MS
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Basic Research

RECENT IMMUNOLOGIC, VIROLOGIC AND CYTOLOGIC FINDINGS

• HLTV-I (a leukemia virus) has been associated with degenerative spinal cord disease (myelopathy) in both the Caribbean and Japan. Canadian researchers, however, found an absence of HTLV-I and HTLV-III antibody in patients with multiple sclerosis and chronic spinal cord diseases. [*Comment: Indirect evidence for an association between HTLV-I virus and some chronic spinal cord diseases in the West Indies and Japan has been accruing for more than two years and is of great interest to MS researchers. While data useful for the understanding of MS will undoubtedly emerge from this line of research, it is likely that tropical spastic paraparesis (which has some clinical overlap with MS) will emerge as a disease distinct from typical MS. Tropical spastic paraparesis may be related to a condition seen in the temperate latitudes called chronic progressive myelopathy.*]

• A component of myelin called myelin basic protein (MBP) is thought to be a potentially important antigen (agent which stimulates immune reactions) in the MS disease process. This hypothesis is supported by findings that levels of free MBP (i.e., MBP which is not bound in antigen-antibody complexes) have been found in the cerebrospinal fluid (CSF) of MS patients with active disease and by the fact that MBP CSF levels correlate well with the level of disease activity, as do levels of the antibody (substance released upon antigenic stimulation) called anti-MBP. Furthermore, anti-MBP is present predominantly in the free form in MS patients who are undergoing exacerbations and in bound form in patients with chronically progressive disease. Corroborating these findings, investigators from the University of Alberta Hospital, Edmonton, Canada, have found that free levels of MBP correlate well with free levels of anti-MBP and that bound levels of MBP correlate well with bound levels of anti-MBP in MS patients. Likewise, exacerbations were characterized by higher free and lower bound CSF levels of MBP and anti-MBP. The researchers believe that the immunoregulation of anti-MBP may play an important role in the development of MS.

• Medical scientists from University Hospital, Bangkok, Thailand, and from the Johns Hopkins University, Baltimore, have found high levels of anti-MBP in the CSF of patients who suffered major neurologic complications following rabies vaccination. The presence of antibody to myelin as well as to brain chemicals called gangliosides and cerebrosides indicates that these substances may play an important role in the course of immunologic events which produce these complications. Nevertheless, CSF MBP was not found to be a prognostic indicator.

• Investigators from the University of Modena and the Polyclinic of Modena, Italy, have tested levels of CSF MBP in MS patients, optic neuritis patients and patients with other, nondemyelinating neurologic diseases. They found significantly greater MBP concentrations in the MS group than in the other two groups, but no significant differences between MS patients in exacerbation and those in remission.

• Researchers from the Hôpital Henri Modor and the Hôpital de la Salpêtrère, France, found MBP in the CSF of MS patients with an active, progressive form of the disorder as well as in patients undergoing exacerbations which produced new signs and symptoms of MS. MBP was not found

RESEARCH EMPHASIS AT THE NATIONAL MULTIPLE SCLEROSIS SOCIETY — 1987 UPDATE

Stephen C. Reingold, PhD

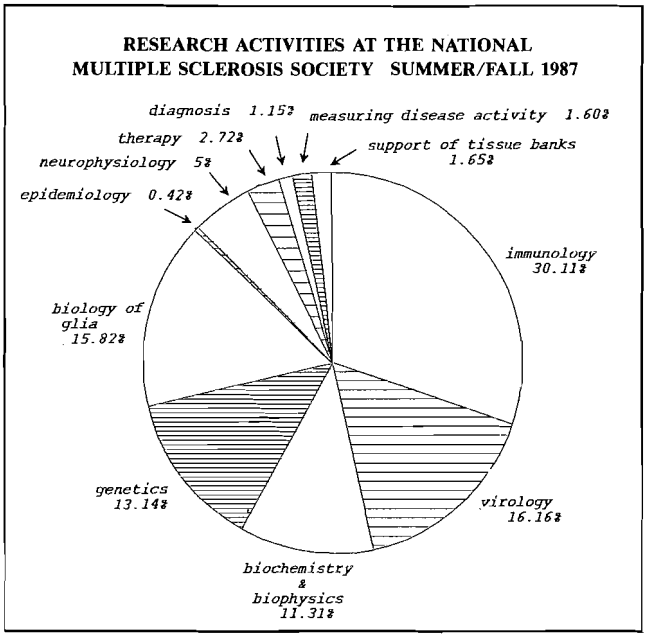
Research directions and specific research topics in the programs funded by the National Multiple Sclerosis Society are not pre-determined by any decision-making body. Rather, projects considered relevant to multiple sclerosis are funded in order of scientific merit, determined by committees of peer-reviewers. (See "Research Funding and Directions at the National Multiple Sclerosis Society," *MS Quarterly Report,* October 1984). In 1987, an annual research budget of nearly $7 million has allowed growth in the size of the Society's research and training programs. Yet the specific areas of research emphasis have remained relatively stable (with some significant exceptions) for at least the past decade (see figure).

