

Seeing the Unseen: Revelations From Peripheral Nerve MRI

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For 200 years, the anatomical basis of intraneural ganglia was not fully understood. Now it is. Intraneural ganglia, mucinous cysts in the epineurium of nerves, have been difficult to treat because of a high rate of recurrence after surgical intervention. New MRI techniques at Mayo Clinic have revealed the reasons why and have added substance to a new theory about the pathogenesis of intraneural ganglia. These same techniques, unique to Mayo Clinic, are also changing the management of peripheral nerve lesions and improving outcomes.

Kimberly K. Amrami, MD, a Mayo Clinic musculoskeletal radiologist, and her colleagues have dramatically improved peripheral nerve lesion identification and localization by using improved high-resolution and interval MRI technology combined with MR neurography (Figure).

The MR neurographic technique, developed at the University of Washington, Seattle, in the mid 1990s, is a direct imaging technique that produces images of individual nerves and reveals actual nerve pathologic characteristics. Previous techniques relied on inferences derived from muscle denervation. Advances at Mayo Clinic have turned inferences into precision targeting and have shed light on pathogenesis.

Depending on individual case requirements, advanced MR nerve imaging techniques at Mayo Clinic include the following:

Custom-made dedicated-radiofrequency coils, fabricated at Mayo Clinic

Multiplanar MR images with the highest possible spatial resolution through 2-D and 3-D techniques

Advanced postprocessing for optimal image reformatting and reconstruction

Customized Imaging Protocols

Imaging protocols are individualized, taking into account all of the patient's available clinical and diagnostic information. This individualization is particularly important, given both the distance that some peripheral nerves travel from the spinal cord to target muscles and the fact that there may be bilateral and multifocal involvement. As Dr Amrami points out, the localization of a foot drop due to a lower motor neuron lesion may be anywhere from the L4 nerve to the deep branch of the peroneal nerve. Thus, determining how much anatomy to include for MR imaging depends on the patient's history, findings on physical examination (including presence of a Tinel sign), and results from EMG and other tests. Dr Amrami notes that balancing the precision



Figure. Enhanced MRI techniques at Mayo Clinic allow improved, precise identification and localization of peripheral nerve lesions.



Robert J. Spinner, MD, and Kimberly K. Amrami, MD

gained from using the smallest possible radio-frequency coils against the need to image large anatomical areas can be challenging. Multiple imaging sequences and, sometimes, several imaging sessions may be required for optimal results.

Examples of Impact on Outcomes

Schwannomas

Schwannomas, the most common type of benign tumor in the peripheral nervous system, have long been thought to be based on single-fiber involvement. Technical improvements in the past 20 years have made it possible to resect schwannomas at the fascicular level. Yet, as Mayo neurosurgeon Robert J. Spinner, MD, notes, resection has not always had the predicted outcome, regardless of surgical expertise. “The question is ‘why?’ And the answer turns out to be that not all schwannomas are the same,” he says.

A retrospective review at Mayo Clinic, published in the February 2010 issue of *Journal of Neurosurgery*, found that in a subgroup of schwannomas, several fibers—not just one—were involved. Tumor resection in such cases can result not only in nerve loss, but also in loss of function. Preoperative and intraoperative assessment may not reveal the distinguishing features of this subgroup, but enhanced imaging techniques, such as those used at Mayo Clinic, can. That information can help guide the surgeon and influence preoperative patient counseling.

Localization for Targeted Biopsies

MR technologic advances have also greatly improved lesion localization for targeted fascicular biopsy. In the past, sampling was nonspecific, with results that did not necessarily enhance diagnosis or that caused further neurologic deficit. As Dr Amrami explains, rather than identifying a general location, such as the brachial plexus, her team typically can specify the size of the lesion and its precise location. In an increasing number of cases, their experience and expertise with a wide

range of peripheral nerve disorders allow Dr Amrami and her colleagues to diagnose the entity, as confirmed by biopsy performed in a safe manner.

Intraneural Perineuriomas

Intraneural perineuriomas are a benign form of focal hypertrophic neuropathy affecting young people. Most often affecting major nerves, such as the sciatic, radial, and ulnar nerves and the brachial plexus, this condition is frequently underrecognized. Diagnosis rests on identifying the focal nerve enlargement through imaging and a targeted fascicular biopsy. MRI is particularly important for localization. As reported in the August 2009 issue of *Brain*, a Mayo Clinic study found that standard MRI failed to reveal abnormalities in many of the 32 subjects, yet these abnormalities were revealed with Mayo’s advanced high-field (3-Tesla) MRI with custom coils designed to image specific nerves.

