Summary of a Workshop on Research in Multiple Sclerosis, April 5-6, 2001

Prepared by Miriam Davis and Janet E. Joy, Board on Neuroscience and Behavioral Health

ISBN: 0-309-07569-6, 32 pages, 6 x 9, (2001)

SUMMARY OF A WORKSHOP ON RESEARCH IN MULTIPLE SCLEROSIS April 5-6, 2001

Based on the Institute of Medicine report on
MULTIPLE SCLEROSIS: CURRENT STATUS AND STRATEGIES FOR THE FUTURE
prepared by Miriam Davis and Janet E. Joy

Board on Neuroscience and Behavioral Health
INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C.

NATIONAL ACADEMY PRESS 2101 Constitution Avenue, N.W. Washington, DC 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

Support for this project was provided by the National Multiple Sclerosis Society. The views presented in this report are not necessarily those of the funding agencies.

International Standard Book Number 0-309-07569-6

Additional copies of this report are available for sale from the National Academy Press , 2101 Constitution Avenue, N.W., Box 285, Washington, D.C. 20055. Call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP's home page at **www.nap.edu.**

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu .**

Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply. Willing is not enough; we must do.

—Goethe

INSTITUTE OF MEDICINE

Shaping the Future for Health

THE NATIONAL ACADEMIES

National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Acade my has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Bruce M. Alberts is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. William. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Kenneth I. Shine is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Bruce M. Alberts and Dr. William. A. Wulf are chairman and vice chairman, respectively, of the National Research Council.

www.national-academies.org

CONTENTS

	Introduction	1
	Workshop Format	1
	Strategies for Future Research on Disease Mechanisms	4
	Strategies for Future Research on Disease Management	6
	Therapeutics	6
	Quality of Life	7
	Patients and Priority Setting	8
	Building and Supporting the Research Enterprise	9
	Recruitment of Younger Researchers	9
	MS Centers and Program Projects	11
	Clinical Trials Network	12
	Protecting Against False Leads	13
	Closing Remarks	13
Appendix A:	List of Report Recommendations	15
Appendix B:	IOM Committee Members and Staff	19
Appendix C:	Workshop Agenda	21
Appendix D:	Meeting Participants	23

INTRODUCTION

More than 50 invited experts representing international organizations supporting MS research participated in an April, 2001, workshop held in Washington D.C. to advance research recommended by the report, *Multiple Sclerosis: Current Status and Strategies for the Future*.[1] That report identified promising areas of multiple sclerosis (MS) research based on a strategic analysis of the current state of knowledge. The report was written by the Institute of Medicine (IOM) Committee on MS Research Strategies.

The specific goals of the workshop, articulated by Dr. Richard B. Johnston, Chairman of the IOM Committee, were to disseminate information about the report, foster collaboration, and serve as a launch pad for implementation of the report's recommendations. In his opening remarks, Dr. Johnston remarked on the innovative nature of the workshop which, to his knowledge, was "the first time that a finished [IOM] report had been ... used to develop a workshop and, from that, to extend the report."

WORKSHOP FORMAT

The workshop agenda was organized around formal presentations by Committee members, question-and-answer sessions, and breakout groups. The workshop began with an overview and discussion of the report's 18 recommendations (Appendix A). Committee members (Appendix B) provided background information and insights about the Committee's deliberations. Following their presentations and discussion in plenary session, three concurrent breakout sessions focused on a cluster of recommendations under each of these categories: disease mechanisms, disease management, and building and supporting the research enterprise (See Appendix C). Each breakout group was asked to consider:

1. how particular recommendations might be implemented most effectively, and
2. how the recommendations within each category might be prioritized.

Proposals from each breakout group were later reported back to the plenary session by an appointed rapporteur, followed by a general discussion of suggestions and conclusions made by the breakout groups.

This workshop summary presents the reports from each breakout group and summarizes the plenary session discussion. For clarity, the recommendations are grouped slightly differently from the grouping in the report (see box). In keeping with the written policies of the National Academy of Sciences, this workshop summary contains particular viewpoints attributed to individual participants or to groups of participants (including breakout groups), but does not contain statements about what "the workshop" or "all its participants" concluded. This summary is not a formal product of the IOM Committee on MS Research Strategies.

[1] The report and the workshop, held April 4-5, 2001, were sponsored by the National Multiple Sclerosis Society.

Recommendations for Future Research on Disease Mechanisms

BREAKOUT GROUP A: *Discussion Leaders,* Jack Antel and Jesse Cedarbaum; *Rapporteur,* Robert Lisak

RECOMMENDATION 1: Research on the pathological changes underlying the natural course of MS should be emphasized, because it provides the key to predicting disease course in individual patients, understanding the physiological basis of MS, and a basis for developing improved therapeutic approaches.

RECOMMENDATION 2: Research should be pursued to identify how neurons are damaged in MS, how this damage can be prevented, and how oligodendrocytes and astrocytes are involved in damage and repair processes.

RECOMMENDATION 3: The genes that underlie genetic susceptibility to MS should be identified, because genetic information offers such a powerful tool to elucidate fundamental disease processes and prognosis, and to develop new therapeutic approaches.

RECOMMENDATION 4: Because the discovery of an MS pathogen would likely provide the single most important clue for identifying effective treatments, this search must remain a high priority, but should be conducted using powerful new and efficient methods.

RECOMMENDATION 5: Research to identify the cascade of immune system events that culminates in the destruction of myelin should remain a priority.

RECOMMENDATION 6: The power of neuroimaging as a tool for basic research and for clinical assessment should be taken advantage of more extensively.

RECOMMENDATION 7: Animal models should be developed that more faithfully mirror the features of MS and permit the analysis of how specific molecules and cells contribute to the disease process.

Recommendations for Future Research on Disease Management

BREAKOUT GROUP B: *Discussion Leaders,* Stephen Hauser and Sharon Juliano; *Rapporteur,* Henry Claman

Therapeutics

RECOMMENDATION 8: Strategies for protection and repair of neural cells, including the use of neuroprotective factors as well as stem cells, hold great promise for the treatment of MS and should be a major research priority.