Projects in the area of immunology account for the largest single expenditure on an annual basis — just over 30% of the total. These include continued studies of immune function in experimental autoimmune encephalomyelitis (EAE), an animal model for MS. Increasingly sophisticated immunological studies of antigen specificity, T-lymphocyte receptor biology, and monoclonal antibodies are becoming more and more a part of current research to determine the exact immune regulation problem underlying MS.

Studies of viruses which may be associated with MS continue, but in recent years have decreased in number. Current projects include attempts to clarify how virus infection might lead to autoimmune disease and demyelination, studies to search for evidence of specific viruses related to MS, and attempts to better understand the mechanisms of viral persistence.

The study of glial cells, especially the oligodendrocytes which are responsible for making and maintaining myelin, have increased — from about 8% of the total three years ago to almost 16% in 1987. Understanding glial cells as targets of immune attack, developing ways to stimulate glial growth and development, and further analysis of the ways glia interact with nerve fibers are key to developing ways to prevent demyelination and to trigger remyelination.

Genetic aspects of MS have become a significant part of the research programs at NMSS. Three years ago, such studies made up



only a fraction of the total; now some 13% of the Society's investment is in genetics. This includes studies of MS and EAE susceptibility factors, molecular biology of genes controlling myelin development and function, and attempts to better understand the genetic basis of "self" and "non-self" which could underlie autoimmunity related to MS.

Continuing studies of the biochemistry and biophysics of myelin remain an important aspect of the NMSS research activity (about 11%) and smaller amounts are going toward epidemiology, neurophysiology, diagnostics, and therapeutic trials. In addition, the Society supports two MS tissue banks to preserve brain and spinal cord samples for use by investigators around the world.

Beginning this fall, the Society is actively encouraging grant applications in the area of patient management technology. This will bring a vitally important but previously underrepresented research area into the programs of the Society.

For over 40 years, research projects funded by the National Multiple Sclerosis Society have led the way nationally in basic and clinical studies related to multiple sclerosis. Core information gained in many disciplines is resulting in the development of new diagnostic methods, better intervention techniques, and better management tools for people with MS.

Stephen C. Reingold, PhD, is assistant vice president for research and director of grants management at the National Multiple Sclerosis Society in New York City.

RESTORING MOTOR FUNCTION THROUGH ELECTRICAL STIMULATION

by Gerald E. Loeb, MD

In 1791, Luigi Galvani reported that electricity could elicit a contraction in a muscle removed from a frog. Since then, electrical stimulation has figured prominently in putative cures for an

extraordinary range of medical disorders. However, it was not until the work of Gasser in the 1920's and Hodgkin and Huxley in the 1930's that the mechanisms of bioelectricity were sufficiently understood to permit systematic inquiry. There has been and continues to be an aura of "magic" to the phenomenon, which occasionally interferes with the effective design of useful therapeutics and the sound rejection of useless approaches. On the whole, however, recent advances in basic neurophysiology and in microelectronic and biomaterials technologies are starting to produce significant restoration of function in otherwise untreatable disorders.

A wide range of neural prosthetic devices are now clinically available or under development. These include regulators of visceral function (pacemakers for heart rate and respiration and bladder evacuation), replacements for sensory modalities (artificial ears and eyes), and myoelectric and neural recording devices to pick up control signals for robotic limbs. This review will concentrate on functional neuromuscular stimulation (FNS), whereby Galvani's original technique has been much expanded.

Biophysical Mechanism of Neuromuscular Stimulation

Alternating electrical current flowing through body tissues and parallel to elongated cells such as neurons and muscle fibers causes changes in the electrical potential that such cells normally maintain across their cell membranes. When sufficently depolarized, most such cells discharge action potentials that are identical to those that are caused normally by chemical synaptic transmission. In the neuromuscular system, the resulting mechanical output depends on the temporal and spatial patterning of excited elements.

It happens that neurons are much more excitable than muscle fibers and that large caliber nerve fibers are more excitable than small fibers. In a typical mixed environment of peripheral nerve and muscle, a given electrical stimulus is most likely to excite both motor and sensory nerve fibers, resulting in both muscle twitches and cutaneous and proprioceptive sensations such as light touch, vibration, and muscle stretch. Higher strength electrical current may recruit smaller sensory nerve fibers that send pain information to the central nervous system.