Intraneural Ganglion Cysts

The 3-D imaging techniques used at Mayo Clinic have helped to substantiate a theory of intraneural ganglion cyst pathogenesis, the *unifying articular (synovial) theory*, formulated by Dr Spinner and his colleagues in 2003. The theory, further elaborated on in the October 2009 issue of *Neurosurgery*, holds that synovial joints are the origin of the cysts that dissect along an articular branch of the involved nerve into the parent nerve. Without advanced imaging, the extent of such cysts and their connection to the joint via the twig-like articular branch could not be seen. A prospective study of every case of peroneal intraneural ganglia treated at Mayo Clinic in the past 10 years (>30 cases), as well as a retrospective study (>30 cases), showed that the joint itself was always the source of the cyst. This finding helps explain previous recurrence after resection: typically, only part of the cyst was removed. Now, because the joint connection of the intraneural cyst has been established and can be seen on imaging, the articular branch connection can be purposefully disconnected at surgery, significantly improving surgical outcomes.

Intraneural ganglion cysts are rare; only 400 cases have been reported in the medical literature. However, major advances in imaging and radiology at Mayo Clinic are improving surgical outcomes and revealing pathogenesis for far more common peripheral nerve lesions, both benign and malignant.

Meeting Increased Demand: Clinical Neurophysiology Across Mayo Clinic

In 2009, more than 200 physicians from 12 countries attended the annual Mayo Clinic conference on clinical neurophysiology. They came for application updates and training in EMG and EEG, evoked potentials, autonomic testing, and intraoperative monitoring. They knew they would be taught by experienced specialists—first- and second-generation mentees of Edward Lambert, MD, and Donald W. Mulder, MD, who established the nation's first EMG laboratory at Mayo Clinic; Reginald Bickford, MD, and Donald W. Klass, MD, who vastly expanded the knowledge of EEG findings in many neurologic and medical disorders; and Philip A. Low, MD, who established the tests, norms, and national standards for quantified autonomic function evaluation.

The work of these five ground-breaking specialists continues to inform refinements in the science and practice of neurophysiologic testing and monitoring across Mayo's three sites, where procedures are performed by experienced specialists in neuromuscular and autonomic diseases. Large patient volumes and a caseload that, in addition to more common conditions, includes complex neuromuscular diseases, brachial plexus injuries, rare neuropathies, atypical seizure disorders, and postural orthostatic tachycardia syndrome, enhance the breadth and depth of specialist experience (Box 1).

Tests rarely performed at other institutions, such as repetitive stimulation for neuromuscular junction diseases and single-fiber EMG, are done daily by Mayo's electromyographers (Figure, see page 4). The EMG laboratory at Mayo Clinic in Rochester, Minnesota, is the largest in the world. There, electromyographers conduct more than 11,000 EMG studies per year. Mayo Clinic in Jacksonville, Florida, and Scottsdale, Arizona, conducts more than 4,500 and 3,700 EMG studies per year, respectively.

The Autonomic Laboratory at Mayo Clinic in Rochester, Minnesota, is the largest in the United States. Autonomic testing, also available at Mayo's Florida and Arizona sites, helps determine the presence, severity, distribution, and localization of autonomic dysfunction. Routine autonomic evaluation includes tests of sudomotor, cardiovagal, and adrenergic function (Box 2, see page 4).

Expanding the Practice

"Awake anesthesia" has made EMG in children feasible. The child is sedated enough to mini-

mize discomfort but awake enough for voluntary movement. The studies take place in a special suite connected to an operating room. The combination of pediatric anesthesiologists titrating the sedation and neurologists experienced in pediatric EMG helps ensure that the tests are completed in the shortest time possible, with minimal discomfort, and in a safe environment. Mayo Clinic neurologists are among the only physicians in the world who perform single-fiber EMG studies in children. Last year, they conducted approximately 200 pediatric EMG studies in Rochester for diagnostic testing and medication monitoring. Neurologists at Mayo's Florida campus regularly assist in complicated EMG studies in children at the Nemours Children's Clinic in Jacksonville.