RECOMMENDATION 9: New, more effective therapeutic approaches to symptomatic management should be pursued, including those directed at neuropathic pain and sensory disturbances.

RECOMMENDATION 10: In the absence of any fully effective therapies, integrated approaches for the delivery of currently available therapeutic agents should be investigated.

RECOMMENDATION 11: Better strategies should be developed to extract the maximum possible scientific value from MS clinical trials.

Quality of Life

RECOMMENDATION 12: Health status assessment methods for people with MS should be further developed and validated to increase the reliability and power of clinical trials and to improve individual patient care.

RECOMMENDATION 13: Research strategies aimed at improving the ability of people with MS to adapt and function should be developed in partnership with research practitioners, managers, and patients; toward this end, a series of forums to identify the most pressing needs experienced by people with MS should be convened.

RECOMMENDATION 17: New strategies should be developed to encourage more integration among the different disciplines that support and conduct research relevant to improving the quality of life for people with MS.

Recommendations for Building and Supporting the Research Enterprise

BREAKOUT GROUP C: *Discussion Leader,* Ray Roos; *Rapporteur,* Christine Purdy

RECOMMENDATION 14: New researchers should be actively recruited to work in MS, and training programs should be designed to foster productive interactions with established investigators both within and outside the MS research community.

RECOMMENDATION 15: Concerted efforts should be made to stimulate enduring interdisciplinary collaborations among researchers in the biological and non-biological sciences relevant to MS and to recruit researchers from other fields into MS research.

RECOMMENDATION 16: Programs to increase research efficiency should be developed, including collaborations to enable expensive large-scale projects (for example, clinical trials, genome screens) and to organize collection of scarce resources (for example, human tissue).

RECOMMENDATION 18: To protect against investing research resources on false leads, there should be an organizational structure to promote efficient testing of new claims for MS pathogens and disease markers.

STRATEGIES FOR FUTURE RESEARCH ON DISEASE MECHANISMS

The breakout group on disease mechanisms reviewed recommendations (#s1–7) relating to pathology, neuronal degeneration, genetic susceptibility, pathogens, immunopathogenesis, neuroimaging, and animal models. Dr. Robert Lisak, the group's rapporteur, relayed that the group decided not to prioritize this set of recommendations because all were deemed to be important and "absolutely intertwined." As Dr. Jerry Wolinsky noted, "things shift so quickly in science . . . depending on where the data come from and how hot . . . it looks" that any prioritization made at the workshop might shift too soon to be useful. The group also pointed out that the report's recommendations for research on disease mechanisms were already underway.

The group agreed with the IOM report that priorities should balance scientific opportunity with organizational goals. Given the rapidly evolving nature of biomedical research, the real question posed by the group is whether funding agencies, such as NIH and the National MS Society, have adequate systems in place to monitor the latest research opportunities. The group proceeded to answer that question affirmatively—that funding agencies are using appropriate means to actively monitor research developments, and that they have the flexibility to take advantage of new trends. According to Dr. Wolinsky, one member of the group,

> "When we decided not to prioritize, we also decided that we can feel comfortable doing that because ... the National MS Society, the NIAID, the NIH, and the NINDS were doing an adequate job of reviewing the landscape of science priorities and changing priorities and that we didn't see that there was an important need to change those structures or how they are functioning ... this is an important aspect on which there was consensus."

The group also discussed whether any large-scale scientific initiatives were warranted to advance understanding of disease mechanisms. They regarded the ongoing international initiative, "The MS Lesion Project," as fulfilling an important research question that a large-scale initiative should address—namely, whether there are distinct neuropathological subtypes of MS. This project, the largest ever supported by the National MS Society, integrates tissue samples and imaging in a longitudinal study design. The breakout group stressed the benefit of frequent monitoring of the project's progress and the importance of smaller-scale studies to confirm findings.

The breakout group emphasized that the report contained many other suggestions for promising areas of research not highlighted as formal recommendations, for example, tissue banks and gender. The breakout group also agreed that far more research emphasis was warranted on microglia, other antigen-presenting cells, and endothelial cells, as well as on the interactions between all cell types involved in MS pathogenesis. Further, the group proposed that the Committee's recommendation (#3) to study genetic susceptibility in MS be expanded to incorporate the role of genes

in disease heterogeneity, clinical course, and response to drug therapy. The group did not agree as to whether there are leading genetic "hot spots" to pursue more vigorously.

In studying the role of pathogens in MS, Dr. Lisak reported that the group felt that research on pathogens should not focus on a "single causative agent," but on the multifarious roles of infectious agents in "possible initial triggers, and ... in relapses, and secondary damage." The group also emphasized the importance of studying interactions between pathogens and the immune system, as well as studying the possibility of distinct pathogens being involved to varying degrees in different patients.

In the previous day's discussion of pathogens, Committee member Dr. Raymond Roos explained that the Committee had recommended pathogen research because "whether MS is an inflammatory disease because a pathogen is involved, or whether it is an inflammatory disease for another reason is an open question." He also pointed to the existence of "wonderful tools that haven't really been exploited" for identifying pathogens in MS. Reflecting his skepticism, Dr. Kees Lucas retorted, "Having a wonderful rod is not a reason to go fishing." Thus although the group reported that they agreed in general that it was unwise to prioritize recommendations #s1–7, at least one participant felt that recommendation #4 was less important than the others.

The breakout group highlighted investment in animal models. "We thought it was important to reaffirm that animal models are important ... and that different animals and different models are important ...," said Dr. Lisak. The group agreed that many types of animal models are needed, as was animal imaging, to study distinct aspects of pathogenesis. The group did not reach consensus about whether there was a need for a central facility for studying nonhuman primate models. They acknowledged the significance of primate models in current research, but did not agree on the need for extra investment in a central facility.