Dr. Loeb is a principal research scientist at the Bioengineering Center, Georgia Institute of Technology, adjunct professor of physiology at Emory University, and President of Biomed Concepts, Inc., Atlanta, Georgia.

Direct electrical stimulation of denervated muscle is difficult to achieve and may not replace entirely the trophic influence whereby motoneurons maintain the integrity of muscle fibers. The almost unavoidable activation of sensory as well as motor nerve fibers often leads to more widespread CNS and muscular responses via reflex loops, which may be undesirable or usefully exploited.

Many different electrode configurations have been employed to attempt to achieve better control over these responses. The simplest are skin surface electrodes, similar to those used in transcutaneous electrical nerve stimulation (TENS) to relieve pain by masking it with skin sensations. However, the nerves innervating various muscles tend to lie deeply within the electrically conductive tissues of the body, making it difficult to activate any particular muscle. Percutaneous insertion of fine, flexible wires into muscles has been employed extensively as a research tool, but the wires tend to be broken by the constant motion of the skin and muscles and the exit sites require careful medical attention to avoid infection. There is now general agreement that the restoration of complex mechanical functions such as grasp and walking will require surgically implanted electrodes that are carefully oriented with respect to individual nerves.

Clinically Useful Effects of FNS

There are a wide range of short-term and long-term effects resulting from artificial activation of the sensorimotor apparatus of muscles. The following is a list of these in order of increasing complexity. Also mentioned is the status of clinical devices attempting to exploit such effects.

1. *Direct Mechanical Output*

Obviously, the contraction of an otherwise paralyzed muscle promises direct restoration of the mechanical function provided by that muscle. For the past twenty years, numerous groups around the world have worked with a variety of approaches to reanimate limbs that have been paralyzed partially or completely by upper motor neuron damage such as stroke and spinal cord injury. Some devices for limited motor deficits such as footdrop have been produced commercially, but systems for walking and for hand function are still undergoing laboratory development.

2. *Reflex Effects*

Stimulation of sensory fibers can set off reflex circuits and pattern generators that pro-

duce complex motor outputs. This has been exploited in experimental devices to control bladder function via the micturition reflex and as a component of FNS locomotion systems to produce coordinated flexion of the leg during the swing phase of walking.

3. *Biasing of Reflexes*

Many motor disorders produce spasticity of the muscles rather than flaccidity because the intact reflex pathways tend to become hyperexcitable from disuse or because the normal control systems for phasing the recruitment of antagonistic muscles have been damaged. It has been noted that chronic FNS, even of nonspecific muscles, reduces this problem for some patients. While such stimulation is relatively easily and safely achieved, the unpredictable natural fluctuations in spasticity in a given patient and among patients with the same disorder have made it difficult to obtain objective measurements of success for such therapy.

4. *Conditioning Muscle Strength*

Chronic FNS has been used successfully in animals and humans to achieve much the same improvements in strength and fatigue resistance as conferred by natural exercise. It is starting to be used widely in the physical therapy community to reduce muscle wasting during recovery from peripheral nerve damage and from strokes. While FNS does not lead to replacement of motor neurons once they are lost, it can greatly improve the functional capability of remaining motor units. One of the problems with FNS for direct restoration of complex motor behavior is that the large motor axons which are most readily stimulated tend to innervate muscle fibers that produce large, fast twitches that easily become fatigued with repeated use. Chronic electrical stimulation tends to convert these muscle fibers into slower, more fatigue resistant forms that can produce smoothly graded tension for longer periods of time.

5. *Influencing Musculoskeletal Development*

Muscles, tendons and bones respond to mechanical forces by structural remodeling. FNS has been applied to try to reverse developmental abnormalities such as scoliosis and orofacial abnormalities. It is also being explored to reduce osteoporosis during prolonged confinement to bed and weightlessness during space travel.

6. *Reteaching Higher Motor Function*

Perhaps the most controversial of FNS applications stems from the notion that patterned electrical stimulation of sensory and motor neurons will become stored in the brain as new motor programs to replace those lost by strokes and degenerative disorders. Physical therapists have long used patterned manipulation to activate the somatosensory system and to improve conscious awareness of limb position, but this does not activate the recurrent pathways whereby the CNS monitors the natural output of the motoneurons themselves. FNS almost certainly activates such pathways, but little is known about the role of these efferent collaterals beyond their local, fairly weak effects in the spinal cord. In the absence of any clear theoretical direction, development or rejection of this clinical approach depends on objective, empirical evaluations, still largely lacking.

Work Needed in FNS

After many years of what is viewed as frustration with technology, the availability of reliable, multichannel implantable stimulators seems imminent (ironically, largely as a spin-off from another neural prosthetic area, cochlear implants for sensorineural deafness). However, considerable work remains to be done on the electrical configuration and mechanical reliability of implantable electrodes for selective activation of muscles.

