Special Issue

A collection of presentations from *Frontiers in Neuromuscular Disease and Neurorehabilitation*, a conference honoring Dr. Robert L. Ruff
FROM THE EDITOR

Dear Colleague,

I am pleased to bring you the Winter 2013 issue of the UH Neurological Institute Journal as we welcome in the new year.

Through continuing collaboration with scientists at Case Western Reserve University School of Medicine, physicians at UH Neurological Institute test and refine the latest advances in treatment for patients with disabling neurological disorders. The Journal highlights these advances and demonstrates our interdisciplinary strengths. As an added benefit for our readers, CME credit is available for the busy practitioner interested in receiving AMA PRA Category 1 Credits™.

Our winter issue summarizes the proceedings of a recent conference honoring Dr. Robert L. Ruff, a valued member of our Case Western Reserve family and the current National Director of Neurology for the Department of Veterans Affairs. In his 28-year career at the university, Dr. Ruff has directed the Neurology Residency Program and served as Vice Chair of the Department of Neurology. During these years, Dr. Ruff has mentored and trained many individuals—and many of the contributors to the conference were his former pupils and colleagues.

Held at the Louis Stokes Department of Veterans Affairs Medical Center on October 18-19, 2012, the Frontiers in Neuromuscular Disease and Neuromuscular collaboration brought together 32 basic researchers and clinician scientists of national and international standing. The topics covered are presented here in four categories: (1) Muscle, Nerve, and the Neuromuscular Junction; (2) Rehabilitation of Patients with Neuromuscular Disorders; (3) New Developments in the Diagnosis and Management of Stroke; and (4) Frontiers of General Neurology. Following a foreword provided by Dr. Story Landis, Director of the National Institute of Neurological Disorders and Stroke, an abstract of each of the presentations summarizes the importance of their messages and clinical relevance.

For this issue, I invited conference host Dr. R. John Leigh to serve as Guest Editor. All of us at the Journal are tremendously thankful to Dr. Leigh for the time and energy he has put forth in helping us produce this special issue of the UH Neurological Institute Journal.

The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S. News & World Report. Through their faculty appointments at the Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

Dr. Robert Ruff

University Hospitals Case Medical Center

The UH Neurological Institute Journal is a collection of presentations from Frontiers in Neuromuscular Disease and Neuromuscular Rehabilitation, a conference honoring Dr. Robert L. Ruff.
Foreword: Harnessing Basic Science Discoveries to Advance Diagnosis and Treatment

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The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disorders through research. To fulfill our mission, we fund a broad range of research from basic research aimed at understanding how the normal nervous system functions to Phase III clinical trials.

Over his long career, Dr. Robert Ruff has made significant contributions across this broad range from basic neuroscience to studies in patients. He started with studies of the biophysics of muscle and the neuromuscular junction, expertise that he later applied to understanding myasthenia gravis and developing new rehabilitative techniques for neuromuscular disorders, spinal injuries, and stroke. In addition, Dr. Ruff has promoted the careers of young investigators, showing a knack for identifying young people who share curiosity, imagination, and an interest in research. He has suggested their projects, guided their research, and helped them to publish their studies. At a national level, he has influenced the direction of research in the field of neurorehabilitation through his role in peer review. The clinician-scientists who are center-stage at this meeting, with presentations by an impressive number of young investigators whom Bob has nurtured, represent his mentorship (Figure 1).

One question that I hear all the time is whether there will be room for clinician-scientists like Bob in the biomedical research enterprise, particularly given the uncertainty of federal funding. Some would argue that basic research should be left to PhDs and that the proper role of clinician investigators is to conduct clinical trials. To fulfill our mission, we fund a broad range of research from basic research aimed at understanding how the normal nervous system functions to Phase III clinical trials.

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The NINDS believes that physician-scientists can play essential roles not just in disease-related research but across the entire spectrum. We recognize the importance of nurturing new physician-scientists in enabling our mission by providing support from residency to their first independent funding. Research in residency and fellowship can be supported through an R25 grant to institutions, which should enable physician-scientists to compete successfully for a mentored K award, which in turn should provide data for a successful R01, and we are preferentially funding new investigators. While the NINDS has created sequential mechanisms of support, success requires the same passionate commitment to the scientific enterprise that has characterized Bob’s career, a strong research environment and an outstanding mentor who is generous with time – no better exemplified than by Bob Ruff.

Story Landis, PhD, reports no financial relationships with commercial interests relevant to the content of this article.

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Over the past 20 years, my colleagues and I have exploited the differential involvement of extraocular muscle (EOM) as a window to understanding neuromuscular disease pathogenesis (Figure 1). Despite the long- appreciated clinical observations of sparing of eye movements in many muscular dystrophies, as well as the early and severe involvement of EOM by myasthenia gravis, there had been limited formal research dedicated to EOM biology and pathophysiology. A review article, written with Bob Ruff, sparked my interest in why the EOM was preferentially involved by myasthenia gravis. This question then led to ultrastructural, immunohistochemical, and genomic profiling analysis of EOM, which appreciated that an intrinsic lack of complement inhibitors could contribute to their susceptibility. Along the way, our observations inspired development of complement inhibitor therapeutics for myasthenia gravis, which have moved to clinical trials. In 1992, Bob and I (and others) documented sparing of fast eye movements in severely compromised patients with Duchenne’s muscular dystrophy. In a series of studies with John Porter, we concluded that intrinsic properties of EOM appear to account for the sparing of EOM. Specifically, the extracellular matrix organization likely supports myofibers during the constant, high-level activity in normal EOM and fortuitously guards against eccentric contraction damage in mdx mice. Linda Kusner has now extended the “uniqueness” of EOM to its supporting perimysial fibroblasts, which has relevance to Gravez’s ophthalmoplegia. Finally, my laboratory, with the help of John Stahl and Francisco Andrade, has focused on understanding the control of the EOM phenotype by the Pitx2 transcriptional factor, discovering that its conditional knockout in mice alters ocular motility in a subtle fashion. These findings led to the hope that, one-day, educated genetic manipulation may become a treatment for strabismus and ocular motility disorders. Thus, one simple question asked by Bob Ruff led to a career.

Henry J. Kaminski, MD, reports no financial relationships with commercial interests relevant to the content of this article.
Synaptic Autoimmunity 2012

Immunoglobulins targeting ectodomains of plasma membrane signaling proteins cause synaptic autoimmunity. First hypothesized to impair neuromuscular transmission in myasthenia gravis,1 the hypothesis was extended in 1971 to the autonomic and central nervous systems and endocrine system.2 Synaptic autoantibodies frequently coexist but are not found in healthy control subjects. Nervous system autoantigens include presynaptic, postsynaptic, and perisynaptic neurotransmitter receptors, channels, and interacting proteins. Immunoglobulin G (IgG) impairs synaptic functions by preventing or inducing allosteric transition of signaling proteins, cross-linking (inducing endocytosis and degradation), activating complement, and disrupting neurotransmitter, ion, and water homeostasis. These events can initiate inflammatory, cytotoxic, or demyelinating sequelae. Peripheral synaptic disorders include myasthenia gravis, Lambert-Eaton syndrome, neuromuscular hyperexcitability, dysautonomias, and gangliosidosis-encephalopathies. Central disorders include myeloneuropathies, neuromyelitis optica spectrum disorders (NMOSDs), dysautonomias, and encephalopathies. NMOSDs principally affect spinal cord and optic nerves but do not spare the brain. Relapses are frequent, and multiple sclerosis is a common misdiagnosis. Pathogenic IgG targets astrocytic aquaporin-4 water channels at astro-endothelial, astro-glial, and astro-neuronal synapses. Demyelination is a secondary event (Figure 1).

Synaptic autoimmune disorders begin subacutely or insidiously, generally respond favorably to early-initiated antibody-depleting therapies, and can occur in a para-neoplastic context. Serum and spinal fluid autoantibody profiles aid diagnosis, have prognostic and therapeutic implications, and guide cancer investigation, therapy, and post-therapy monitoring. Immunosuppressive therapy may be required five years or longer to maintain remission. Newly recognized synaptic autoimmunity manifestations include intractable seizures, chronic pain syndromes, psychoses, dementia, movement disorders, and gastrointestinal dysmotilities. Paraneoplastic disorders sometimes remit and relapse but usually progress unless diagnosed and treated early. Early diagnosis is critical for optimal outcomes. Initiation of appropriate therapies directed at the tumor and the immune system is often delayed because autoimmune neurological disorders tend to be misdiagnosed as stroke, multiple sclerosis, psychiatric disorders, or neurodegenerative disorders.

Vanda A. Lennon, MD, PhD, is an investigator for RSR/Kronus, though this relationship has not affected the content of this article and the CME Program has determined there is no conflict of interest.
Decrement of Endplate Safety Factor in Myasthenia Gravis and Susceptibility of Extraocular Muscles

In the neuromuscular junction (NMJ) of skeletal muscle, fidelity of neural transmission is guaranteed by an appropriate magnitude of the safety factor (SF), which ensures that an action potential (AP) is always triggered following the neurotransmitter release. The magnitude of the SF depends on the density of acetylcholine receptors (AChRs) and Na+ channels (NaChs) at the endplate. AChRs and NaChs are both depleted in myasthenia gravis (MG), following an autoimmune complement-mediated destruction of the postsynaptic folding, where AChRs and NaChs are more concentrated. Electrophysiological studies show that loss of AChRs and NaChs indeed account for 59% and 40% reduction, respectively, of the SF at the “myasthenic” endplate. Extraocular muscles (EOM) show some intrinsic characteristics that make them particularly susceptible to damage in myasthenia as eye movement disorders in such disease are encountered in as many as 80% of patients. Specifically, the majority of NMJ fibers of the EOM physiologically lack a well-developed system of postsynaptic folding, which results in a lower baseline SF than skeletal muscle NMJ. Thus development of fatigue in MG during “high performance” eye movements, such as saccades, is a very common clinical finding. However, when horizontal and vertical saccades in patients with MG are recorded, they show stereotyped, binocularly conjugate normal initial components with only later appearing disconjugacy (Figure 1). This is different from the early and sustained disconjugacy observed, for example, in internuclear ophthalmoplegia or ocular nerve palsies. Initial conjugacy of saccades in MG might reflect relatively preserved fidelity of neuromuscular transmission at the NMJ of one specific kind of EOM fibers – the fast, pale global fibers. Among the six different kinds of EOM fibers, only the pale global fibers have well-developed postsynaptic folding, and they are believed to briefly discharge at the beginning of a saccade providing the initial drive for rapid and binocularly conjugate eye movements.