The ensuing discussion focused on the value of a central primate facility. Dr. Reingold of the National MS Society indicated that the Society and NIH had co-funded a central facility for many years, yet eventually abandoned it. Several participants noted the advantages of such a facility: primates' close biological fidelity to humans, their utility for uncovering medication safety problems prior to human clinical trials, and their role in teasing apart disease pathogenesis. The disadvantage is that a primate facility requires large, long-term investment that may not be fruitful.

Another discussion centered on the value of supporting a large-scale initiative to screen mouse mutants for abnormalities that resemble MS. Screening would be followed by intensive efforts to identify which genes are mutated, what their function is, and how they contribute to the observed abnormality. Some participants suggested that an initiative for MS could be conducted as part of a wider initiative to screen mouse mutants for many neurological diseases simultaneously. Others cautioned that with models of other diseases, intensive, years-long investigation of mutant mice had been unsuccessful because the model did not sufficiently resemble the human disease.

STRATEGIES FOR FUTURE RESEARCH ON DISEASE MANAGEMENT

The breakout group on disease management also elected not to prioritize their assigned set of recommendations (recommendations #s 8–13, 17) because all were viewed as worthy objectives, according to Dr. Henry Claman, the group's rapporteur. He added that "it is probably a logical mistake to prioritize groups of recommendations that are so heterogeneous."

THERAPEUTICS

The breakout group felt that the recommendation (#8) for protection and repair of neural cells, including stem cells, was a "good area for collaborative and interdisciplinary research among various people in neurobiology, including partnerships with the pharmaceutical industry," said Dr. Claman. Despite controversy over stem cells in federally supported research, the group noted that the National MS Society has an explicit policy permitting their use in research.

The breakout group noted that improvement and validation of therapeutic approaches to symptom management has received relatively scant scientific attention (#9). As background, Committee member Dr. Patricia Coyle pointed out that, while better symptomatic treatments were being developed, "there is much room for improvement" because symptoms of fatigue, depression, spasticity and pain, among others, have "tremendous impact for every patient on their quality of life" and that clinicians are not managing these symptoms with available treatments.

Dr. Claman relayed that the breakout group found symptom management to be a "good candidate for collaborative research." If the National MS Society is interested in promoting this area, the group felt the Society should take active steps to raise awareness within the scientific community and to ask leaders in the field what directions should be taken. Dr. Claman noted that symptom management could be addressed within ongoing discussions, spearheaded by the National MS Society, on the needs of patients grouped according to gender and age.

Regarding the recommendation (#10) for integrated approaches for delivery of currently available therapies, Dr. Claman relayed the group's support for the recommendation and a role for the pharmaceutical industry, but the group did not devote much discussion to implementation.

The recommendation (#11) for better strategies to extract maximum scientific value from MS clinical trials was, according to Dr. Coyle, an outgrowth of the following concerns: the limited number of MS patients; growing ethical problems with placebo-controlled trials; the need for standardized protocols and assessment methods; the economic constraints on pharmaceutical companies to minimize the length of treatment trials; and the breadth of unanswered treatment questions, including which patients should be treated with disease-modifying therapies for their first attack of MS. The breakout group did not discuss this recommendation except to note that the International MS Trials Research and Resource Center is now being set up to provide a database of existing clinical trials.

QUALITY OF LIFE

The quality of life recommendations by the IOM committee featured the need for better health status assessment methods (#12), better integration of disciplines studying quality of life (#17), and the need for more quality of life research with input from patients in setting priorities (#13). Improving the quality of life for MS patients was discussed by two separate breakout groups—those on disease management and research infrastructure.

Committee member Dr. Lisa Iezzoni pointed out that there are numerous functional status and disability measures, yet no consensus on which were best applied to MS patients. The exception is the Expanded Disability Status Scale (EDSS), yet this scale is seen by researchers as outdated, limited, and placing too much emphasis on physical dysfunction. Other problems are the dearth of health services researchers interested in MS, of longitudinal studies, and of communication across disciplinary lines (nursing vs. health services research) and across chronic and disabling diseases.

The breakout group on disease management agreed with the importance of better health status assessment scales, according to Dr. Claman. The group felt that a single new scale is likely to be insufficient and that more than one scale is needed depending on the study question. To simplify research, the group suggested developing a core data scale for all patients, with additional modules for assessment of different patient sub-groups, for example, patients with relapsing-remitting disease versus secondary progressive disease. The group pointed out that the National MS Society, NIH, and health insurance organizations would need to agree on the advisability and details of different scales before their validation. Several participants pointed to the difficulty of arriving at an internationally acceptable scale. In addition to problems with translation to different languages, cultures vary with respect to patient willingness to disclose their functional performance, particularly in relation to cognitive dysfunction, depression, and sexuality.

The National MS Society's Dr. Nicholas LaRocca noted that the Society is updating earlier scholarly reviews of MS assessments and, to increase awareness in the scientific community, is exploring the possibility of making assessment information available on the World Wide Web. He also reported that the North American Research Committee on MS has an ongoing project examining standardization of data collection methods.

Extended discussions concentrated on the availability of funds for rehabilitation and disability research. Committee member Sharon Juliano spotlighted the apparent “disconnect” between health services researchers' frustration at being turned down for funding and reports by funding agencies of unused funds. Several members of the IOM Committee remarked upon their surprise in learning of untapped pockets of grant funding. Representatives of several funding agencies, including the National MS Society, the Veterans' Administration (VA), and the NIH's National Center for Medical Rehabilitation Research (NCMRR) said they were at a loss to explain the discrepancy. They reported receiving few applications for funding MS rehabilitation and health services research in spite of their efforts to announce availability of funds. Dr. Reingold of the National MS Society

noted that his Society's efforts to recruit applicants actively tried to reach beyond the MS field when publicizing the availability of funding. Yet he too conveyed his frustration that the few applications his Society received were of poor quality, even though the Society worked with researchers to help shape their applications.