Box 1. EMG Referral Characteristics

Common symptoms

- Weakness
- Numbness
- Sensory loss
- Neuropathic pain

Common conditions

- Brachial and lumbar plexopathies
- Carpal tunnel and ulnar neuropathies or cubital tunnel syndrome
- Cranial nerve disorders
- Motor neuron disease
- Muscle cramps or hyperexcitable nerve syndrome
- Myopathies (congenital and acquired)
- Neuromuscular junction disorders (eg, congenital and acquired myasthenia gravis, Lambert-Eaton myasthenic syndrome)
- Nerve terminal disorders
- Peripheral neuropathy
- Pediatric muscular dystrophies, inherited neuropathies, metabolic myopathies, congenital myasthenia syndromes
- Radiculopathies



Mark A. Ross, MD



Devon I. Rubin, MD



Eric J. Sorenson, MD

Box 2. Symptoms That May Benefit From Autonomic Testing

- Anhidrosis
- Bladder and bowel dysfunction
- Cognitive dysfunction
- Dizziness
- Endocrine dysfunction
- Extreme fatigue
- Flushing
- Gastrointestinal distress
- Orthostatic intolerance
- Painful feet
- Parkinson-like symptoms
- Syncope
- Tachycardia

Box 3. Intraoperative Monitoring at Mayo Clinic

Spine surgery

Functional stimulation of motor and sensory nerves

Brainstem surgery

Auditory evoked potentials during surgery for cranial tumors, trigeminal neuralgia, facial spasm, and other conditions

Peripheral nerve surgery

Nerve stimulation and recording to assist in locating and defining injury in complex peripheral injuries, such as those affecting the brachial plexus

Increased Volume of Intraoperative Monitoring

The volume of Mayo's intraoperative electrophysiologic monitoring has increased. Last year, across Mayo's three sites, its physicians conducted monitoring in 1,300 surgeries (Box 3). Eric J. Sorenson, MD, director of the EMG Laboratory at Mayo Clinic in Rochester, Minnesota, notes that "at the vast majority of institutions, evoked potentials waveforms are monitored at off-site centers by technicians who are monitoring numerous cases simultaneously and do not know the patient or the operating conditions. At Mayo, we have people in the operating room who understand the individual case and know if there are changes in anesthesia, the patient's status, or technical concerns during the procedure. It makes a difference."

Centralized Laboratory Facilities Coming to Mayo Clinic in Florida

Devon I. Rubin, MD, director of the Neurophysiology Laboratory at Mayo Clinic in Florida, is looking forward to a new laboratory, scheduled to open in October 2010, that will centralize testing for movement disorders, EEG, EMG, and autonomic disorders.

Located down the hall from the clinical neurology practice, it will add convenience for both patients and physicians.

Uniformity of Practice: The Three-Site Advantage

Mark A. Ross, MD, director of the Neurophysiology Laboratory at Mayo Clinic in Arizona, agrees with Drs Rubin and Sorenson that a major advantage of their practice is the standardization of techniques and laboratory procedures across the three sites. This standardization enhances collaboration in the practice, in research, and in education.

Research

Uniformity is particularly important in clinical and research EMG studies, for which procedures and interpretations can vary greatly. "Standardized techniques and a broad subject pool for research help us evaluate diagnostic techniques for neuromuscular conditions," notes Dr Rubin. Dr Ross points to an upcoming international study that will use the compound muscle action potential (CMAP) scan as an example. He notes, "With this scan technique, electrical nerve stimulation is divided into very small increments, which allows demonstration of the components of the CMAP. We hope this technique will reveal abnormalities that are not apparent with the routine CMAP measurement and that it may prove to be a very early predictor of certain nerve and muscle disorders."

Education and Training

Most physicians performing EMG at Mayo have been trained at Mayo. In addition to the annual conference, physicians from each of the sites visit the other sites to staff the residents and fellows and participate in conferences. "It gives all of us a chance to participate in patient care and training at the other sites," notes Dr Sorenson. Mayo's residents are required to take a two-month comprehensive neurophysiology course. A monthly teleconference for complex case presentations provides another opportunity for cross-site training and collaboration.

In addition, Dr Ross points out, "our technicians are also mostly Mayo trained. They're very dedicated, experienced, and conscientious. Their outstanding work makes our work much easier." Dr Rubin adds, "The depth of experience and training of the technicians across Mayo allows for the high quality of the studies we perform."

Referrals for autonomic, EMG, EEG, and outpatient evoked potentials come from many sources beyond neurology practice. Increasing demand has been met with improved efficiency at all three sites.



Figure. Tests rarely performed at other institutions, like single-fiber EMG, are done daily by Mayo Clinic electromyographers.

