cells. This type of cell infusion has been used safely in people with some blood disorders and to a limited extent in people with MS. Clinical trials to test the ability of mesenchymal cells to alter MS disease activity are getting underway in several parts of the world.

For example, an international collaborative study is going to launch a phase I/II study in people with inflammatory MS, including RRMS, SPMS, and PPMS. "Inflammatory" in this study means that there are signs of active inflammation on brain MRI scans, even in the absence of clinical relapses. This will be a one-year study with 150 participants at multiple sites, using a "crossover" design in which everyone will receive treatment eventually. Disease activity seen on MRI scans will be the primary outcome measured. The team hopes that the mesenchymal cells will create a more favorable environment in the nervous system to stimulate repair of the nervous system.

Clinical Trials

A WORD ABOUT CLINICAL TRIALS

Clinical trials are an essential step before any promising new drug or other medical therapies can be approved by the U.S. Food and Drug Administration (FDA). The National Institutes of Health (NIH), the National MS Society, MS Society of Canada, or pharmaceutical and biotechnology companies sponsor clinical trials in MS (for more information, see: **nationalMSsociety.org/research/clinical-trials/clinical-trial-resources/index.aspx,** or **clinicaltrials.gov**).

SHOULD I PARTICIPATE IN A CLINICAL TRIAL?

My Life, My MS, My Decisions is a series of online classes that will help you boost your decision-making power. It's your MS and it's your medical care, but sometimes it can feel like other people are making your decisions for you. These classes keep you in the driver's seat. The **Considering Clinical Trials class,** which is part of the series, will help you decide if a clinical trial is right for you. For more information, visit **nationalMSsociety.org/living-with-multiple-sclerosis/getting-the-care-you-need/my-life-my-ms-my-decisions/index.aspx.**

Michael, diagnosed in 2004

How Are Clinical Trials Conducted?

Clinical trials are usually conducted in steps, called **phases,** which almost always follow substantial laboratory research. By the time human testing begins, the manufacturer is confident that the drug stands a good chance of meeting the need for which it was developed and that it will likely be safe. In some cases, drugs undergoing testing in the U.S. have already been approved in Europe or elsewhere. Depending on the quality and nature of these studies, these data may shorten the trial in the U.S.

Phase I trials usually enroll a small number of people (20–80), last about a year, and determine what dose is safe, how a new agent should be given, how often it should be given, and whether it has any harmful side effects.

Phase II trials often involve 100–300 people and can last several years. Participants are usually divided into a group that receives the active drug and a **control group** that receives either an existing treatment or a placebo.

Phase III trials are the last step before a drug is approved by the FDA for general use. They can involve 1,000–3,000 people and may last for up to 5 years. To be approved, a new drug must be at least as effective as one or more treatments already in use, and/or be demonstrably better than a placebo.

Phase IV trials further evaluate the long-term safety and effectiveness of a treatment after it is approved. Additional uses can also be explored. Several hundred to several thousand people might take part in the trial, and any problems must be reported to the FDA.

Many years can elapse between early laboratory research and an approved treatment, and the time and effort involved come at an enormous cost. Most potential treatments fail along the way because they are ineffective or toxic.

To date, studies that have looked at the issue of slowing disability progression have had mixed results, with some providing evidence for effectiveness while others have not. In particular, the studies that raise questions about the ability of approved disease-modifying therapies to significantly delay progression of disability report mixed findings, highlighting the need for more long-term well-designed studies.

How Are Clinical Trials Designed?

The best clinical trials are prospective, randomized, cross-over, and double-blinded studies. You will see these and several other terms frequently in any discussion of clinical trials.

PROSPECTIVE: Participants are identified before the study begins and then followed over time.

RANDOMIZED: Participants are grouped by chance, usually through a computer program. One group receives the treatment being evaluated and the other receives either the current standard treatment or a placebo.

CROSS-OVER: Each participant receives both the treatment and a placebo, but at different times.

DOUBLE-BLINDED: Neither the participants nor the researchers know which group a participant is in the group receiving the active treatment being studied.

OPEN LABEL: This means that both the participants and the treating researchers know that the participant is receiving the treatment and not a placebo.

ELIGIBILITY CRITERIA: Every clinical trial has guidelines, or **eligibility criteria,** about who can or cannot participate in the study. They describe characteristics that must be shared by all participants – these might include age, gender, previous treatment history, and other medical conditions – and they often require that participants have a particular type and stage of MS. Enrolling individuals with similar characteristics helps ensure that researchers will be able to achieve accurate and meaningful results.