Alessandro Serra, MD, PhD, reports no financial relationships with commercial interests relevant to the content of this article.

Figure 1: Representative time records (top row) and phase planes (bottom row) of single upward saccades made by a healthy control subject (A and B), a patient with ocular myasthenia (C and D), and a patient with right oculomotor nerve palsy (E and F). The normal subject shows tight conjugacy of saccades. The patient with ocular myasthenia generates saccades that are initially conjugate (arrow) but subsequently very disjunctive. The patient with oculomotor nerve palsy shows saccades that are disjunctive from their onset (arrow). Eye movements were recorded using the magnetic search coil technique. Positive values on time plots indicate upward eye movements.
Novel Complement Inhibitor in Myasthenia Gravis

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Complement is involved in the pathophysiology of several diseases. The destruction to the neuromuscular junction by complement-mediated lysis is the hallmark of myasthenia gravis. The induction of myasthenia gravis through passive and active animal models targets antibodies to the skeletal muscle acetylcholine receptor (AChR), leading to weakness. Although these antibodies may compromise the neuromuscular transmission by blocking AChR function or antigenic modulation, the predominant mechanism of injury to the neuromuscular junction is complement-mediated lysis of postsynaptic membrane. Autoantibodies that target the neuromuscular junction trigger the classical complement pathway through the recognition of the antigen-antibody complex by C1q. Initiation of the cascade results in the activation of C3, which allows C3b to accumulate at the site. Formation of C5 convertase by C3b binding to C3 convertase cleaves C5 into C5b. The formation of the membrane attack complex begins with the accumulation of the C5b-C6-C7, which will recruit C8. Finally, several C9 molecules form the pore of the complex, which inserts in the plasma membrane and opens the cell to the extracellular space. Animal models’ complement-deficient components show the importance of the complement-mediated lysis in experimental autoimmune myasthenia gravis. These animals demonstrate the binding of the antibodies to the AChR but lack the ability to complete the cascade and form the membrane attack complex. Membrane associated complement regulators are present on all host cells to inhibit complement activity. The complement regulatory proteins have many roles in reducing the activation of the complement cascade and inflammation. Decay accelerating factor acts by accelerating the removal of C3/C5 convertases. The function of CD59 is to inhibit the membrane attack complex formation. Mice deficient in complement regulatory proteins, decay accelerating factor, and CD59 demonstrate a significant increase in the destruction at the neuromuscular junction (Figure 1). Taken together, the inhibition of complement-mediated injury is an attractive approach for therapeutic development in myasthenia gravis.

Linda Kusner, PhD, reports no financial relationships with commercial interests relevant to the content of this article.

Figure 1: Electron micrograph shows a neuromuscular junction of a diaphragm from a decay accelerating factor and CD59 deficient mouse induced by experimental autoimmune myasthenia. Neuromuscular junction displayed simplification of synaptic folds and electron dense material within the cleft (May视听post-synaptic membrane).

The Human Blood-Nerve Barrier

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As I had been inspired by physician-scientists Bob Ruff, Henry Kaminski, and John Leigh during my residency, with further exposure to neuromuscular medicine during my clinical fellowship, and a unique opportunity to study basic and translational neuroscience, I developed a burning desire to understand how the internal microenvironment of peripheral nerves is regulated in health and disease. I was curious to understand how the systemic immune system interacts with peripheral nerves during immunosurveillance and is altered during immune-mediated inflammatory disorders such as Guillain-Barré syndrome (GBS). Despite significant advances in endothelial biology, our knowledge of the blood-nerve barrier (BNB) is limited. The BNB can be considered a physiologically active interface between circulating blood and peripheral nerve endoneurium formed by specialized tight-junction forming microvascular endothelial cells based on ultrastructural and restrictive macromolecular functional studies in mammals initially performed in the 1960s. Phenotypic and functional differences exist between macro- and microvascular endothelial cells from the same tissue and between microvascular endothelial cells from the same tissue in different species, emphasizing the need to study the human BNB using endothelial cells derived from peripheral nerve endoneurium. Thanks to the encouragement and support of Dennis Lands, we started the journey to isolate, characterize, and study BNB-forming primary human endoneurial endothelial cells (pHiEndECs) in 2007. Following our publication of the first paper characterizing pHiEndECs in 2010, we have determined an important role of glial-derived neurotrophic factor in restoring BNB function following injury via RET-tyrosine kinase signaling pathways and the role of αv-integrin (CD11b)-intercellular adhesion molecule-1 signaling in GBS patient-derived peripheral blood mononuclear leukocyte trafficking at the BNB in vitro under estimated capillary hydrodynamic forces. We are currently studying the development of BNB, adaptations in health and disease, and its regenerative capacity with the hope to better understand and discover targeted molecular therapies for peripheral neuropathies (Figure 1).

Eroboghene E. Ubogu, MD, is a speaker for Cubist Pharmaceuticals, a shareholder with and employee of Kelsey Seybold Clinic, and an employee of Baylor College of Medicine, though these relationships have not affected the content of this article and the CME Program has determined there is no conflict of interest.

Figure 1: Digital photomicrograph depicting mononuclear leukocytes from the peripheral blood of a patient with untreated Guillain–Barré syndrome that are firmly adherent to the cytokine-treated human blood-nerve barrier endothelial cell layer surface (blue background) under estimated capillary flow conditions in vitro.
In recent years, there has been remarkable progress in understanding the molecular mechanisms for myotonic dystrophy type 1 (DM1). The most prevalent form of muscular dystrophy affects approximately 40,000 people in the United States. This condition is caused by expansion of a CTG repeat in the 3’ untranslated region of the Dystrophia myotonica protein kinase (DMPK) gene. The CTG expansion leads to RNA dominance, in which DMPK transcripts containing an expanded CUG repeat (CUGexp) exert a toxic RNA gain-of-function. CUGexp RNA is retained in the nucleus and alters the function of RNA binding proteins, which leads to misregulated alternative splicing for a group of muscle-expressed transcripts. The effect on splicing regulation is linked to the development of myotonia and may also contribute to other aspects of muscle impairment. As compared to the protein-based loss-of-function mechanisms that underlie most neurogenetic disorders, the RNA-mediated disease process in DM offers several unique opportunities for therapeutic intervention. One strategy of RNA-targeted therapy employs antisense oligonucleotides (ASOs) to direct endonuclease cleavage of the toxic RNA, resulting in its clearance from cells. Recent data from our group have found that systemic administration of ASOs caused a rapid knockdown of CUGexp RNA in skeletal muscle, correcting the physiological, histopathological, and transcriptomic features of the disease. The effect of ASOs was sustained for up to one year after treatment was discontinued. Optimization and preclinical studies for investigational new drugs are currently in progress and estimated to reach clinical trials in 2013. The rapid development of RNA-targeted therapy underlines the need for better knowledge about the natural history for DM1. Additionally, studies are needed to determine which outcome measures and biomarkers are the most sensitive for detecting disease progression and the most responsive to treatments. Under support from the Wellstone Muscular Dystrophy Cooperative Research Center and the Muscular Dystrophy Association, I am currently working on the project entitled “Study of Pathogenesis and Progression in Myotonic Dystrophy” (STOPP-DM) (Figure 1). This three-year longitudinal study is paving the way to clinical trials in DM1. Through this project, I have developed new techniques to (1) quantify muscle stiffness (myotonia) in the patients’ hand using a video record of the time taken to open their hand; and (2) measure the amount of lean muscle tissue in the most severely affected part of the lower limb using subregional DEXA analysis. My data will be correlated with disease severity and biomarkers from muscle biopsy tissue. These outcome measures could be important in the future to determine whether new treatments, if they are developed, are having a beneficial effect.

Araya Puwanant, MD, reports no financial relationships with commercial interests relevant to the content of this article.
In order to execute accurate movements, the brain must shape motor neuron firing to account for the neuromechanical properties of the limbs. These properties include limb mass, leverage of the muscles, and the relationship between muscle electrical activity and force generation as well as the elastic and viscous properties of the muscles and supporting tissues. One approach to studying brain function begins with determining these neuromechanical properties. Once the neuromechanical properties are known, one can proceed to determining how the brain generates the necessary command signals. The approach is facilitated in the ocular motor system because the mechanical properties of the eyeball and associated muscular and nonmuscular tissues (an assembly collectively termed the “ocular motor plant”) are simple compared with the mechanical properties of a multijointed limb.

Prior work in humans, rhesus monkeys, and cats has demonstrated that ocular motor plant mechanics are dominated by the viscoelastic properties of muscle – the eye acts as if it is suspended between assemblies of springs placed in parallel with viscous elements (“shock absorbers”). However, a detailed, realistic model of these mechanics as well as an understanding of how the mechanics are determined have remained elusive. Studies of plant properties in mice can be rewarding for two reasons. First, the mouse is much smaller than previously studied species, providing an opportunity to investigate how size influences mechanical properties. Second, it is possible in the mouse to use tools of modern genetics to alter structural and contractile proteins; studying the effects of these perturbations may lead to an understanding of how individual protein properties contribute to the overall mechanical properties.

One method of characterizing ocular motor plant mechanics is to determine the mathematical relationship between firing rate of the extraocular motor neurons and eye position. We conducted simultaneous recording of eye position and firing rate of single neurons within the abducens nucleus, which contains the motor neurons innervating the lateral rectus muscle. We analyzed firing rates to extract eye position and eye velocity sensitivities of the neurons. We found that the sensitivities changed with the frequency of eye oscillation as expected for an ocular motor plant dominated by cascaded, parallel spring and viscous elements, the same arrangement that dominates the mechanics in larger species. In comparison to previously studied animal species, the mouse plant is stiffer than the rabbit but laxer than the cat and the rhesus (Figure 1).