Research Highlights

PET-CT in Paraneoplastic Neurologic Disorders

Published online in *Archives of Neurology*, this Mayo Clinic study found that in paraneoplastic neurologic disorders, PET-CT improves the detection of cancers when other screening test results are negative, particularly in the clinical setting of seropositivity for a neuronal nuclear or cytoplasmic autoantibody marker of cancer. Authors: A. McKeon, M. Apiwattanakul, D. Lachance, V. Lennon, J. Mandrekar, B. Boeve, B. Mullan, B. Mokri, J. Britton, D. Drubach, and S. Pittock.

Physical Exercise, Aging, and Mild Cognitive Impairment

In this Mayo Clinic population-based case-control study, any frequency of moderate exercise performed in midlife or late life was associated with a reduced odds of having mild cognitive impairment. This study was published in the January 2010 issue of *Archives of Neurology*. Authors: Y. Geda, R. Roberts, D. Knopman, T. Christianson, V. Pankratz, R. Ivnik, B. Boeve, E. Tangalos, R. Petersen, and W. Rocca.

Mild Cognitive Impairment: 10 Years Later

Ten years ago, Mayo Clinic investigators published a seminal paper on mild cognitive impairment. Since then, thousands of papers have appeared in the medical literature focusing on this early stage of cognitive disorders. Mayo Clinic investigators authored a review paper in the December 2009 issue of *Archives of Neurology* summarizing both the progress that has been made in the field of mild cognitive impairment and the challenges that remain. Authors: R. Petersen, R. Roberts, D. Knopman, B. Boeve, Y. Geda, R. Ivnik, G. Smith, and C. Jack.

New Technique to Pinpoint Seizure Location and Improve Surgical Outcomes

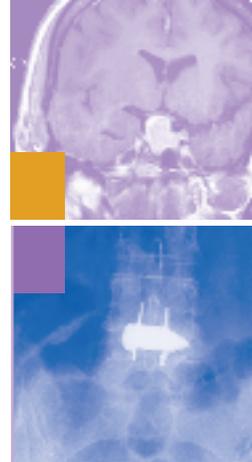
Mayo Clinic researchers have developed a new technique known as STATISCOM to identify seizure origins in the brain. The increased accuracy of STATISCOM over the SISCOM technique, used previously, improves surgical accuracy and increases probability of seizure freedom for patients with epilepsy. The new technique was described in the January 5, 2010, issue of *Neurology*. Authors: N. Kazemi, G. Worrell, S. Stead, B. Brinkmann, B. Mullan, T. O'Brien, and E. So.

First Comprehensive Report of Pork-Processing Plant Illness

The first complete report of Mayo Clinic physicians' initial assessment of pork-processing plant workers with a unique neurologic disorder was published in the January 2010 issue of *Lancet Neurology*. The report includes the detailed results of the diagnostic assessment and clinical care of these patients and a description of some of the scientific investigations performed to try to understand the nature of the illness, as well as Mayo Clinic's involvement with components of the public health investigation. Authors: D. Lachance, V. Lennon, S. Pittock, J. Tracy, K. Krecke, K. Amrami, E. Poeschla, R. Orenstein, B. Scheithauer, J. Sejvar, S. Holzbauer, A. DeVries, and P. Dyck.

Brain Waves Can "Write" on Computer in Early Tests

Neuroscientists at the Mayo Clinic campus in Jacksonville, Florida, have demonstrated how brain waves can be used to type alphanumeric characters on a computer screen. By merely focusing on the "q" in a matrix of letters, for example, that "q" appears on the monitor. Researchers say these findings, presented at the 2009 annual meeting of the American Epilepsy Society, represent concrete progress toward a mind-machine interface that may, one day, help people with various disorders control such devices as prosthetic arms and legs. Authors: J. Shih and D. Krusienski.



• To read more about Mayo Clinic neurosciences research and patient care, visit www.mayoclinic.org.

Advances in Seizure Prevention and Prediction



S. Matthew Stead, MD, PhD, Gregory A. Worrell, MD, PhD, and W. Richard Marsh, MD

The earlier seizure activity is detected, the better the chance of preventing it. For several years, neurologists Gregory A. Worrell, MD, PhD, and S. Matthew Stead, MD, PhD, and their neurosurgical colleagues W. Richard Marsh, MD, and Frederic B. Meyer, MD, at Mayo Clinic in

Rochester, Minnesota, have been working to pinpoint the exact moment and the precise location of seizure generation.