Dr. Iezzoni of the IOM Committee urged more "beating of the bushes" by funding agencies after she recounted that even though she is an established health services researcher, she had only learned of funding opportunities at the MS Society second-hand through her colleagues and not directly through any of the channels used by the Society. She encouraged funding agencies to be more proactive in recruiting health services researchers from outside the MS field who are studying symptoms (e.g., incontinence) of relevance to MS patients. She also suggested that funding agencies could act as brokers to link up practicing neurologists with health services researchers at nearby universities, to which Dr. Michael Weinrich of the NIH, National Center for Medical Rehabilitation replied that "I think certainly we would be very happy to coordinate with the MS Society or other agencies," to promote awareness of funding.

The discussion was summarized by Dr. Richard Johnston, who observed that current approaches by funding agencies are not working. The recommendation to encourage more quality of life research (#17) was also discussed by the third breakout group, which described the need for research as "an absolute must." That breakout group suggested workshops to facilitate the transfer of ideas among biomedical researchers and allied health professionals at international meetings such the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS).

PATIENTS AND PRIORITY SETTING

Participants also debated the role of patients in the research priority-setting process. The breakout group agreed with the report's recommendation that patients and caregivers must have a voice in identifying quality of life research needs through various venues and forums. Dr. Reingold raised the broader question of whether patients should participate more generally in priority-setting across all types of MS research. Several participants described their experience in other health fields where patients successfully contributed to prioritizing research, in part, by lending urgency and direction to the discussion. Others pointed to the pitfalls. As both researcher and patient, Dr. Iezzoni observed that patients are heterogeneous and do not speak with one voice. Some emphasize research on a cure, while others are more concerned about their quality of life, often depending on age and severity of symptoms. A recent study of patients, conducted in Denmark and soon to be published, has borne this out, according to Dr. Clausen of the Danish MS Society. Some workshop participants were concerned about the hazards of having patients advise on scientific priorities in which they lack expertise. Finally, Dr. Claman commented on the unfairness of asking patients to prioritize when experts themselves are similarly divided.

BUILDING AND SUPPORTING THE RESEARCH ENTERPRISE

In plenary presentation, Dr. Stephen Hauser drew attention to the importance of a "functional superstructure" to support MS research in a highly dynamic and changing scientific and clinical environment. He referred to MS as a "prototypic multidisciplinary disease" that transcends individual disciplines and specialties. Although neurologists have traditionally viewed MS as an immunological disease, Dr. Hauser noted that in light of renewed awareness about neural degeneration and remyelination, "This all might change." He urged participants to view the workshop as "an opportunity for us to really re-think, in a somewhat more radical way, how we might bring a new model to this clinical problem."

The breakout group focused its discussion on the following topics: recruitment of young researchers, centers and program projects, clinical trials network, and protection against false leads. The breakout group refrained from prioritizing their recommendations (14–16 and 18), because according to Christine Purdy, the group's rapporteur, the group agreed that with one exception the recommendations were equally important. The single exception was the recommendation (#18) for an organizational structure to protect against investing research resources on false leads for MS pathogens and disease markers. Most members of the breakout group did not accept this recommendation.

RECRUITMENT OF YOUNGER RESEARCHERS

The breakout group pointed out that fellowships are readily available for recruitment of young researchers (recommendation #14). The real problem in their view is lack of sufficient motivation to pursue clinical research in general and MS research in particular. The group underscored the importance of encouraging young researchers, as early in their careers as possible, by providing visible role models and mentors, career excitement and challenge, long-term security, and scientific opportunity. The breakout group suggested the following steps to stimulate young investigators to enter the field:

- Hold a series of workshops around particular topics to attract young investigators from different disciplines, including medical students, pre-doctoral students, postdoctoral candidates, and neurology residents;
- Provide medical students with summer fellowships or year-long fellowships in MS research;
- Bring into the MS field recent graduates, as well as established scientists, in related disciplines, for example, genomics, bioinformatics;
- Offer MS weekend retreats to accompany Keystone symposia and satellite symposia for the annual Society for Neuroscience meeting;
- Offer research grants in partnership with bioengineering researchers;

- Offer more fellowships in conjunction with MS funding proposals;
- Create partnerships between industry and government to support MS centers patterned after a Switzerland-based center for neuroscience;
- Offer a postdoctoral financial package that includes postdoctoral training as well as a career transition award that carries over to a junior faculty position.

The final step (above) is designed to ease the often difficult transition from fellowships to faculty position. The concept of combining postdoctoral training with a career transition award is a new approach being funded and implemented in a variety of ways by industry, professional organizations, foundations, NIH institutes, and the Medical Research Council of Canada, according to several participants.

Dr. Toby Behar of NINDS remarked that the concept is "probably one of the most exciting proposals I have heard ... because I think it would really work in attracting the best and the brightest and especially for the issue of the physician-clinician in training new clinician researchers." Another advantage is that it offers stable funding for the recipient and enhances his or her attractiveness to the institution offering the faculty position.

During the previous day's presentation, Dr. Stephen Hauser drew special attention to the importance of attracting young physicians to MS research. "Not only is there a national plight vis-a-vis physician scientists, but in MS we are underrepresented in attracting the best minds ... the physician scientist is the person who is connecting and sustaining the connections between the bedside and the science, be it immunology, health sciences, or health services research, ..."

Hauser described a program at his institution that offers medical residents five years of funding for research together with core curricula and close mentoring. He stressed that young people are drawn to a field if they perceive the problem to be soluble and the funding to be stable.

Dr. Audrey Penn of NINDS described some new NIH initiatives to recruit physicians into clinical research and expressed the desire "to partner with the National MS Society on getting people started."