The greater stiffness of the mouse compared with the rabbit may be accounted for by the smaller size of the mouse orbit. The lesser stiffness of the mouse plant as compared to the cat or the rhesus may relate to the differing ocular motor repertoires of animals with and without a fovea or area centralis. The higher stiffness of the plants of mammals with fovea-like retinal specializations could be generated by a higher average level of motor neuron firing, although species-related differences in muscle composition still need to be excluded.

Figure 1: Timing relationship of neuronal firing rate vs. eye position, plotted as a function of oscillation rate of the eye. These data are available for rabbit, mouse, cat, and rhesus macaque. Species with more rightward-shifted curves have stiffer ocular motor plants. Hz = hertz
Thigh Muscle Infarction in the Diabetic

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Dr. Robert Ruff served as mentor for my first publication while I was a resident in 1985. The subject was the rare condition of diabetic thigh muscle infarction (DTMI). We had one patient from the VA, and Dr. Susan Chester from Metro General had a second, and, with the assistance of radiologist Dr. Stephen Weiner, we arranged for them to undergo the then new imaging modality of magnetic resonance imaging (MRI) (0.15 Tesla magnet) at Mt. Sinai (Figure 1). This demonstration was the first of DTMI using MRI, and it emphasized that the diagnosis could be made noninvasively, sparing the patient a biopsy. Thigh muscle infarction is a rare and underappreciated complication of diabetes in contrast with other more common and well-recognized neuromuscular complications, such as symmetrical sensory-motor polyneuropathy, autonomic neuropathy, lumbar radiculoplexopathy, and others. A literature review in 2003 found 86 reports of DTMI (another review in the same year found 166 episodes in 115 patients) and, since then, at least 50 additional cases have been reported. The first report of DTMI is attributed to Angervall and Steiner: “Tumoriform focal muscle degeneration in two diabetic patients.” In 1973, Banker and Chester of MetroHealth Medical Center of Cleveland reported two cases with extensive pathology and concluded that “the mechanism of muscle infarction [...] depends on thrombotic occlusive disease of muscular and small arteries.” Thirteen years later, Banker and Chester reported six cases and emphasized that the stereotypical clinical presentation of DTMI obviated the need for biopsy, which was often associated with complications. Thigh muscle infarction is typically encountered in middle-aged people with longstanding diabetes, either type 1 or type 2, usually with other complications, such as nephropathy, neuropathy, and retinopathy. It begins acutely or subacutely with pain and swelling in the thigh (anterior > lateral > posterior thigh) but can involve the calf and rarely the upper limb. Laboratory studies in DTMI are usually unrevealing, but there may be a mild leukocytosis and modest elevation of sedimentation rate or creatine kinase. Although self-limited, about 30% of patients with DTMI will have a recurrence in another location, usually in close temporal proximity to the initial infarction, and some patients have multifocal infarctions at presentation. The diagnosis of DTMI hinges on clinicians being familiar with this entity and the use of noninvasive imaging, with MRI being the modality of choice. MRI demonstrates increased T2-weighted and FLAIR signal, edema, and gadolinium enhancement. As emphasized by Banker and Chester 40 years ago and demonstrated by our report in 1985 and many subsequent others, biopsy is usually not necessary and is often followed by hemorrhage and other complications. Pathology of DTMI reveals focal areas of muscle necrosis, perivascular lymphocyte cuffing, mononuclear infiltrates, hemorrhage, edema, and occlusion of small arteries, arterioles, and capillaries consistent with being a microvascular complication of diabetes. There is a long differential diagnosis to consider for acute thigh pain and swelling in the diabetic, ranging from deep vein thrombosis to large artery ischemia, abscess, necrotizing fasciitis, and neoplasm among others. The importance of recognizing DTMI and promptly differentiating it from other more serious conditions is that, despite being very painful and debilitating in terms of ambulation, DTMI is self-limited. Treatment is symptomatic, consisting mainly of pain control and a short period of bed rest, followed by gradual rehabilitation; it typically resolves in several weeks to months.

Stephen G. Reich, MD, reports no financial relationships with commercial interests relevant to the content of this article.

References
An Overview of VA Contributions to Neurorehabilitation

Since President Abraham Lincoln affirmed the federal government’s responsibility to care for injured/disabled veterans in his second Inaugural Address in 1865, major progress has been made in neurological rehabilitation as a result of wartime developments, from a limited framework emphasizing orthotics during the Civil War to development of physical/occupational therapy and vocational rehabilitation during World War I (WWI) and development of comprehensive integrated rehabilitation and specialized spinal cord injury (SCI) centers during and after World War II (WWII). The focus of rehabilitation efforts has shifted as a consequence of medical capabilities and the injuries sustained (and survived), from peripheral nerve injuries from the Civil War to SCI and severe traumatic brain injury (TBI) of WWII, and to milder TBI sustained in the War on Terror.

Wartime developments in rehabilitation had a limited impact on the care of post-service veterans or civilians until after WWII. During WWII, rehabilitation was greatly expanded into an integrated comprehensive multidisciplinary program in the United States military, largely because of the efforts of Howard Rusk, initially in the Army Air Corps and later across all of the services. With Bernard Baruch’s assistance, Rusk was also successful in swaying President Franklin Delano Roosevelt to support rehabilitation for injured veterans and to give official standing to rehabilitation medicine in the military and the Veterans Administration (VA) after WWII. WWII developments also had a profound effect on the care, functional outcomes, and survival of veterans with SCI. Neurosurgeon Donald Munro’s prototype SCI unit at Boston City Hospital in 1936 – the first in the United States – influenced the Army to establish several SCI centers during WWII and influenced urologist Ernest Bors to pioneer SCI care in VA medical centers. These SCI centers provided a comprehensive spectrum of care, including medical, neurological, and surgical management, psychological counseling, and rehabilitation focused on improving self-care, mobility, and reintegration into society.

After WWII, military developments in rehabilitation of TBI/SCI were promulgated to, and developed in, the revitalized VA system and then disseminated to civilian populations. Shortly after WWII, the VA became a leader in comprehensive neurological rehabilitation, a status that has continued to the present-day Department of Veterans Affairs. In retrospect, Rusk, the “father of multidisciplinary rehabilitation,” was struck by the irony of having made such progress in rehabilitation medicine as a result of a brutal war. “It is paradoxical that through war, a concerted effort to annihilate man, we have learned more and better ways to preserve him” (Figure 1).1,2

Douglas Lanska, MD, is an editor and author for MedLink Neurology and a speaker for the Mayo Clinic, though these relationships have not affected the content of this article and the CME Program has determined there is no conflict of interest.

References
Neurological rehabilitation seeks to restore skills, such as locomotion, that have been impaired by injury or disease. Present therapies consist mainly of the repeated practice of these skills, with the expectation that practice will induce plasticity that improves function. Although this strategy is logical and often beneficial, it is seldom fully effective.

The skills that rehabilitation attempts to restore normally depend on plasticity throughout the CNS, from the cortex to the spinal cord. The location and nature of the damage that impairs performance differs widely from person to person and from disorder to disorder. Thus, the changes that are needed to restore a skill are also likely to differ widely across people. New therapies that can induce changes in specific neuronal pathways, thereby targeting each person’s particular deficits, might substantially improve rehabilitation outcomes. Operant conditioning protocols can modify the simplest spinal reflex pathways in both animals and humans. These protocols create hierarchies of plasticity that involve changes at multiple sites in the brain and spinal cord. Because spinal reflex pathways participate in important skills, such as locomotion, conditioning protocols could reduce the disabilities due to spinal cord injuries, strokes, and other disorders. For example, a conditioning protocol can strengthen or weaken the wholly spinal and largely monosynaptic pathway of the H-reflex, the electrical analog of the spinal stretch reflex, or tendon jerk. In rats or humans in which an incomplete spinal cord injury has impaired locomotion, appropriate H-reflex conditioning can reduce impairment and restore a normal step cycle (Figure 1).

Because they can target specific pathways, spinal reflex conditioning protocols can address an individual’s particular deficits and might thereby complement current therapies. They could be particularly useful when significant spinal cord regeneration becomes possible. At that point, precise methods will be needed for educating the new spinal neurons and synapses so that they function effectively. (Supported by NIH Grants NS21189, HD36020, NS061823, HD32571 and The NYS Spinal Cord Injury Trust Fund.)

Jonathan R. Wolpaw, MD, reports no financial relationships with commercial interests relevant to the content of this article.

References

Figure 1: The effects of H-reflex up-conditioning on locomotion in a rat with mid-thoracic right lateral column transaction. Traces show EMG bursts from right and left soleus muscles during treadmill locomotion before (top) and after (bottom) H-reflex up-conditioning has increased the size of the right soleus H-reflex. The presumed onsets of the right (●) and left (○) stance phases of locomotion are indicated in the middle, between the right and left burst traces. The short vertical dashed lines mark the midpoints between right burst onsets where the left burst onsets should occur. Before H-reflex up-conditioning, the left burst onset occurs too early, and the gait is asymmetrical (i.e., the rat is limping). H-reflex up-conditioning strengthens and lengthens the right soleus EMG burst, which corrects the left burst onset timing and eliminates the gait asymmetry. Horizontal scale bar: 0.5 s; vertical scale bar: 100 and 150 μV for the right and left EMG bursts, respectively. (From Chen Y, Chen XY, Jakeman LB, et al. Operant conditioning of H-reflex can correct a locomotor abnormality after spinal cord injury in rats. J Neurosci 2006;26:12537-12543. Image courtesy of The Journal of Neuroscience.)
Recovery of Coordinated Gait: Trial of Functional Electrical Stimulation (FES) versus No FES, with Weight-Supported Treadmill and Over-Ground Training

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No single intervention restores the coordinated components of gait after stroke with persistent gait dyscoordination. The purpose of this study was to test the multimodal Gait Training Protocol, with or without functional electrical stimulation (FES), for its capability to restore the volitional (no FES activated) coordinated movement components of normal walking for stroke survivors with persistent (> six months) dyscoordinated gait. Subjects (n = 44) were stratified and allocated to either FES with intramuscular (IM) electrodes (FES-IM) or No-FES. Both groups received 1.5 hours/session, four sessions/week, 12 weeks, including coordination exercise, body weight supported treadmill training (BWSTT), and over-ground gait training, either with FES-IM or No-FES. Results showed no baseline difference between the two groups, according to subject characteristics (P ≥ .189) and the Gait Assessment and Intervention Tool, a comprehensive measure of the coordinated movement components of gait (GAIT; P = .470), strength (MMT; P = .327), coordination (FM; P = .076), 6 Minute Walk Test (6MWT; P = .281), and Functional Independence Measure, Locomotion/Mobility subscales (FIM; P = .291). According to the GAIT, there was an additive advantage of FES-IM versus the comparable comprehensive gait training with No-FES (parameter statistic = 1.101, P = .045, 95% CI, .023, 2.179). There was no significant difference between the groups for all other measures, including gains in muscle strength, joint coordination, balance, gait speed, and mobility and locomotion function. Up to the post-treatment data acquisition, subjects continued to improve, indicating the potential benefit for a protocol longer than 48 visits. The FES-IM group maintained gains in coordinated gait components at follow-up, whereas the No-FES group did not.1

Janis Daly, PhD, reports no financial relationships with commercial interests relevant to the content of this article.