As it becomes possible to control larger numbers of independent channels, the problem of control signals looms larger. If normal individuals had to decide consciously which muscles to activate and when, they would function little better than if they were completely paralyzed. FNS systems must produce and coordinate quite sophisticated motor programs on the basis of a small number of high level commands from the patient, adapting outputs to each muscle in order to handle a wide range of exigencies such as mechanical obstructions and muscle fatigue. The greater the loss of motor function, the more benefit the prosthesis can provide for the patient. There are fewer sources of commands under voluntary control of the patient, however, the controller must be more sophisticated. Robotic control theory has been shown to be awkward at best even for robots and will require considerable expansion to handle the nonlinear, multiarticular actuators known as muscles.

Implications for MS and Degenerative Disorders

FNS presents complex biological and technological problems that so far have been studied mostly in more straightforward neurological disorders such as spinal cord injury

and cerebral stroke. As familiarity with the techniques and availability of reliable equipment spreads in the physical therapy community, various of the above-listed FNS effects will be explored in a wider range of diseases. History suggests that some of the results will find a well-deserved place in the therapeutic armamentarium while others will eventually be shown to stem from the vicissitudes of variable disease processes and wishful thinking. For patients, clinicians, and engineers alike, it will be most helpful to keep in mind that, far from being magical, the electrical activation of neurons is one of the best understood and most readily controlled biophysical process.

Book Reviews

Multiple Sclerosis: A Guide for Patients and Their Families (2nd Ed)
by Labe C. Scheinberg;
Nancy J. Holland (editor)

There have been many books and publications for the MS patient in the last decade, some good and some bad. This is the best of the good. Dr. Scheinberg, who has been a leading expert on the care and management of the MS patient, has brought forward an excellent publication on the various aspects of MS. He has gathered together some of the other leading experts in the field to lend credence to this 2nd Edition.

It is difficult to write a book for MS patients because one has to deal with both the newly diagnosed patients, who may have few problems or difficulties, and the long-standing MS patient who has many chronic difficulties. This book, however, shows a great sensitivity to patients with varying levels of disease and varying problems. The section by Poser and Aisen on diagnosis, and on bladder and bowel management by Holland and Francabandera, are especially good.

This excellent volume is a significant contribution to the management of MS patients and should be widely used by physicians and patients.

The Neuro-Immune-Endocrine Connection
by Carl W. Cotman, Roberta E. Brinton, Albert Galaburda, Bruce McEwen and Diana M. Schneider: Raven Press, New York, 1987

This book, which is based on a 1985 meeting entitled, "Neuroimmunology: Crossroads Between Behavior and Disease," addresses an evolving field that considers the interactive relationship among the immune, endocrine and nervous systems. It was written for a multidisciplinary audience and addresses issues of interest to immunologists, endocrinologists, neurologists and psychologists.

Chapters one through four provide a review of relevant topics in basic immunology, neurochemistry and physiology. Subsequent chapters discuss such diverse areas as hormonal and behavioral influences on immune function, plasticity of brain after injury, and possible immunological bases for various neurological conditions.

The book samples current research in the field and is not intended to be a comprehensive overview. It is concise and readable and should be of interest to researchers and clinicians.

Neurological Disorders of Pregnancy
by Phillip J. Goldstein (editor):
Futura Publishing Co., Mt. Kisco, NY 1986.

Issues concerning pregnancy and parenting confront many couples in which one partner has MS. Controversies have been sharpened by the recent publicity surrounding the Baby M case, in which a couple contracted to have a surrogate mother because they feared the effects of pregnancy on the health of the wife with MS.

This timely subject is thoroughly and well-reviewed in a chapter by Justin McArthur, MD and Fran Young, RN in the recently published *Neurological Disorders of Pregnancy.* Although the book is intended for primary care physicians, the chapter is so clearly written that it can be understood by a layperson familiar with some medical terminology.

The authors recognize that little definitive data exists on many important aspects of this subject. They present a balanced, comprehensive discussion of a variety of issues and point out that MS appears to have little effect on fertility or pregnancy, but that certain symptoms such as paraplegia and bladder dysfunction can pose special problems. The effect of pregnancy on MS is particularly controversial, but the data indicate that fewer relapses occur during pregnancy. However, during the six months after delivery, relapses occur at a higher rate and disease may progress. Dr. McArthur and Ms. Young correctly emphasize that "counseling in the obstetric clinic" must be tailored according to the patient's desire to have children. The chapter concludes with brief discussion of counseling about "risks to the baby" and "the ability to raise a child."

The authors have provided a well researched, scholarly and yet readable update on a critical subject for many MS families. The chapter provides a valuable resource for both medical practitioners and patients.