Ray, diagnosed in 2003

People with progressive MS have often been frustrated by the relatively small number of clinical trials designed to slow or stop the disease process for progressive MS as compared to those that have led to major advances in the management of the disease process in RRMS. Fewer clinical trials have focused on progressive MS for several important reasons:

- Unless the mechanism by which a disease occurs is understood, it is difficult to develop a drug that will directly affect the disease process. We have less understanding of the process underlying progressive MS than we do of relapsing-remitting MS.
- PPMS and PRMS can be more difficult to diagnose or to distinguish from other disease courses, at least initially, and the development of SPMS proceeds with a variable timeline so that individuals may be partially transitioned for long periods of time.
- When a disease is slowly progressive, it is more difficult to see an immediate effect of a new drug. Most trials are designed to last no more than 36 months.
- There are no easily identifiable outcome measures that can be used in clinical trials of progressive MS, such as the number of relapses and the number of new lesions seen on MRI over the course of a two- or three-year trial – the most common measures used to study relapsing MS. Developing such measures is a high priority for research.
- The traditional measurement of disability progression, the EDSS scale, is not very sensitive to subtle change and focuses mostly on physical function, which poses a significant problem in monitoring progressive MS.
- Especially for PPMS and PRMS, it is difficult to recruit the number of people needed to participate in a clinical trial in order to analyze the results in a meaningful way.
- Currently available disease-modifying therapies act by controlling inflammation, a major characteristic of relapsing MS. These medications do not seem to be as effective in progressive MS.

When people with progressive MS **have** been included in clinical trials, it has tended to be for agents developed to manage symptoms. Fortunately, this is a crucial issue for people with progressive MS, because better symptom management translates into better overall health and quality of life.

Drugs studied for potential use in progressive MS fall into two general categories. The first most commonly includes drugs that have proved effective in relapsing MS that are now being tested in progressive MS; these most often affect the immune process in MS. A second group of drugs are often termed **rescue therapies** – treatments designed to halt the rapid progress of either SPMS or PPMS when they are taking a particularly aggressive and rapid course.

Research to Evaluate Pharmacologic Interventions

FINGOLIMOD (GILENYA™)

Gilenya (fingolimod) is a new class of medication called a **sphingosine 1-phosphate receptor modulator,** which is believed to act by retaining certain white blood cells in the lymph nodes, thereby preventing those cells from crossing the blood-brain barrier into the CNS, which reduces inflammatory damage to nerve cells. This oral therapy was approved by the FDA in 2010 for adults with relapsing forms of MS, to reduce the frequency of clinical relapses and to delay the accumulation of physical disability. Gilenya is now being tested in an international study of 654 people with PPMS. It will study the safety and effectiveness of fingolimod capsules versus inactive placebo. The trial is funded by Novartis Pharmaceuticals AG, and is also known as the INFORMS study.

MIS416—AN ACTIVATOR OF THE IMMUNE RESPONSE

This "therapeutic vaccine" is a potent activator of innate immune responses. It has been primarily tested in cancer and acquired infections, with the goal of enhancing the inherent capability of a person's immune system to fight disease.

A Phase I/II study with 24 participants will determine the safety and tolerability, dose-limiting toxicities, maximum tolerated dose, and recommended therapeutic dose of intravenously administered MIS416 given weekly for 4 weeks in patients with either PPMS or SPMS. The sponsor is Innate Therapeutics Limited, and the Society's Fast Forward initiative is a cosponsor. Although this is primarily a safety and tolerability study, effects on progression as measured by MRI and clinical status will be made at 6 months.

RITUXIMAB (RITUXAN®)

Rituximab is a monoclonal antibody that inhibits the activity of B cells to produce antibodies. Like a number of other drugs in early phases of testing for progressive MS, it has previously been used to treat rheumatoid arthritis and various types of cancers. A new Phase I/II double-blind study of 80 people with low-inflammatory SPMS, sponsored by the National Institute of Neurologic Diseases and Stroke, is testing rituximab versus placebo (RIVITaLISe). The study is currently recruiting participants.

Researchers will determine whether the drug is able to target certain white blood cells that are thought to play a role in the progression of SPMS. To ensure that the drug will reach the brain and spinal cord, participants will receive it by intravenous drip and by intrathecal injection (through a lumbar puncture into the cerebrospinal fluid).

The study will involve a 1-year pretreatment baseline series of visits, followed by a 2-year treatment period. Participants will provide blood samples throughout treatment, and additional studies may be performed.