Reference

After stroke with persistent dyscoordinated gait, significant recovery of coordinated gait and function were produced by the multimodal Gait Coordination Training Protocol, with or without FES (Figure 1). FES-IM had significant additive advantage, in coordinated gait component gains versus No-FES, according to the GAIT coordination measure. There was no significant difference between the groups for all other measures, including gains in muscle strength, joint coordination, balance, gait speed, and mobility and locomotion function. Up to the post-treatment data acquisition, subjects continued to improve, indicating the potential benefit for a protocol longer than 48 visits. The FES-IM group maintained gains in coordinated gait components at follow-up, whereas the No-FES group did not.1

Janis Daly, PhD, reports no financial relationships with commercial interests relevant to the content of this article.

Reference
The Safety and Efficacy of Percutaneous FES Electrodes in Subjects with Stroke

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Percutaneous FES (functional electrode stimulation system) has been used for 20 years in the rehabilitation of stroke subjects. These electrodes have been implanted unilaterally in the lower extremities of stroke survivors to improve their volitional movement and gait parameters during rehabilitation. The objective of this study is to determine the safety and efficacy of FES system over time in terms of incidence of infections or erythema, breakage, and efficacy of stimulation.

Up to eight electrodes were implanted subcutaneously from the trigger point of selected lower extremity muscles to an exit site on the thigh in subjects with stroke. These electrodes were used to stimulate the paretic muscles with programmed electrical stimulation to enhance muscle contraction during stance phase and gait according to the rehabilitation protocol. During the therapeutic phase the electrodes were monitored as to the presence of erythema or infection, efficacy of stimulating the muscles, breakage of electrodes, and occurrence of discomfort on stimulation. At the end of the rehabilitation protocol, the percutaneous portion of the electrode was removed. The presence of erythema or infection continued to be assessed of the remaining fragments by subject report.

Figure 1: Mechanical durability over time.

These studies were done at the Louis Stokes Cleveland VA Medical Center in Cleveland, Ohio, in the Gait Research Laboratory with ambulatory outpatient subjects with stroke from 1988 to 2006. The subjects were a convenience sample of post-stroke patients. 42 subjects were studied with a total of 312 electrodes implanted. They underwent 2,905 electrode months of adequate stimulation during rehabilitation therapy. The subjects had impairment of gait during stance or swing phase but had sufficient voluntary muscle contraction of the lower extremity muscles that could be enhanced with stimulation. The placement of electrodes was unilaterally in the lower extremities of stroke survivors to improve their volitional movement and gait parameters during rehabilitation. The objective of this study is to determine the safety and efficacy of FES system over time in terms of incidence of infections or erythema, breakage, and efficacy of stimulation.

The main outcome measure was the incidence of adverse events of infection and erythema with FES electrode use. The secondary measure was the maintenance of adequate muscle stimulation of electrodes. There were 37 incidents of persistent erythema with FES electrode use. The presence of erythema or infection continued to be assessed of the remaining fragments by subject report.

The incidence of erythema or infection can be controlled through monitoring. After the rehabilitation protocol, the remaining electrode fragments have minimal risk to the subjects.

Eric Fredrickson, MD, reports no financial relationships with commercial interests relevant to the content of this article.

Brain Neuroplasticity Driven by Rehabilitation in Chronic Stroke

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In chronic stroke, recovery of coordinated reaching is critical to arm function and quality of life. Improvement of motor function can be achieved with intensive rehabilitation even years after stroke, but current methods fall short of restoring normal movement for many stroke survivors. Little is known regarding the change in brain function that is required to improve shoulder/elbow reach function. Therefore, the aim of this study was to characterize the change in brain activity of bilateral motor-sensory brain regions, which may drive recovery of functional reach. We enrolled 22 stroke subjects (> six months post-stroke) with arm motor deficits and treated them with intensive arm rehabilitation (five hours/day, five days/week for 12 weeks). Outcome measures were (1) functional magnetic resonance imaging (fMRI) during a shoulder/elbow reach task and (2) skilled motor function (Arm Motor Assessment Test [AMAT]). The fMRI activation (voxel count) was calculated for bilateral sensory-motor control regions. Multiple linear regression analysis was conducted to determine the relationship between the change in brain function and recovery of functional reach. Co-variates included pretreatment AMAT, age, and time-since-stroke. Subject characteristics were 56.3 years of age (± 12.8 years), 41% female, and 1.8 years (± 1.1) post-stroke. As a result of rehabilitation, AMAT improved from 1636.63 (± 668.41) to 1213.67 (± 664.37) seconds (P < .0001). Regional fMRI activation increased in some subjects and decreased in others. For those with increased activation in the ipsilesional primary motor and sensory cortices, their baseline function was poorer yet their functional gains were greater (P < .05). Regression analyses demonstrated that greater improvement of the AMAT score was associated with an increase in activation in the ipsilesional primary motor (P = .02) and in the contralesional regions as follows: primary motor (P = .02), primary sensory (P = .03), secondary sensory (P = .03), premotor (P = .009), supplementary motor (P = .05), thalamus (P = .02), putamen (P = .03), and cerebellum (P = .009). Based on these findings, we conclude that, in chronic stroke, important gain in functional reach is associated with increased activation, not only in the ipsilesional primary motor region but also in the contralesional motor-sensory regions, which occurred in response to intensive neurorehabilitation. Baseline patterns of task-related brain activation are related to rehabilitation-induced changes. Arm neurorehabilitation methods should be based on principles that engage this brain plasticity, which may drive recovery of arm function (Figure 1).

Svetlana Pundik, MD, reports no financial relationships with commercial interests relevant to the content of this article.

Figure 1: An illustration of increased task-related brain activation for an individual whose arm function improved following intensive arm rehabilitation.
Development of Artificial Muscles to Restore Function and Decrease Morbidity in Patients with Neurological Weakness

Over 3 million patients per year are diagnosed with a neurological disorder resulting in weakness. The courage displayed by many of these patients is inspirational as they often face progressive diseases with worsening weakness and co-morbidities, such as contractures, which further limits their function. Degenerative neuromuscular diseases present the unique challenge of balancing muscle atrophy from disuse with muscle destruction from overuse as both of these will cause muscle loss and further weakness.

To keep a patient at a steady state between disuse atrophy and overuse destruction, we have an innovative orthotic design concept using electrically active polymer actuators as artificial muscles. This novel device will amplify a patient’s existing strength to increase functionality and decrease co-morbidities. We hypothesize that this novel technology will allow patients to maintain their natural muscle mass for as long as possible and, therefore, decrease muscle disease progression. To translate this design idea into a functional prototype, the primary requirement is to create a lightweight artificial muscle. We are synthesizing electrically active biomimetic polymers to function as artificial muscles. By applying an electric voltage, the polymer actuator will contract and provide amplification of strength for a patient.

Our preliminary research on human muscle and polymers has led to the conclusion that the best class of materials to duplicate the properties of natural muscle is dielectric elastomers, specifically polyurethanes. We aim to utilize thermoplastic polyurethane (TPU) with hydrophobic soft segments as electroactive dielectric elastomers. To create a truly biomimetic polymer actuator, we will design our synthetic muscle to have a high dielectric constant, low modulus, low leakage current, and high breakdown strength.

Our initial studies have shown that the dielectric properties of TPUs far exceed that of most other elastomers. Our polymers are three to four times more electrically powerful while retaining their compliance and low leakage current (Figure 1). We are carrying out systematic dielectric and electro-mechanical response studies on various TPU dielectric elastomers. As we tailor the polymer chemistry of these TPUs further, we will be able to maximize the dielectric attributes and electromechanical properties. To achieve an even higher permittivity with losses lower than we are now measuring, we are varying the chain extender, hard-to-soft segment ratio, and polymer chemistry of the soft segments. Through these thoughtful iterative choices, we will optimize the most desirable characteristics for our biomimetic polymers to create an artificial muscle. Eventually, we will employ these biomimetic polymers in external orthotic devices to help mitigate weakness and associated co-morbidity in patients with neurological weakness.

Rahila Ansari, MD, is a collaborative researcher for Lubrizol, though this relationship has not affected the content of this article and the CME Program has determined there is no conflict of interest.
Microglia Mediated Neurotoxicity after Oligodendrocyte – Apoptosis in the Central Nervous System

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Multiple sclerosis (MS) is a primary demyelinating disease of the central nervous system (CNS). Although inflammatory mediated destruction of myelin is the primary noted pathology of the disease, disability in patients is primarily a consequence of axon loss. This has been demonstrated repeatedly using multiple modalities. Thus secondary tissue damage before, during, and after acute loss of myelin, particularly to axons but also to infiltrating reparative oligodendrocyte stem cells, is an important target for intervention. The objective of this study is to better understand the relationship between the microglia response to oligodendrocyte cell death and local tissue damage after demyelination in the absence of systemic inflammation so that strategies to modulate microglia output can be developed as novel therapies for MS.