Dr. Johnston described a successful recruitment program for clinician-scientists that involves a partnership between the academic pediatric community and the NIH, and that might be emulated by the MS research community. The academic pediatric societies, the American Academy of Pediatrics, and March of Dimes, formed a consortium that included the National Institute of Child Health and Human Development (NICHD) and created a program in which academic departments identify a promising resident and propose that they apply to the program. The program provides a 3-year fellowship at a good stipend that the fellow can take to any basic science laboratory in the United States. The fellow has the assurance that he or she can return to the sponsoring department at the end of the fellowship, but he or she is not required to, and that puts the onus on the sponsoring department to make an attractive offer, an offer which is enhanced by the provision of start-up faculty funds at the sponsoring department. The program has been very successful in encouraging

clinicians to pursue pediatric research and, as Dr. Johnston described, it has "generated a coterie of real leaders, really solid clinician scientists who are now distributed across American pediatrics and have been highly successful."

MS CENTERS AND PROGRAM PROJECTS

The breakout group discussed centers of excellence as a way of creating a stimulating environment that supports a critical mass of investigators, serves as a magnet for trainees and young investigators, has discretionary funds, and can support a set of core resources, including imaging technology, statisticians, bioinformatics, and administration. They described a model from Melbourne, Australia in which an MS research center occupies one floor, Alzheimer's disease another floor, and a third floor a different discipline, all sharing core resources funded by government, local philanthropy, and industry. Some centers could be devoted to high-risk and multidisciplinary research. Although there are some MS research centers with multiple programs funded through multiple sources, there are no centrally funded MS centers today,[2] though the NIH and the National MS Society have funded MS centers in the past. Center grants were discontinued by the National MS Society because of their high, long-term cost without the benefits of sustained excellence, innovation, and productivity. To overcome these problems, the breakout group suggested greater oversight and more accountability through competitive renewal of funds every 5 years on the basis of both training and productivity.

The breakout group also discussed program project grants, which support three to five interrelated research projects with central core and administrative framework. They too could be designed for high-risk, multidisciplinary projects, and include a training component, according to Dr. Ray Roos, a Committee member assigned to the breakout group.

In their discussion of the proposal for MS research centers, several participants noted the lack of accountability and high investment that detracts from funding for investigator-initiated research. Dr. Celia Brosnan observed that, "they don't have that rapid response" to take advantage of new scientific leads and to support high-risk research.

Dr. Paul Hoffman of the Veterans Administration pointed out that 2.5 years agothe VA invested in a new mechanism, somewhat smaller than a center, called REAPS, Research Enhancement Award Programs. These are investigator-initiated grants funded at $250,000 per year, focused on an area or a particular disease, such as Parkinson's or dementia.

"The idea was to be something totally new ... to use these funds for ... pilot projects ... core facilities, and to do training ... The word out that we hear is that they have been highly successful and we are in the process of reviewing them. ..."

The NIH has established various new initiatives to foster interdisciplinary collaboration that are relevant to MS research; for example, the Bioengineering Research Partnerships and Bioengineering Research Grants, which are broadly based, cross-institute awards for multidisciplinary teams to develop knowledge or methods to prevent, de

[2] With the exception of an MS center at the University of Washington

tect, diagnose, or treat disease—including behavioral and rehabilitation research.

Program project grants can be organized along multidisciplinary lines as well, according to Dr. Reingold whose organization jointly funded a program project grant with NIAID on the concept of gender and autoimmunity.

The real dilemma facing funding agencies, said General Dugan of the National MS Society, is that funding of big projects comes at the expense of more widely distributed investigator-initiated projects. A question he raised was, by what criteria should centers be judged to ensure their productivity?

Dr. Lisak pointed out that some centers funded by the National Cancer Institute are judged not only on the basis of their accomplishments through the center grant but also on other measures of productivity, including success with program projects, investigator-initiated grants, and clinical trials. The Dutch MS Society's recent experience with a multidisciplinary center, said Dr. Lucas, has been highly successful in stimulating more grant applications, publications, and post-docs than would have occurred with separate funding streams.

The VA had been skeptical of the value of a center, noted Dr. Hoffman. But they decided to proceed cautiously with REAPs once they had identified highly focused problems that could only be addressed by some type of center. They plan to perform a careful evaluation of the program according to the criteria developed by the center applicant. “We are willing to partner at the VA ... we are very interested in expanding our funds to expand the whole pool, but we don't want to be duplicative.”

Dr. Reingold commented that centers represent opportunities and risks that might be more palatable if they were shared across funding agencies. Dr. Behar of NINDS questioned whether a center has advantages over a program project. Yet she pointed to the value of a center targeted to a particular problem (e.g., the need for translational research) rather than focused on a particular disease.

When Dr. Behar asked what type of center of excellence is recommended by the workshop, Dr. Hauser replied that there was “one clear need ... for a network of dedicated imaging facilities.” Several participants had highlighted the lack of uniformity or standardization in imaging, which precludes sharing of data, and the need for surrogate markers to assess the progression of MS. Dr. Wolinksy called for four to six regional centers of “imaging excellence” with unlimited use of scanner time and an excellent network to provide “cross-sectional longitudinal data across all subtypes of MS with multimodal imaging that is highly integrated with the occasional pathological correlate.”

CLINICAL TRIALS NETWORK

To increase research efficiency (#16), the breakout group supported the establishment of a network of clinical trials with the following goals: to link up clinical investigators, avoid duplication of effort, provide for quality control, clarify diagnoses, and develop standardized measures for clinical trials outcomes. “There was a feeling among the group that this was an idea whose time had come,” said Christine Purdy, the group's rapporteur.

In the discussion, Dr. Wolinsky reported that the Clinical Trials Commit

tee of the MS Society is slated to consider the pros and cons of creating a clinical trials network. Similar discussions are underway in Europe, according to Dr. Thompson. There currently are networks for Parkinson's disease and several other neurological disorders. One of the advantages of a clinical trials network, according to several participants, is to provide a mechanism for academic medical centers to organize and facilitate trials funded by government or the pharmaceutical industry. Through its collective expertise, the network can set the terms of protocols, including setting of standards for data collection and access to data. The disadvantages, according to some participants familiar with other networks, is that pharmaceutical companies may not be pleased with the terms of participation and may turn instead to clinical investigators outside the network who have less expertise. Other problems are that a network may not be flexible enough and that it may slow down, instead of facilitate, patient recruitment when several studies are conducted in parallel.