OCRELIZUMAB

Like rituximab, ocrelizumab is a monoclonal antibody that targets immune B cells and is given as infrequent cycles of intravenous infusions. A planned phase III international clinical trial of ocrelizumab, called the ORATORIO study and sponsored by Roche and Biogen Idec, will involve 630 people with primary-progressive MS.

CYCLOPHOSPHAMIDE

Treatment of progressive MS with high-dose cyclophosphamide is not new; its use predates release of the first DMT in the early 1990s. It is a rather toxic anti-cancer drug, with the typical side effects of this class of drugs. It has limited its use in MS, and is now used mostly for progressive disease that has not responded to more than one of the approved DMTs. Results have been mixed, but reports of good results on slowing disease progression have led to its continued use as a rescue therapy.

A Phase III clinical trial with 360 participants is now being carried out at the University Hospital in Bordeaux, France. It is comparing the efficacy of cyclophosphamide to methylprednisolone in SPMS. The study began in December 2005, and is scheduled for completion in July 2011. Participants receive IV cyclophosphamide or IV methylprednisolone every 4 or 8 weeks for the first year and every 8 weeks during year 2.

IDEBENONE FOR NEUROPROTECTION

Idebenone (Catena®, Sovrima®) is an experimental drug, initially developed for the treatment of Alzheimer's disease and other cognitive defects. Chemically, it is a synthetic analog of coenzyme Q10. It is being explored in MS because **oxidative stress** has been postulated to play a role in oligodendrocytes death — which has been linked to MS progression — and coenzyme Q_{10} appears to play a major role in this process. The agent therefore has a possible **neuroprotective** effect.

A double-blind, placebo-controlled Phase I/II clinical trial of idebenone, sponsored by the National Institute of Neurologic Disorders and Stroke, is currently recruiting participants with PPMS who have no to moderate disability. This safety/efficacy trial will assess safety, therapeutic efficacy, and mechanism of action of idebenone. It has 80 participants; it began in July 2009 and is scheduled for completion in May 2015.

Research to Evaluate Non-Pharmacologic Interventions

FUNCTIONAL ELECTRICAL STIMULATION FOR FOOT DROP

Foot drop is caused by weakness or paralysis of the muscles involved in lifting the front part of the foot. It causes a person either to drag the foot and toes or to develop a high-stepping walk. It is typically treated using exercises and/or an ankle-foot brace.

Functional electrical stimulation (FES) uses low levels of electrical current to stimulate nerves, innervating extremities impaired by MS. It is not a cure, but may temporarily restore or improve function in the nerves that control specific muscles or muscle groups.

A recent study based in Salisbury, UK, led by Julie Esnouf, DipCOT, and Paul Taylor, PhD, included enrolled 53 people with secondary-progressive MS and foot drop. The FES device, the Odstock Dropped Foot Stimulator, was reported to significantly improve self-reported performance of daily activities and satisfaction scores in people with MS who experience foot drop.

Participants were randomly assigned to a group using the FES device or a control group who received physical therapy exercises for 18 weeks. Performance of daily activities and satisfaction scores were significantly increased in the FES group over the control group. The FES group also reported significantly fewer falls, reduced tripping, and an increase in the distance they could walk.

HIP FLEXION ASSIST DEVICE TO IMPROVE GAIT PERFORMANCE

In addition to weakness of the lower leg muscles that move the foot, the muscles that lift the leg and swing it forward – the hip flexors – may also be weak and cause people to stumble or fall because the foot drags on the ground.

A group at the Cleveland Clinic's Mellen Center, led by Francois Bethoux, MD, completed a pilot study of the lightweight, low-cost Hip Flexion Assist Device (HFAD). It uses a combination of straps and elastic bands to supplement the activity of weak hip flexors. The HFAD improved walking and leg strength, and was safe to use. In a new research project, the group is evaluating its effectiveness in 88 people with MS. Half the participants will wear the device for eight weeks, and the other half will not (the control group). A series of tests will evaluate muscle strength, spasticity, and walking ability with and without the brace. The data will be analyzed to determine whether use of the HFAD improves walking performance. They will also gauge usage and satisfaction with the brace, and determine potential side effects. This study will also determine how this type of device can best be evaluated in a full clinical trial. The results will also be used to generate ideas for new active mobility devices.

IDENTIFYING FACTORS INVOLVED IN BALANCE PROBLEMS

A team at the University of Massachusetts in Amherst, led by Richard Van Emmerik, PhD, is working to identify factors involved in balance problems in the poor balance control during standing and walking that many people with MS experience. They are investigating gait and balance in 20 people with MS without walking problems, 20 with MS who have walking problems but who do not use mobility aids, and 20 without MS. They are assessing posture, gait initiation, and walking, using state-of-the-art electronic motion tracking systems.