This study utilizes a novel model of CNS demyelination that relies on the controlled, focal induction of apoptosis in adult oligodendrocytes. Activation of focal apoptosis in the central nervous system results in focal demyelination, axon damage, and repair failure as well as a rapid and robust microglia response. We hypothesize that this microglia response is responsible for axon damage at the lesion site, and inhibition of this response may promote myelin repair. To test this hypothesis, we treated mice with Resveratrol (a naturally occurring polyphenol shown to modulate the output of microglia cells) and monitored lesion development, cellular response, and axon damage after oligodendrocyte apoptosis. Mice treated with Resveratrol showed a significant delay in myelin clearance, a decrease in the overall size of the demyelinated lesion, and a decrease in the number of amyloid precursor protein (APP) positive axon segments at the lesion site. These changes were coupled with a decrease in detectable reactive oxygen species (ROS) at the site of demyelination. These data suggest that, in the process of clearing myelin, microglia shift to a neurotoxic phenotype releasing ROS, which mediates damage to demyelinated axons at the lesion site.

Stephen Selkirk, MD, PhD, reports no financial relationships with commercial interests relevant to the content of this article.

Figure 1: Treatment of mice with Resveratrol significantly decreases reactive oxygen species (ROS) production at the site of focal demyelination (white box) compared to untreated animals. This decrease is coupled with decreased axon damage, suggesting ROS-mediated neurotoxicity during myelin clearance.

Mild Traumatic Brain Injury and the Genesis of Post Traumatic Stress Disorder

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Traumatic brain injury (TBI) has long been recognized as a disease with significant psychological morbidity. The selective vulnerability of the frontal and temporal lobes to acceleration-deceleration forces as well as the impact of axonal injury on neuronal networks brings cognitive and behavioral change at the forefront of post-TBI life. TBI has been labeled the signature injury of our current conflicts; however, those who treat the Iraq and Afghanistan veteran population recognize the prevalent co-morbidities of pain and Post-Traumatic Stress Disorder (PTSD) in the TBI population. The large population-based studies of Hope and colleagues have quantified this association: 43% of veterans who have TBI with loss of consciousness (but only 9% of those with no injury) meet the criteria for PTSD.1 When the need arose in Cleveland to stand up a process to evaluate local returning veterans for TBI, Dr. Ruff accepted that challenge and thoughtfully examined hundreds of returning veterans with TBI and PTSD. Within this population, retrospective analysis of their injuries, symptoms, and neurological exam demonstrated a clear relationship between the number of TBI events and the development of PTSD as well as a linear relationship between the number of injuries and severity of PTSD (Figure 1). The identification of this relationship allows for earlier identification of those at risk for PTSD and interventions (pharmacologic and nonpharmacologic) directed at lessening the severity of not only the PTSD but also headaches and cognitive impairments.

Ronald G. Riechers II, MD, reports no financial relationships with commercial interests relevant to the content of this article.

References

Figure 1: Effect of number of episodes of loss of consciousness (LOC) on outcomes for veterans with combat-acquired mild traumatic brain injury: (A) olfaction scores; (B) post-traumatic stress disorder (PTSD) severity as measured by the PTSD Checklist Military Version (PCL-M) score; (C) the Montreal Cognitive Assessment (MoCA) score; and (D) the prevalence of abnormalities on neurological examination (unfilled circles) or PTSD (filled squares).
Disequilibrium Due to Vestibular Disturbance in Traumatic Brain Injury

Dizziness and balance complaints are common after civilian and combat-related mild traumatic brain injury (mTBI). Here we focus on those who have continuous feelings of disequilibrium and impaired balance that may last for months to years after the TBI event. The overall goals of this study are to (1) characterize physiologically the deficit in balance in these veterans, and (2) investigate the possible contribution of impaired vestibular reflexes, particularly those derived from otolithic inputs.

We studied 15 veterans of Operation Enduring Freedom/Operation Iraqi Freedom with mTBI; nine reported disequilibrium and six reported no dizziness. Ten nonveteran control subjects who had neither a history of mTBI nor vestibular symptoms were also studied. Gait and postural stability were tested using an infrared motion-tracking system. Static balance was tested while standing on a firm surface (the floor) and a compliant surface (thick foam). Dynamic stability was measured with sudden postural perturbations. Vestibulo-ocular reflexes were recorded in response to translational (otolith-mediated) and rotational (semicircular-canal-mediated) motion on a computer-controlled motion platform.

Veterans with mTBI and disequilibrium demonstrated increased postural sway under static and dynamic conditions, compared with nonveterans and veterans who had a history of mTBI but no current vestibular complaints. In dizzy veterans, postural sway was greatest when vision was eliminated by eye closure. For dynamic balance, responses to both forward and lateral perturbations were similarly impaired (Figure 1).

To assess the integrity of otolith-mediated vestibular reflexes, we measured the translational vestibulo-ocular reflex (TVOR) by oscillating subjects either vertically (primarily stimulating the saccular organs) or side-to-side (stimulating the utricles) at 2 Hz, recording eye movements using video-oculography or scleral coils. TVOR gain was calculated as the ratio of the amplitude of the recorded eye velocity to the expected eye velocity that would be required to maintain retinal stability of the fixation target. Although there was considerable overlap of TVOR gains among the three groups, there was a tendency for lower gains in the group with TBI and disequilibrium. In particular, four of nine dizzy subjects had lateral TVOR gains that were lower than all subjects in the other two groups, suggesting an impairment of utricular function. However, there was no consistent correlation of TVOR gain to specific measures of imbalance.

In conclusion, our initial data confirm that there are physiological balance correlates to chronic subjective disequilibrium in veterans with a history of combat-induced mTBI, even long after the initial injury. Reduced TVOR gains in about half of these veterans suggest that vestibular mechanisms may be playing a role. The lack of clear correlation between TVOR gain and postural sway may indicate that other factors, such as impaired motor control, are contributing to imbalance to a different extent in each individual. It may also reflect different degrees of compensation of the vestibulo-ocular and vestibulo-spinal reflexes.

Mark Walker, MD, reports no financial relationships with commercial interests relevant to the content of this article.
Novel Methods for Treating Pressure Ulcers in Persons with Spinal Cord Injury

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The management of veterans with spinal cord injury (SCI) is a priority of the Department of Veterans Affairs. Of the many potential complications following SCI, pressure ulcers are one of the most common, expensive and difficult conditions that are associated with significant morbidity and mortality. Despite the extent of the problem, scientific evidence on the treatment is lacking, including widely used modalities such as hydrotherapy. Over the last 12 years, Kath Bogie and I have been studying the use of different modalities in the treatment of pressure ulcers after SCI (Figure 1). Through support from Bob Ruff and funding by the VA Rehabilitation Research & Development Service, we carried out the first ever double-blind, randomized, controlled trial on the use of low-pressure pulsatile lavage in the treatment of pelvic stage III and IV pressure ulcers in persons with SCI. Pulsatile lavage is a portable hydrotherapy that encompasses all the clinical benefits of conventional hydrotherapy in a whirlpool tank, without the potential adverse effects such as cross-contamination. It is also much more easily administered by clinical staff. Twenty-eight subjects were enrolled, with the treatment group (n = 14) receiving standard dressing changes and pulsatile lavage. The sham treatment (control) group (n = 14) received only standard dressing changes. We studied clinical efficacy by measuring the rates of change in linear and volume measurements of pressure ulcers over three weeks. The results showed that pulsatile lavage enhanced stage III and IV pelvic pressure ulcer healing in persons with SCI relative to standard treatment alone. Additionally, we studied potential environmental contamination issues and the safety profile of pulsatile lavage. The results showed that with our treatment protocol and infection control method, there was no concern with environmental contamination due to Acinetobacter baumannii, previously reported to be a potential issue, nor was there a safety concern.

Chester H. Ho, MD, reports no financial relationships with commercial interests relevant to the content of this article.

Figure 1: Low-pressure pulsatile lavage has since been fully implemented in the routine treatment of pressure ulcers in persons with spinal cord injury at the Louis Stokes Cleveland VA Medical Center.

Learning the Art and Science of Thrombolytic Therapy and Endovascular Care in the Treatment of Acute Ischemic Stroke

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The first use of intra-arterial thrombolysis for acute ischemic stroke occurred in November 1993 at UH (Figure 1). It was so successful that we energetically developed and used a “Brain Attack” program—a genuine partnership of neurology, neurosurgery, and neuroradiology. Because so little was certain, a faculty member was present at the patient’s bedside whenever thrombolytic therapy was initiated. A central component was an effort to encourage patients to present earlier in the course of their disease. Local first responders cooperated in devising prehospital care protocols. As more patients arrived earlier, it was possible to use early intravenous therapy more frequently. This pattern accelerated after the publication of a related study by the National Institute of Neurological Disorders and Stroke. Efforts to complement thrombolysis led to involvement in a series of multicenter trials of various neuroprotective agents. Experience with intra-arterial administration of thrombolytic medication also led to early efforts with stenting in the setting of acute large vessel occlusion. As magnetic resonance imaging on an emergency basis became available, it was used to combine intravenous and intra-arterial therapy. As more and better care was provided to patients, the Department of Neurology at Case Western Reserve University School of Medicine and UH also evolved. Impatient census increased, resident physicians became more interested in cerebrovascular disease, the intensive care program gained impetus, and an enlarging faculty launched serious new clinical investigations in addition to their clinical care.

Dennis Landis, MD, reports no financial relationships with commercial interests relevant to the content of this article. Article includes discussion of unlabeled/investigational use of a commercial product.

Figure 1: Success with the first use of intra-arterial thrombolysis at University Hospitals Case Medical Center. (Left) Cerebral angiogram of a 76-year-old man, obtained four hours and 45 minutes after the onset of right hemiparesis and aphasia. The horizontal portion of the middle cerebral artery is occluded. (Right) Cerebral angiogram two hours later, after intra-arterial infusion of urokinase. Anterograde flow has been completely restored.
Neuroprotective Window for Thiazolidinediones in Ischemic Stroke

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Stroke is a devastating disease with limited treatment available. Although neuroprotective agents have been identified in rodent ischemia models, these successes have yet to be replicated in human trials. It is widely believed that the rapid progression of irreversible injury limits our ability to prevent cell death and disability in humans. If neuroprotective agents could be administered prior to vessel occlusion, the chances for neuroprotection in humans would be increased. The idea of pretreatment is usually thought of as impractical, but if a putative neuroprotective agent was also used to treat a chronic medical condition, then pretreatment would be a viable and immensely practical option.