PROTECTING AGAINST FALSE LEADS

The IOM Committee was concerned about the amount of time and resources spent on verifying what turned out to be false leads about the causes of MS, according to Dr. Raymond Roos, a Committee member. He observed that because of the years spent unsuccessfully tracking down at least 15 different pathogens, the committee wanted to provide “an infrastructure and strategy to test the validity” of claims regarding pathogens, as well as other claims about diagnosis and treatment.

Ms. Purdy summed up the breakout group's nearly unanimous rejection of the recommendation: “There was no desire to be the police officer for science,” she said. Expanding on the group's rationale, Dr. Fred Lublin said that no single group could assign itself the task or has the competence to refute evidence with extremely complicated assays. Instead, the group adopted the view of “scientific Darwinism”— namely, that “good ideas will rise to the top and bad ideas will sink.” The group did not feel that people should be appointed to oversee claims because it was “presumptive and likely to fail,” said Dr. Lublin.

In further discussion Mr. Richard Slifka of the National MS Society noted that “whether we like it or not the MS Society in some ways does” organize efforts to verify claims. “But for the MS society to appoint itself as the policeman of science” is not “an appropriate role for our organization,” he added. Dr. Johnston reflected that the committee's recommendation was not directed at the National MS Society but was intended for the MS community.

CLOSING REMARKS

Dr. Celia Brosnan echoed a sentiment voiced by many of the participants throughout the workshop when she commented, “how valuable it has been to have people from so many different walks of life together in the same room. I think that this is a fairly unique opportunity, especially for discussions that bridge the government funding and private foundations.”

In his concluding remarks, Dr. Johnston observed how impressed he was with the terrific discussion at the

workshop and expressed the hope that the workshop would foster collaborations between the Society and other funding agencies with a similar commitments to MS research. And, finally, he applauded the efforts of the leadership of the National MS Society to encourage creativity and vision in pursuing their mission.

APPENDIX A: LIST OF REPORT RECOMMENDATIONS

RECOMMENDATIONS FOR FUTURE RESEARCH ON DISEASE MECHANISMS

RECOMMENDATION 1: Research on the pathological changes underlying the natural course of MS should be emphasized because it provides the key to predicting disease course in individual patients, understanding the physiological basis of MS, and a basis for developing improved therapeutic approaches.

RECOMMENDATION 2: Research should be pursued to identify how neurons are damaged in MS, how this damage can be prevented, and how oligodendrocytes and astrocytes are involved in damage and repair processes.

RECOMMENDATION 3: The genes that underlie genetic susceptibility to MS should be identified, because genetic information offers such a powerful tool to elucidate fundamental disease processes and prognosis, and to develop new therapeutic approaches.

RECOMMENDATION 4: Because the discovery of an MS pathogen would likely provide the single most important clue for identifying effective treatments, this search must remain a high priority, but should be conducted using powerful new and efficient methods.

RECOMMENDATION 5: Research to identify the cascade of immune system events that culminates in the destruction of myelin should remain a priority.

RECOMMENDATION 6: The power of neuroimaging as a tool for basic research and for clinical assessment should be taken advantage of more extensively.

RECOMMENDATION 7: Animal models should be developed that more faithfully mirror the features of MS and permit the analysis of how specific molecules and cells contribute to the disease process.

RECOMMENDATIONS FOR FUTURE RESEARCH ON DISEASE MANAGEMENT

Therapeutics

RECOMMENDATION 8: Strategies for protection and repair of neural cells, including the use of neuroprotective factors as well as stem cells, hold great promise for the treatment of MS and should be a major research priority.

RECOMMENDATION 9: New, more effective therapeutic approaches to symptomatic management should be pursued, including those directed at neuropathic pain and sensory disturbances.

RECOMMENDATION 10: In the absence of any fully effective therapies, integrated approaches for the delivery of currently available therapeutic agents should be investigated.

RECOMMENDATION 11: Better strategies should be developed to extract the maximum possible scientific value from MS clinical trials.

Quality of Life

RECOMMENDATION 12: Health status assessment methods for people with MS should be further developed and validated to increase the reliability and power of clinical trials and to improve individual patient care.

RECOMMENDATION 13: Research strategies aimed at improving the ability of people with MS to adapt and function should be developed in partnership with research practitioners, managers, and patients; toward this end, a series of forums to identify the most pressing needs experienced by people with MS should be convened.

RECOMMENDATION 17: New strategies should be developed to encourage more integration among the different disciplines that support and conduct research relevant to improving the quality of life for people with MS.

RECOMMENDATIONS FOR BUILDING AND SUPPORTING THE RESEARCH ENTERPRISE

RECOMMENDATION 14: New researchers should be actively recruited to work in MS, and training programs should be designed to foster productive interactions with established investigators both within and outside the MS research community.

RECOMMENDATION 15: Concerted efforts should be made to stimulate enduring interdisciplinary collaborations among researchers in the biological and non-biological sciences relevant to MS and to recruit researchers from other fields into MS research.

RECOMMENDATION 16: Programs to increase research efficiency should be developed, including collaborations to enable expensive large-scale projects (for example, clinical trials, genome screens) and to organize collection of scarce resources (for example, human tissue).

RECOMMENDATION 18: To protect against investing research resources on false leads, there should be an organizational structure to promote efficient testing of new claims for MS pathogens and disease markers.