IMPROVING THE MEASUREMENT OF BALANCE

A team at the Oregon Health & Science University is trying to develop a reliable way to assess balance. They have developed wireless sensors to evaluate exactly how mobility is affected by MS-related balance issues. Using devices that are about the size and weight of a watch and that contain small velocity and acceleration sensors, they are obtaining data that allows them to assess stability and mobility, to pick up some early measures of balance and gait problems, and accurately measure changes following a pharmacologic or lifestyle intervention.

REHABILITATION FOR BALANCE DISORDERS

A pilot trial at the Italian MS Society Rehabilitation Center in Genoa involved 36 people with MS with balance disorders. Half received traditional rehabilitation therapy for 12 one-hour sessions, and half received rehabilitation with a balance board. Both groups showed significant improvements in measures of fatigue and mobility, but those using the balance board also showed significant improvement in measures of balance and stability with eyes open and closed.

EXERCISE & MS

People with MS not only tolerate exercise, but it is now known that exercise leads to improvements that fight fatigue and improve functional ability and quality of life. A number of studies are now underway to quantify the types and extent of exercise that are helpful in MS, and to develop better-designed and controlled clinical trials of exercise to maximize the potential impact of exercise in people with MS. Some of these include:

- Resistance training as a way to help people with MS enhance the muscle strength and endurance they need for function, and to reduce the fatigue associated with deconditioning
- Improving mobility with robot training that simulates walking on a treadmill and comparing its effects strength training

- Boosting daily activity with the goal of improving symptoms, mobility, and quality of life
- Constraint-induced therapy, involving restraining a stronger limb so that the weaker one must be used
- Cycling regimens as a way of reducing spasticity
- Evaluating and comparing the effect of various exercise programs on a comprehensive set of measures of mobility disability, lung function, muscle strength, and balance

EXERCISE TO IMPROVE COGNITION

Many people with MS experience some cognitive impairment, such as difficulty with tasks that involve memory, sustained attention, or thought. More information about cognitive issues in MS is on the National MS Society's website at: **nationalMSsociety.org/about-multiple-sclerosis/what-we-know-about-ms/symptoms/cognitive-function/index.aspx.** Aerobic exercise improves cognition in healthy individuals, and some preliminary data have suggested that it also may improve thinking ability in people with MS who have cognitive impairments. Barbara Giesser, MD, and her team at UCLA are comparing the effects on cognitive performance of a 6-month aerobic exercise program to one of non-aerobic stretching exercise. They are also measuring levels in the blood of a number of substances – including immune messengers and cell growth factors – that may influence the health of nerves in the brain, in order to determine the mechanism by which exercise may act to improve cognition.

MEDITATION

Although the disease-modifying therapies for MS can reduce disease activity for many people, impact the disease course, they alone do not usually cause significant improvement in an individual's health-related quality of life (HRQOL, or a sense of well-being). For this and many other reasons, a key part of the National MS Society's 2011–2015 Strategic Response initiatives is to encourage research that addresses quality of life.

An example of research related to quality of life is a recent Swiss study, led by Paul Grossman, PhD, at the University Hospital in Basel. It involved 150 people with relapsing-remitting and secondary-progressive MS. The study, the largest of its kind to date, showed that mindfulness-based meditation significantly improved HRQOL, depression, and fatigue, as compared to a control group of 74 individuals who received regular medical care. This form of meditation is mental training aimed at changing an individual's perception, creating awareness and acceptance of moment-to-moment experiences, with the goal of reducing reactions that may worsen the pain or emotional distress that may occur as the result of the health-related changes that often result from MS.

Summary

Research in Understanding & Treating Progressive Multiple Sclerosis

Kim, diagnosed in 1986

The development in the 1990's of the first disease management therapies appears to have slowed disease activity and progression for many people with the remitting-relapsing form of the disease. However, no therapy can stop MS completely, and many people with MS either do not respond to these medications or have a form of the disease that is progressive and does not appear to respond as well to these therapies.

As a result, a substantial number of people with MS face issues of progression, and working with their doctors and healthcare team to take advantage of treatment and rehabilitation strategies to help them manage their symptoms can substantially improve their quality of life.