Thiazolidinediones (TZDs) are excellent candidates for pretreatment of cerebral ischemia. TZDs are FDA-approved for the treatment of type 2 diabetes, a major risk factor for stroke. TZDs are agonists for peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear transcription factor that regulates adipocyte differentiation and lipid metabolism. It has been appreciated that PPARγ agonists are anti-inflammatory and ameliorate injury in inflammatory disease models. TZDs reduce proinflammatory cytokine expression as well as limit leukocyte infiltration and macrophage differentiation, all of which exacerbate injury following ischemic stroke. Additionally, TZDs increase superoxide dismutase and catalase levels, enhancing free radical scavenging.

We have found that TZDs are neuroprotective in a rodent transient cerebral ischemia model when administered within the first few hours following ischemia (Figure 1). Importantly, they are most effective when administered prior to reperfusion. Neuroprotection is associated with suppression of the inflammatory response to stroke, including the influx of systemic inflammatory cells into the ischemic tissue, a process that is more robust following reperfusion. Importantly, we have also found that pretreatment with doses of TZDs similar to those used to treat human diabetes is associated with both reduced infarction volume and enhanced neurological recovery. The Insulin Resistance Intervention after Stroke (IRIS) trial is currently ongoing and tests the use of a TZD, pioglitazone, as a preventative agent in insulin-resistant nondiabetic patients. If pioglitazone is found to be effective in preventing ischemic stroke in these patients, then the number of patients at high risk of stroke taking TZDs is likely to increase as does the importance of understanding potential neuroprotective actions of TZDs.

Sophia Sundararajan, MD, PhD, reports no financial relationships with commercial interests relevant to the content of this article. Article includes discussion of unlabeled/investigational use of a commercial product.

Figure 1: Rats were treated with oral pioglitazone at 0.20 mg/kg, 0.40 mg/kg, or 0.65 mg/kg dissolved in dimethylsulfoxide (DMSO) or DMSO daily for five days prior to a two-hour middle cerebral artery occlusion (MCAO). Twenty-one days later, MCAO rats were sacrificed and infarct volumes determined. Infarct volumes were measured by an examiner blinded to the treatment assignment. Animals treated with 0.20 mg/kg had infarction volumes that were not significantly different from those in vehicle-treated rats. Rats treated with either 0.40 or 0.65 mg/kg had significantly smaller infarct volumes than vehicle-treated animals (Student’s t-test P = 0.001; n = 14 [DMSO], n = 8 [0.2mg/kg], n = 8 [0.4mg/kg], n = 11 [0.65mg/kg]).

Clues to the Mechanism of Wake-Up Stroke

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The relationship between ischemic stroke and obstructive sleep apnea (OSA) is complex. OSA is an independent risk factor for incident stroke and is associated with poor neurological recovery following stroke. Stroke occurring during sleep or wake-up stroke (WUS) is common, accounting for about one-quarter of all ischemic strokes. In this study, we aimed to determine if characteristics of WUS differed from strokes occurring during wakefulness and if persons suffering WUS were more likely to have OSA. To do this, 56 subjects with ischemic and hemorrhagic stroke were studied. Subjects completed questionnaires screening for OSA (Berlin questionnaire) and assessing sleep characteristics. Other collected data included age, gender, stroke severity (NIH Stroke Scale), stroke localization, and mechanism. In our sample, WUS occurred in 22 out of 56 subjects (39.9%)—one of eight (12.5%) hemorrhagic strokes and 21 of 48 (43.8%) ischemic strokes. Positive screening for OSA by Berlin questionnaire occurred in 33 out of 56 subjects (60.1%)—66.7% of WUS subjects and 50.0% of non-WUS subjects among the ischemic stroke group (P = 0.25). Of those suffering ischemic stroke, subjects with WUS trended toward being younger (60.7 ± 16.2 vs. 68.1 ± 15.2; P = 0.12) and having higher low-density lipoprotein levels (124.6 ± 41.5 vs. 106.0 ± 39.0; P = 0.07). Subjects with WUS were significantly less severe by NIH stroke scale (3.7 ± 4.7 vs. 7.6 ± 7.3; P = 0.03) and those suffering WUS reported significantly fewer hours of total sleep time at night (6.2 ± 3.5 vs. 8.1 ± 2.1; P = 0.04) (Figure 1). Small vessel disease mechanism occurred more commonly in WUS, although this difference was not statistically significant (47.4% in WUS and 32.0% in non-WUS; P = 0.30). WUS is common among ischemic strokes and is associated with less severe neurological deficit. Persons suffering WUS report fewer hours of habitual sleeping time but are not more likely to screen positive for sleep apnea. Additional research is needed to determine whether mechanistic differences exist between WUS and non-WUS and whether WUS relates to sleep apnea.

Brian Koo, MD, reports no financial relationships with commercial interests relevant to the content of this article.

Figure 1: Stroke severity as measured by NIH Stroke Scale (NIHSS) is significantly less in wake-up stroke (WUS) as opposed to non-WUS (6.2 ± 4.7 vs. 7.6 ± 7.3; P = 0.03) and patients suffering WUS were more likely to have OSA. To do this, 56 subjects with ischemic and hemorrhagic stroke were studied. Subjects completed questionnaires screening for OSA (Berlin questionnaire) and assessing sleep characteristics. Other collected data included age, gender, stroke severity (NIH Stroke Scale), stroke localization, and mechanism. In our sample, WUS occurred in 22 out of 56 subjects (39.9%)—one of eight (12.5%) hemorrhagic strokes and 21 of 48 (43.8%) ischemic strokes. Positive screening for OSA by Berlin questionnaire occurred in 33 out of 56 subjects (60.1%)—66.7% of WUS subjects and 50.0% of non-WUS subjects among the ischemic stroke group (P = 0.25). Of those suffering ischemic stroke, subjects with WUS trended toward being younger (60.7 ± 16.2 vs. 68.1 ± 15.2; P = 0.12) and having higher low-density lipoprotein levels (124.6 ± 41.5 vs. 106.0 ± 39.0; P = 0.07). Subjects with WUS were significantly less severe by NIH stroke scale (3.7 ± 4.7 vs. 7.6 ± 7.3; P = 0.03) and those suffering WUS reported significantly fewer hours of total sleep time at night (6.2 ± 3.5 vs. 8.1 ± 2.1; P = 0.04) (Figure 1(6,8),(995,988)). Small vessel disease mechanism occurred more commonly in WUS, although this difference was not statistically significant (47.4% in WUS and 32.0% in non-WUS; P = 0.30). WUS is common among ischemic strokes and is associated with less severe neurological deficit. Persons suffering WUS report fewer hours of habitual sleeping time but are not more likely to screen positive for sleep apnea. Additional research is needed to determine whether mechanistic differences exist between WUS and non-WUS and whether WUS relates to sleep apnea.
Subarachnoid hemorrhage (SAH) is a common neurological emergency that carries high morbidity and mortality rates. Of all the medical treatments studied, only calcium-channel blockers provide modest improvement in functional outcome. The results for improved poor outcome depend largely on a single large trial of oral administration of nimodipine. The evidence for nimodipine is not beyond all doubt (5% absolute risk reduction of poor outcome). Additional new treatments that are safe and efficacious are desperately needed. Due to the complex cerebral cascade of events unleashed by SAH, the administration of a multifunctional substance, such as 25% human albumin (ALB), is very compelling. This theory is supported by promising preliminary evidence showing neuroprotection. The neuroprotective properties of 25% ALB have been evaluated in various animal models of the brain. Our preliminary data indicates that 25% ALB administration is associated with improved clinical outcomes and reduced costs in patients with SAH. In addition, our NINDS-funded Albumin In Subarachnoid Hemorrhage study (ALISAH) looked at several doses of 25% ALB and demonstrated that doses ranging up to 1.25 g/kg/day x 7 days were tolerated by patients without major dose-limiting complications. We also found that outcomes trended toward better responses in those subjects receiving 1.25 g/kg/day x 7 days. Based on these data, we propose the Albumin In Subarachnoid Hemorrhage II study (ALISAH II). ALISAH II is a multicenter, randomized, double-masked, Phase III clinical trial. The primary outcome is the Glasgow Outcome Scale at 90 days after symptom onset. The secondary outcome is serious adverse events considered to be related to (possibly, probably, and definitely) ALB treatment. We will need a sample size of 1,100 subjects for a 90% power. Subjects will be recruited from 85 international sites. ALISAH II has been endorsed by the Neurocritical Care Research Network, the Canadian Critical Care Group, the Australian and New Zealand Clinical Trials Group, the Latin American Brain Injury Consortium, the European Society of Intensive Care Medicine, and the Chinese University of Hong Kong. The Clinical Coordinating Center will be located at the Baylor College of Medicine in Houston, and the Statistical and Data Management Center will be located at the Medical University of South Carolina. The Data and Safety Monitoring Board will be set up by NINDS (Figure 1).

Jose I. Suarez, MD, reports no financial relationships with commercial interests relevant to the content of this article. Article includes discussion of unlabeled/ investigational use of a commercial product.

References
SECTION 3: New Developments in the Diagnosis and Management of Stroke

Safety and Feasibility of Elective Endovascular Coiling of Small Unruptured Cerebral Aneurysms

International Study of Unruptured Intracranial Aneurysms (ISUIA) reported the rupture rate of smaller aneurysms less than 7 mm to be dependent on the location, with 2.5% rupture rate over five years for posterior circulation aneurysm. The ISUIA results are controversial, with many reports showing that ruptured aneurysm sizes encountered in clinical practice are mostly less than 7 mm. Treatment of smaller aneurysms is debatable. However, advances in endovascular coiling may make it feasible and safe to coil smaller aneurysms. The goal of this study is to evaluate the safety of coiling aneurysms 2 – 7 mm in maximum diameter.