APPENDIX B: IOM COMMITTEE MEMBERS AND STAFF

Richard B. Johnston, MD *(Chair)*
Professor, Department of Pediatrics
National Jewish Medical and Research Center and University of Colorado School of Medicine
Denver, CO

Jack P. Antel, MD
Chair, Department of Neurology and Neurosurgery
Montreal Neurological Hospital & Institute, McGill University
Montreal, Quebec CANADA

Samuel Broder, MD
Executive Vice President
Celera Genomics
Rockville, MD

Jesse Cedarbaum, MD
Vice President of Clinical Affairs
Regeneron Pharmaceuticals
Tarrytown, NY

Patricia Coyle, MD
Professor, Department of Neurology
State University of New York at Stony Brook
Stony Brook, NY

Stephen L. Hauser, MD
Professor and Chair, Department of Neurology
University of California, San Francisco
School of Medicine
San Francisco, CA

Lisa Iezzoni, MD
Professor, Division of General Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA

Suzanne T. Ildstad, MD
Professor, Institute for Cellular Therapeutics
University of Louisville
Louisville, KY

Sharon L. Juliano, PhD
Professor, Department of Anatomy and Cell Biology and Neurosciences Program
Uniformed Services University of the Health Sciences
Bethesda, MD

Donald L. Price, MD
Professor of Pathology, Neurology, and Neuroscience
The Johns Hopkins University School of Medicine
Baltimore, MD

Raymond Roos, MD
Chairman, Department of Neurology
University of Chicago
Chicago, Illinois

Alan Thompson, MD, FRCP
Garfield Weston Professor of Clinical Neurology and Neurorehabilitation
Institute of Neurology
Queen's Square, United Kingdom

Stephen Waxman, MD, PhD
Professor and Chairman, Department of Neurology
Yale University School of Medicine
New Haven, CT

Hartmut Wekerle, MD, PhD
Chairman and Director
Max-Planck-Institut für Neurobiologie
Planegg-Martinsreid, Germany

STAFF

Janet E. Joy, Study Director
Amelia B. Mathis, Project Assistant
Lora K. Taylor, Administrative Assistant
Terry C. Pellmar, Board Director

APPENDIX C: WORKSHOP AGENDA

WORKSHOP ON MS RESEARCH STRATEGIES FOR THE FUTURE

April 5–6, 2001
National Academy of Sciences Building
Washington, D.C.

THURSDAY, APRIL 5

8:00 a.m.	CONTINENTAL BREAKFAST	
8:30 a.m.	Welcome and Introduction	Richard B. Johnston, *Chair,* IOM Committee on MS Research Strategies
RESEARCH ON DISEASE MECHANISMS		
8:35 a.m.	Discussion of research related to etiology and pathogenesis: *Recommendations 1–5, 7, 18*	*Chair,* Ray Roos; *Co-Chair,* Hartmut Wekerle
10:00 a.m.	Discussion of neuroimaging research: *Recommendation 6*	*Chair,* Alan Thompson, *Co-Chair,* Jack Antel
10:20	BREAK	
10:45 a.m.	Discussion of therapeutics and clinical research: *Recommendations 8–11*	*Chair,* Jesse Cedarbaum; *Co-Chair,* Patricia Coyle
12:00 noon	LUNCH	
RESEARCH ON DISEASE MANAGEMENT		
1:00 p.m.	Discussion of research related to quality of life: *Recommendations 12, 13, 17*	*Chair,* Lisa Iezzoni; *Co-Chair,* Alan Thompson
BUILDING AND SUPPORTING THE RESEARCH ENTERPRISE		
2:10 p.m.	Discussion of research enterprise: recruitment and collaboration: *Recommendations 14–16*	*Chair,* Stephen Hauser; *Co-Chair,* Hartmut Wekerle
3:20 p.m.	BREAK	

CONCURRENT BREAKOUT SESSIONS

3:45 p.m.	• Strategies for future research on disease mechanisms • Strategies for future research on disease management • Building and supporting the research enterprise	*Chairs:* Jack Antel and Jesse Cedarbaum *Chairs:* Stephen Hauser and Sharon Juliano *Chair:* Ray Roos
5:30 p.m.	ADJOURN	
6:30 – 8:00 p.m	RECEPTION AND DINNER	

FRIDAY, APRIL 6

8:00 a.m.	CONTINENTAL BREAKFAST

PRESENTATIONS FROM BREAKOUT SESSIONS

8:30 a.m.	• Strategies for future research on disease mechanisms
9:30 a.m.	• Strategies for future research on disease management
10:30 a.m.	BREAK
10:45 a.m.	• Building and supporting the research enterprise
11:45 p.m.	WORKING LUNCH
1:00 p.m.	Summary discussion
2:30 p.m.	ADJOURN

APPENDIX D: MEETING PARTICIPANTS

Jack Antel
Chair, Department of Neurology and Neurosurgery
McGill University
W. Montreal
Quebec, Montreal CANADA

Craig Bash
Consultant
Paralyzed Veterans of America
Bethesda, MD USA.

Toby Behar
Program Director
Neural Environment
National Institute of Neurological Disorders and Stroke/NIH
Bethesda, MD USA

Celia Brosnan
National MS Society
Research Programs Advisory Committee
Departments of Neuroscience and Pathology
Albert Einstein College of Medicine
New York, NY USA

Sally Buegeleisen
Director, National Board
NMSS Research Programs Advisory Committee
National Multiple Sclerosis Society
Sarasota, FL USA

Peter Cardy
Chief Executive Officer
National MS Societies-Great Britain and Northern Ireland
London, UK

Cathy Carlson
Director of Research Information
National Multiple Sclerosis Society
New York, NY USA

John Carswell
Associate Executive Director for Health Policy
Paralyzed Veterans of America
Washington, DC USA

Jesse Cedarbaum
Vice President of Clinical Affairs
Regeneron Pharmaceuticals
Tarrytown, NY USA

Henry N. Claman
Professor, Medicine and Immunology
UCHSC
University of Colorado School of Medicine
Denver, CO USA

Jurgen Clausen
Chairman and Professor
Danish MS Society
Valby, DENMARK

Timothy Coetzee
Director, Research Training Programs
National Multiple Sclerosis Society
NewYork, NY USA