There is also exciting research being conducted on a global scale to understand, stop and reverse MS progression. The stage is being set for translating basic laboratory discoveries into clinical efforts to address progressive MS. New research is focusing on understanding the mechanisms that lead to progression, finding ways to repair existing damage to the nervous system, and accelerating the development of new therapies, as well as on finding better rehabilitation and symptom management strategies to improve the lives of those now living with the disability imposed by progressive MS.

Glossary

ACTIVITIES OF DAILY LIVING

Activities of daily living include any daily activity a person performs for self-care (feeding, grooming, bathing, dressing), work, homemaking, and leisure. The ability to perform ADLs is often used as a measure of ability/disability in MS.

ASSISTIVE DEVICES

Any tools that are designed, fabricated, and/or adapted to assist a person in performing a particular task, e.g., cane, walker, shower chair.

ASSISTIVE TECHNOLOGY

A term used to describe all of the tools, products, and devices, from the simplest to the most complex, that can make a particular function easier or possible to perform.

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.

CENTRAL NERVOUS SYSTEM

The part of the nervous system that includes the brain, optic nerves, and spinal cord. The nerves that leave the spinal cord and go to the rest of the body make up the 'peripheral nervous system'.

CHRONIC PROGRESSIVE

A former "catch-all" term for progressive forms of MS.

CLINICAL TRIAL

Rigorously controlled studies designed to provide extensive data that will allow for statistically valid evaluation of the safety and efficacy of a particular treatment.

EXACERBATION

The appearance of new symptoms or the aggravation of old ones, lasting at least twenty-four hours (synonymous with attack, relapse, flare-up, or worsening); usually associated with inflammation and demyelination in the brain or spinal cord.

EXPANDED DISABILITY STATUS SCALE (EDSS)

A part of the Minimal Record of Disability that summarizes the neurologic examination and provides a measure of overall disability. The EDSS is a 20-point scale, ranging from 0 (normal examination) to 10 (death due to MS) by half-points. A person with a score of 4.5 can walk three blocks without stopping; a score of 6.0 means that a cane or a leg brace is needed to walk one block; a score over 7.5 indicates that a person cannot take more than a few steps, even with crutches or help from another person. The EDSS is used for many reasons, including deciding future medical treatment, establishing rehabilitation goals, choosing subjects for participation in clinical trials, and measuring treatment outcomes. This is currently the most widely used scale in clinical trials.

MAGNETIC RESONANCE IMAGING

A diagnostic procedure that produces visual images of different body parts without the use of X-rays. Nuclei of atoms are influenced by a high frequency electromagnetic impulse inside a strong magnetic field. The nuclei then give off resonating signals that can produce pictures of parts of the body. An important diagnostic tool in MS, MRI makes it possible to visualize and count lesions in the white matter of the brain and spinal cord.

MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE

A three-part, standardized, quantitative assessment instrument for use in clinical trials in MS, that was developed by the Task Force on Clinical Outcomes Assessment appointed by the National MS Society's Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. The three components of the MSFC measure leg function/ambulation (Timed 25-Foot Walk), arm/hand function (9-Hole Peg Test), and cognitive function (Paced Auditory Serial Addition Test (PASAT).

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.

PRIMARY-PROGRESSIVE MS

A clinical course of MS characterized from the beginning by progressive disease, with no plateaus or remissions, or an occasional plateau and very short-lived, minor improvements.

PROGRESSIVE-RELAPSING MS

A clinical course of MS that shows disease progression from the beginning, but with clear, acute relapses, with or without full recovery from those relapses along the way.

REHABILITATION

Rehabilitation in MS involves the intermittent or ongoing use of multidisciplinary strategies (e.g., physiatry, physical therapy, occupational therapy, speech therapy) to promote functional independence, prevent unnecessary complications, and enhance overall quality of life. It is an active process directed toward helping the person recover and/or maintain the highest possible level of functioning and realize his or her optimal physical, mental, and social potential given any limitations that exist. Rehabilitation is also an interactive, ongoing process of education and enablement in which people with MS and their care partners are active participants rather than passive recipients.

RELAPSING-REMITTING MS

A clinical course of MS that is characterized by clearly defined, acute attacks with full or partial recovery and no disease progression between attacks

REMYELINATION

The repair of damaged myelin. Myelin repair occurs spontaneously in MS but very slowly. Research is currently underway to find a way to speed the healing process.

SECONDARY-PROGRESSIVE MS

A clinical course of MS that initially is relapsing-remitting and then becomes progressive at a variable rate, possibly with an occasional relapse and minor remission.

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.

Notes

National Multiple Sclerosis Society

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

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Our mission is to be a leader in finding a cure for multiple sclerosis and enabling people affected by MS to enhance their quality of life.

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