Method
Data were collected retrospectively and prospectively by seven medical centers with active neurointerventional service in the United States. Inclusion criteria included unruptured cerebral aneurysm < 7 mm treated electively using endovascular coiling. Data including basic demographics, location, and size of the aneurysm, with all procedural complication and clinical/radiological follow-up, were collected and analyzed. The main study outcome presented is the symptomatic procedural ischemic and hemorrhagic cerebral complication defined as neurological deficit lasting more than 24 hours.

Results
A total of 485 unruptured aneurysms were treated in 445 patients with mean age of 54.3 ± 11.9 years. Seventy-six percent of the patients were female, and 72% of the study population was white. Hypertension was present in 54.6%, diabetes in 10.3%, and smoking in 37.7% of patients. The study aneurysms mean maximum diameter was 4.8 ± 1.4 mm (range of 1.5 to 7 mm). There were 378 (77.9%) anterior circulation aneurysms while 107 (22.1%) were located in posterior circulation/posterior communicating area. The overall asymptomatic and symptomatic peri-procedural complication rate was 5% with a major morbidity rate of 1.55% and no mortality. There was symptomatic hemorrhage in 0.88% (4/445) while asymptomatic hemorrhage was noted in 0.67% (3/445). The overall rate of thromboembolic complications was 3.14% (14/445) of which 0.67% (3/445) were symptomatic and 2.47% (11/445) were asymptomatic. There was no procedure-related mortality.

Conclusion
Advancement in the endovascular intervention has made possible for safe coiling of small aneurysm (2 – 7 mm) with symptomatic hemorrhagic and ischemic complication of 1.55% and no procedure-related mortality in this series (Figure 1). Further studies are required to evaluate the natural history of rupture for small unruptured aneurysms compared with endovascular coiling.

Osama O. Zaidat, MD, reports no financial relationships with commercial interests relevant to the content of this article.

Reference

Figure 1: (A) Lateral projection digital subtraction angiogram and (B) representative illustration of Y-configuration stent implantation for coil embolization of a pericallosal callosomarginal artery bifurcation aneurysm. Reproduced from Darkhabani ZM, Lazaro MA, Zaidat O. Pericallosal artery aneurysm treatment using Y-configuration stent-assisted coil embolization: a report of four cases. J Neurointerv Surg 2012;1(4):459-462 with permission from BMJ Publishing Group Ltd.
New Approaches to Image the Ischemic Brain

Although great progress has been made in the treatment of acute ischemic stroke (AIS) over the past decade, most of these patients go untreated. This fact is largely due to the time-window-based approach to patient selection, which is currently in widespread use. The time-window paradigm is fundamentally flawed in its assumption that there is a uniformity of stroke evolution throughout a diverse population. Driven by novel applications of magnetic resonance (MR) imaging, there will likely be a paradigm shift in the way patients are selected for therapy such that treatments are individualized. Our approach to achieve this goal can be broken down into three components:

1. Better use of the information we are currently acquiring with MR imaging through quantification
2. Extracting novel information out of the standard images through post processing
3. Developing new ways to acquire images that are targeted to specific physiologic and pathologic processes

To address the first component, we have developed an image-processing pipeline that allows real-time quantification and volumetric analysis of diffusion weighted imaging, perfusion weighted imaging, and FLAIR imaging. Such a backbone will allow us to partake in multicenter randomized trials designed to validate the quantitative approach. The focus of the second component has been on developing a method for measuring damage to the blood-brain barrier from perfusion weighted imaging (Figure 1). Preliminary results using this perfusion-based permeability imaging show it to be an independent predictor of intracranial hemorrhage after intravenous tissue plasminogen activator. To address the third component, we have teamed up with several basic science MR physicists who have developed a pulse-sequence that generates pH-weighted images. These images were developed to detect the buildup of lactic acid in the brain that occurs in the setting of poor blood flow (Figure 2). In animal models, this technique has been able to detect at-risk tissue (penumbra) and predict final infarct volume. We are currently enrolling patients into a study approved by our Institutional Review Board to translate this basic science research into clinical utility.

Richard Leigh, MD, reports no financial relationships with commercial interests relevant to the content of this article.
Intracranial Hypertension and Visual Impairment in Outer Space

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Space flight of long duration (Figure 1) results in many physiological changes in astronauts. Recently, a syndrome of visual changes and signs of elevated intracranial pressure (ICP) has been discovered, which mimics findings seen in patients on Earth with idiopathic intracranial hypertension. About 30% of the long-duration astronauts have developed neuro-ophthalmological findings, including flattening of the posterior globe, choroidal folds, acquired hyperopic shift, papilledema, distension and tortuosity of the optic nerve sheath, and visual field disturbances. Post-flight lumbar puncture has shown persistent elevation of the ICP in some astronauts. The visual changes have not always recovered. Pathophysiologic factors may include cephalad shifting of fluids in microgravity, leading to impaired venous or lymphatic drainage of the cranial or impaired cerebrospinal fluid drainage. Other factors may include carbon dioxide exposure, resistive exercise, and other yet known environmental or anatomical factors. An understanding of the normal physiology of cerebral hemodynamics and ICP is essential to understanding the pathophysiology that may be occurring in microgravity. Further research is needed to determine which factors may be variable in individual astronauts, predisposing them to microgravity-induced visual impairment and intracranial hypertension syndrome. Development of noninvasive ICP monitoring devices will be necessary to have a better understanding of the severity of intracranial hypertension in microgravity and effect of provoking or environmental factors on the ICP. Prospective protocols to evaluate astronauts’ visual and neurological condition preflight, intraflight, and postflight are being developed.

Eric Bershad, MD, reports no financial relationships with commercial interests relevant to the content of this article.

Figure 1: International Space Station in low earth orbit. Image courtesy of NASA.

Medication Overuse Headache

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Chronic daily headache (CDH) is the term of art used for long headaches (> four hours) daily or nearly daily (≥ 15 days per month). It is not a diagnosis acknowledged by the International Headache Society classification syndrome. Short daily headaches (< three hours) such as cluster, trigeminal autonomic cephalalgias (TACs), and other primary and related headaches are not included in the definition of CDH. Other terms for CDH include chronic migraine (CM), transformed migraine (TM), medication-overuse headache (MOH), chronic tension-type headache (CTTH), new daily-persistent headache (NDPH), and rebound headache. MOH is defined as a secondary CDH in which headaches have worsened with use of acute medications taken in an excessive frequency. In 2010 in the United States, the FDA defined CM as CDH, including MOH. CDH occurs in about 4% of the general population in the United States, half of which is CM and most of which is MOH. The most important predictors for transformation from episodic migraine to CM include frequency of headache as well as frequency and type of acute treatment medication use.1 Headache frequency and MOH cause structural and functional brain change. However, natural history studies suggest that two-thirds of CM remits by two years, so, although not proven prospectively, it may be possible to reverse these changes for most patients. Headache frequency is linked to transformation to CM for most patients – the higher the baseline frequency of headaches per month, the greater the likelihood for transformation to CDH over the next one to two years. Frequency and type of acute medications used for headache also predicts chronification. Butalbital and opioids should not be used in migraine; they are the most likely to transform patients to MOH. The rule of thumb is to limit the other acute medication use to no more than two days of intake per week. The hierarchy and frequency of medication risk for transformation to MOH is butalbital at five days of use/month, opioids at eight days of use/month, nonsteroidal anti-inflammatory drugs, triptans, and combination analgesics at 10 to 15 headache days per month (Table 1). Wean is crucial in treatment of MOH and must be 100%. OnabotulinumtoxinA is the only FDA-approved medication for CM. OnabotulinumtoxinA or daily prevention should be established at the same time as the wean performed. Interdisciplinary programs can be the fallback position. Follow-up with diaries is key for both prevention of MOH and for following patients with headache for frequency and medication use.

Stewart J. Tepper, MD, is a consultant, advisory board member, and speaker for Allergan, AstraZeneca, Novartis, Merck, Pfizer, and Xomed and has authored books for the University of Mississippi Press, Springer, and People’s Publishing House, through these relationships have not affected the content of this article and the CME Program has determined there is no conflict of interest. Article includes discussion of unlabeled/investigational use of a commercial product.

Table 1: Medication Overuse Headache Genesis1,2

<table>
<thead>
<tr>
<th>Factors most associated with transformation to daily headache</th>
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<tbody>
<tr>
<td>• Baseline headache frequency (&gt; 10 days per month vastly increases the risk of chronification over the next 1 – 2 years)</td>
</tr>
<tr>
<td>• Type and frequency of acute medication use</td>
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<tr>
<td>– Butalbital use at ≥ 5 days/month</td>
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<tr>
<td>– Opioid use at ≥ 2 days/week</td>
</tr>
<tr>
<td>– Triptans, combination analgesics at ≥ 10 days/month</td>
</tr>
<tr>
<td>– NSAID use at 10-15 days/month</td>
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</table>

NSAID: nonsteroidal anti-inflammatory drug

References
Novel Memory-Preserving Interventions in Temporal Lobe Epilepsy

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The goal of my research at Case Western Reserve University was to develop novel surgical therapies for improvement of seizure control in temporal lobe epilepsy, without compromising memory outcome. Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy in adults. One-third of TLE is medically intractable, posing high risks of cognitive decline and increased mortality in addition to enormous social, psychological, and economic burdens. The hippocampus is crucial for memory processing but is also the source of most temporal lobe seizures. In patients with intractable TLE, resection of the temporal lobe, including the hippocampus, has a higher chance of stopping seizures than medical therapy does but with the risk of memory decline, especially in patients with intact-looking hippocampi on imaging.

Multiple Hippocampal Transections
Numerous studies have suggested that the hippocampus contains two types of neural circuits: transverse circuits that are stratified perpendicularly to the long axis of the hippocampus, and longitudinal fibers that run parallel to that axis. Memory processing appears to take place within the transverse circuits whereas seizure generation utilizes the longitudinal pathway, which suggests that disconnecting the longitudinal pathways without injuring transverse circuits may stop seizures without altering memory processing. We have performed the hippocampal transection surgery in several patients and achieved promising results. A controlled study will be needed to confirm safety and efficacy of this novel surgery.