Elaine S. Collier
Chief, Autoimmunity Section
Acting Chief, Clinical Immunology Branch
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases/ NIH
Bethesda, MD USA

Patricia Coyle
Professor, Department of Neurology
SUNY Stony Brook
Stony Brook, NY USA

Michael Dugan
President and CEO
National Multiple Sclerosis Society
Research Programs Advisory Committee
New York, NY USA

David Eckstein
Program Analyst
Neural Environment
National Institute of Neurological Disorders and Stroke, NIH
Bethesda, MD USA

Patricia A. Grady
Director
National Institute of Nursing Research/NIH
Bethesda, MD USA

Diane E. Griffin
Professor and Chair
Department of Molecular Microbiology andImmunology
The Johns Hopkins University
School of Hygiene and Public Health
Baltimore, MD USA

Deanna Groetzinger
Vice-President, Communications
Multiple Sclerosis Society of Canada
Toronto, Ontario CANADA

Andras Guseo
President and Chief Executive
Department of Neurology
St. George Hospital
Seregelyesi, HUNGARY

Stephen L. Hauser
Professor and Chair
Department of Neurology
University of California, San Francisco
School of Medicine
San Francisco, CA USA

Karin F. Helmers
Program Director
National Institute of Nursing Research/NIH
Bethesda, MD USA

Paul Hoffman
Director, Medical Research Service
Department of Veterans Affairs
Washington, DC USA

Lisa Iezzoni
Professor
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA USA

Suzanne T. Ildstad
Institute for Cellular Therapeutics
University of Louisville
Louisville, KY USA

David Jacoby
Medical Director, MS/CNS
Serono, Inc.
Norwell, MA USA

Richard B. Johnston
Professor, Department of Pediatrics
National Jewish Medical and Research Center
University of Colorado School of Medicine
Denver, CO USA

Sharon L. Juliano
Professor, Department of Anatomy and Cell Biology and Neurosciences Program
Uniformed Services University of the Health Sciences
Bethesda, MD USA

Edward A. Kangas
Deloitte Touche
Research Programs Advisory Committee
Wilton, CT USA

Michael Katz
Vice President for Research
March of Dimes Birth Defects Foundation
March of Dimes Society
Research Programs Advisory Committee
White Plains, NY USA

David W. Keer
Program Specialist
National Institute on Disability and Rehabilitation Research
Washington, DC USA

Jurg Kesselring
Professor, Department of Neurology
Chair of Medical Advisory, Swiss MS Society/IFMSS
Rehabilitation Centre
Valens, SWITZERLAND

Rivka Kreitman
Corporate Headquarters
TEVA Pharmaceutical Industries, Ltd.
Petach Tikva, ISRAEL

Nicholas LaRocca
Director, Health Care Delivery and Policy Research Programs
National Multiple Sclerosis Society
New York, NY USA

Roland Liblau
Federation de Neurologie
Toulouse Cedex, FRANCE

Robert Lisak
Chair, Department of Neurology
Wayne State University
Detroit, MI USA

Fred D. Lublin
Professor of Neurology
Director, The Corinne Goldsmith Dickinson Center for MS
Mount Sinai School of Medicine
NewYork, NY USA

Kees Lucas
Professor of Neuroimmunology
Member, Scientific Board
Free University Amsterdam and Dutch Foundation for Support of MS Research
Den Haag, THE NETHERLANDS

Samuel K. Ludwin
Professor of Pathology (Neuropathology)
Chair, MS Society of Canada
Medical Advisory Committee
Queen's University
Kingston, ON CANADA

William McIlroy
National Medical Advisor
MS Society of Canada
Toronto, ON CANADA

Lindsay McMillan
Chief Executive Officer
National MS Society of Australia Ltd.
Toorak, Victoria AUSTRALIA

Patricia O'Looney
Director, Biomedical Research Programs
National Multiple Sclerosis Society
NewYork, NY USA

Anastasios Orologas
Professor of Neurology
University of Thessaloniki
Greek MS Society
Thessaloniki, GREECE

Audrey Penn
Deputy Director, NINDS
Office of the Director
National Institutes of Health
Bethesda, MD USA

Christine Purdy
Chief Executive Officer
International Federation of MS Societies
London, UK

Stephen Reingold
Vice President, Research Programs
National Multiple Sclerosis Society
NewYork, NY USA

Raymond Roos
Chairman, Department of Neurology
University of Chicago
Chicago, IL USA

Nancy H. Ruddle
Professor, Department of Epidemiology and Public Health
Yale University School of Medicine
New Haven, CT USA

Gregory Schuckman
Director of Federal Relations
University of Central Florida
Washington, DC USA

Donald Silberberg
Professor of Neurology
Senior Associate Dean, Director International Medical Programs
University of Pennsylvania School of Medicine
Philadelphia, PA USA

Richard Slifka
Chairman of the Board
Global Petroleum Corporation
Waltham, MA USA

Richard L. Snyder
Foster Hill Farm
Milford, PA USA

Thomas E. Stripling
Senior Health Data Analyst
Health Policy Department
Paralyzed Veterans of America
Washington, DC USA

Alan Thompson
Garfield Weston Professor of Clinical Neurology and Neurorehabilitation
Institute of Neurology
London, UK

Patricia Turner
Program Analyst
Science Policy and Analysis Branch
National Institute of Neurological Disorders and Stroke/NIH
Bethesda, MD USA

Michael Weinrich
National Center for Medical Rehabilitation Research NIH/NICHD
Rockville, MD USA

Hartmut Wekerle
Chairman and Director
Department for Neuroimmunology
Max Planck Institute for Neurobiology
Martinsreid,GERMANY

Caroline C. Whitacre
Professor, Department of Molecular Virology, Immunology & Medical Genetics
The Ohio State University
Columbus, OH USA

Jerry S. Wolinsky
Professor of Neurology
University of Texas-Houston, Health Science Center
Houston, TX USA