Deep Brain Stimulation (DBS) of the Fornix
While DBS has had limited success in epilepsy, fiber tracts have not been stimulated, and low frequencies have not been adequately explored for treatment of epilepsy. In 11 patients with intractable TLE, we implanted depth electrodes in the fornix and applied low-frequency electrical stimulation. The stimulation elicited hippocampal evoked responses, confirming connectivity (Figure 1). There were no complications, and hourly mini-mental status examination scores showed some increase during stimulation. We also found significant reduction of hippocampal spikes, which outlasted the stimulation, and the seizure odds were reduced by 90.3% during and after stimulation. Thus, DBS of the fornix appears to be attractive because it interferes with spontaneous electrical activity of a relatively extensive cortical area and requires less current injection, implying more safety and a longer battery life. We are now preparing for an exploratory trial to confirm safety and tolerability of DBS of the fiber tract.

Sami Harik, MD, reports no financial relationships with commercial interests relevant to the content of this article.

References

Neurological Complications of Bariatric Surgery

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The number of bariatric procedures is rapidly growing as the prevalence of obesity in the United States increases. Such procedures are not without complications, and those affecting the nervous system are often disabling and irreversible. We now describe our experience with these complications and review the pertinent literature.

We describe 26 patients with major neurological conditions that seemed causally related to bariatric surgery encountered in the neurology service of a tertiary referral university medical center over a decade. The neurological complications affected most regions of the nervous system: encephalopathy, optic neuropathy, myelopathy (Figure 1), polynuropathy, and polyneuropathy. Myelopathy was the most frequent and disabling problem; symptoms began about a decade after surgery. Encephalopathy and polynuropathy were acute and early complications. Except for vitamin B12 and copper deficiencies in patients with myelopathy, we could not correlate specific nutritional deficiencies to the neurological complications. All patients had multiple nutritional deficiencies, but their correction did not often yield dramatic results. The best result was achieved in one patient after surgical revision to reduce the bypassed jejunum. A wide spectrum of serious neurological conditions may follow bariatric surgery. These complications may occur acutely or decades later.1

Sami Harak, MD, reports no financial relationships with commercial interests relevant to the content of this article.

References
Doxycycline Mitigates Development of Parkinsonism in a 6-OHDA Mice Model

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Parkinson disease (PD) is one of the most common progressively disabling neurodegenerative disorders. Currently, the common treatment approaches focus on retarding the dopaminergic-neuron degeneration. Unfortunately, presently there is no available therapy for PD patients without long-term debilitating side effects.

6-hydroxydopamine (6-OHDA) damages the nigrostriatal dopaminergic pathway, similarly as seen in PD, characterized by the loss of dopamine neurons in the substantia nigra (SN), decreased striatal dopamine levels, and consequently inducing extrapyramidal motor dysfunction. We used this animal model of PD for this study.

The tetracycline-derivative antibiotic doxycycline has been shown to be neuroprotective in in vivo and in vitro models of neurodegenerative diseases.1 Doxycycline is also one of the tetracyclines most commonly orally administered for conditional transgene expression. Doxycycline is also used for the treatment of central nervous system infections as its high lipid solubility results in good brain penetration.

Consistent with a role of glial cells in PD neurodegeneration, we were able to show that doxycycline inhibits glial activation independently of its antimicrobial properties and mitigates the reduction in nigrostriatal dopaminergic neurons induced by stereotactically 6-OHDA unilateral microinjection into the striatum. C57Bl/6N male mice were randomly divided into experimental groups (6-OHDA) and respective controls (saline) with and without doxycycline administration. Damage to the SN following 6-OHDA-microinjection was quantified by counting tyrosine hydroxylase-positive immunoreactive neurons. Two specific antibodies, macrophage antigen-1 and glial fibrillary acid protein, were used to detect the changes in morphology and numbers of microglia and astrocytes, respectively. In the 6-OHDA mouse model of PD, doxycycline (in a dose that both induces/represses conditional transgene expression in the tetracycline system) mitigates the loss of dopaminergic cell bodies in the SN pars compacta and of nerve terminals in the striatum and prevents astrocytic activation in the SN with minimal effects on the microglial response in striatum (Figure 1). Our results suggest that doxycycline blocks 6-OHDA neurotoxicity in vivo by inhibiting glial expression. Neuroprotective doxycycline may be effective in preventing or slowing the progression of PD and other neurodegenerative diseases.

Walter Stühmer, PhD, reports no financial relationships with commercial interests relevant to the content of this article.

Reference

Figure 1: Double staining of the striatum with tyrosine-hydroxylase (labeling dopaminergic neurons) in red and glial fibrillary acid protein (labeling glia cells) in green. The two left panels are controls, and the two right panels demonstrate the protective effect of doxycycline (DOXY) in 6-hydroxydopamine (6-OHDA)-induced localized lesions.
Status Epilepticus: The Nature of the Beast

Status epilepticus (SE) is one of the few illnesses named by the patients who suffered from it. The expression “etat de mal” was used by the patients at the Bicêtre/Salpetrière and reached the medical literature through the doctoral thesis of Louis Calmeil in 1824. It became “Status epilepticus” in Bazire’s translation of Armand Trousseau’s London lectures in 1867. Trousseau understood that SE was more than just a bunch of seizures: “In [...] status epilepticus when the convulsions are practically continuous, something specific happens (in the brain) that requires an explanation.” We are beginning to put together that explanation today, although many questions remain unanswered.

Clinical Definition
Trousseau recognized, and Gastaut stated, that “there are as many types of status as there are types of seizures.” Gastaut defined SE as “a fixed and lasting epileptic condition,” but recent guidelines of the Epilepsy Foundation of America focus on the “operational” definition (the time when we should treat a condition as SE). For adult convulsive generalized SE (CGSE), this definition is now widely accepted as five minutes of repetitive seizures without full recovery of consciousness between them. We propose a statistical definition of SE based on the usual duration of the seizure type. Since tonic-clonic seizures last about one minute and rarely exceed two minutes, five minutes of continuous convulsive generalized seizures are a rare phenomenon, more than five standard deviation removed from the mean, which should define CGSE. SE in other seizure types can be similarly defined by the usual duration and variability of those types.

Biological Definition
The biological definition should require the presence of self-sustaining seizures. We fortuitously discovered (1974) that electroconvulsive seizures repeated at one-minute intervals lead to self-sustaining SE (SSSE). SSSE is a general phenomenon, reliably induced by clusters of ~10 after-discharges in many excitatory pathways. Repetitive seizures become self-sustaining and independent of their original trigger.

Pathophysiology
Internalization (and subsequent temporary inactivation) of synaptic gamma-aminobutyric acid type A (GABA<sub>A</sub>) receptors may play a major role in the initiation of SSSE in vivo (Figure 1). A rise in extracellular K, changes in turnover of inhibitory transmitters, depletion of inhibitory neuropeptides, and, in neonates, an accumulation of intracellular chloride may also contribute to seizure recurrence. The maintenance of self-sustaining seizures seems at least in part dependent on trafficking of glutamate (especially N-methyl-D-aspartate) receptors to synapses and is associated with changes in calmodulin kinase 2 activity and enhanced long-term potentiation (LTP), suggesting that repetitive seizures may hijack short-term memory mechanisms to cause SSSE. If that is true, and if that memory trace is consolidated, every case of SE should lead to chronic epilepsy; the real figure is around 30%. However, the profound inhibition of cerebral protein synthesis by SE may block consolidation of these changes. Long-term consequences (SE-induced epileptogenesis) are the most robust current model of epileptogenesis and are seen across a variety of models and species. Chronic epilepsy develops after a latent period and is the result of repetitive seizures and not that of hypoxic-ischemic complications of SE because it occurs after complex partial SE with no hypoxic-ischemic component. SE-associated neuronal injury can result from uncontrolled synaptic activity alone. In the immature brain, SE can alter the brain’s developmental networks with cognitive and behavioral consequences.

Conclusion
The very effective homeostatic mechanisms that usually limit cerebral excitation and stop epileptic seizures fail in SE as a result of maladaptive responses to metabolic stresses induced by seizures, which transiently generates both failure of inhibition and a giant LTP-like increase in synaptic excitatory responses. These changes suggest that our current therapeutic strategies address only part of the problems that maintain SSSE.

Claude Wasterlain, MD, reports no financial relationships with commercial interests relevant to the content of this article.
Nuclear Receptors as Therapeutic Targets in Alzheimer Disease

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Alzheimer disease is associated with impaired clearance of β-amyloid from the brain, a process normally facilitated by Apolipoprotein E. ApoE expression is transcriptionally induced through the coordinate action of the nuclear receptors PPARy:RXR and LXR:RXR. Oral administration of the RXR agonist, bexarotene, to a murine model of Alzheimer disease resulted in enhanced and sustained clearance of soluble Aβ from the interstitial fluid within hours in an apoE-dependent manner. Remarkably, Aβ plaque burden in six-month-old APP/PS1 mice was reduced ~50% within 72 hours and by 80% after 14 days (Figure 1). Plaque clearance was associated with the appearance of amyloid-laden microglia, consistent with the induction of phagocytosis following drug treatment. Further, bexarotene stimulated the rapid reversal of cognitive, social, and olfactory deficits and rapidly improved neural circuit function. Analogous changes were observed following a nine-day treatment with the PPAR gamma agonist pioglitazone. Thus, nuclear receptor activation stimulates physiological Aβ clearance mechanisms resulting in the very rapid reversal of a broad range of Aβ-induced deficits. These findings suggest nuclear receptor agonists may be of utility for developing therapeutics for Alzheimer disease and its prodromal states.

Gary E. Landreth, PhD, is the founder of Rexceptor, Inc., though this relationship has not affected the content of this article and the CME Program has determined there is no conflict of interest.
Target Audience
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Educational Objectives
Upon completion of this educational activity, the participant should be able to:
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• Discuss rehabilitation of patients with neuromuscular disorders
• Evaluate new developments in the diagnosis and management of stroke
• Summarize frontiers of general neurology

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Release Date: January 1, 2013
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