Isolating the Where and When of Microseizures

Two years ago, using microelectrodes 40 microns in diameter, or thinner than a human hair, the research team began recording EEG activity from brain regions the size of cortical columns at frequencies beyond the upper and lower limits of standard EEG recordings. Cortical columns, the smallest functional unit in the cortex, are approxi-

mately 300 microns across and contain from 1,000 to 7,500 neurons. In perspective, a typical EEG electrode captures the activity of millions of neurons and hundreds of cortical columns (Figure).

This research revealed that isolated brain regions the size of cortical columns do, indeed, show evidence of seizure activity (microseizures) in humans. The investigators found that microseizures occurred most often in patients with epilepsy but also occurred, although rarely, in control patients without epilepsy. This latter finding demonstrates that pathologic oscillations can occur even in people who do not have epilepsy.

How do microseizures transition to clinical seizures in patients with epilepsy? The findings of Drs Stead and Worrell support the hypothesis that in patients with epilepsy, individual microdomains the size of cortical columns generate frequent hypersynchronous discharges, which recruit other columns of neurons. Similar, noncolumnar groupings of neurons have been identified in the rat hippocampus by Anatol Bragin and colleagues at UCLA, and are known as pathologically interconnected neuron (PIN) clusters. These PIN clusters can be considered microdomains of epileptogenesis

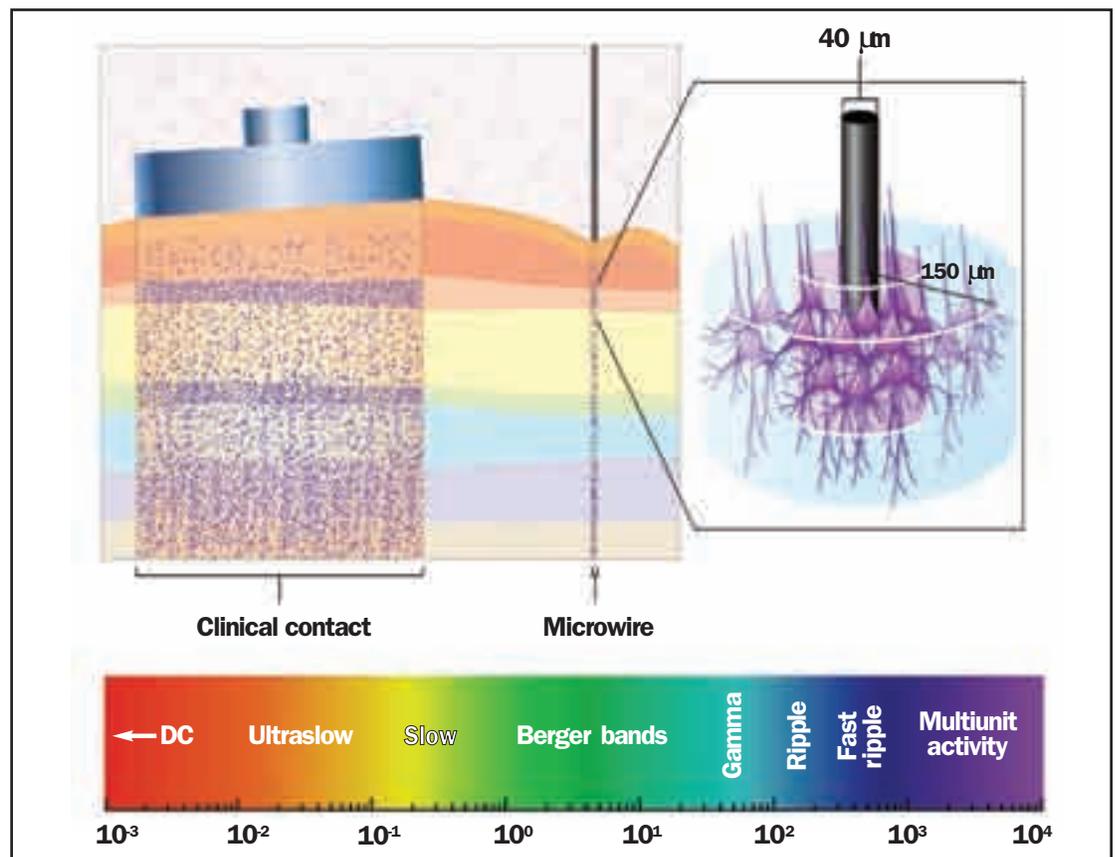


Figure. Top, The large volume sampled by the millimeter-scale clinical electrode ($\sim 10^6$ neurons) versus a 0.04-mm microwire. The cortex is organized into columns of neuronal clusters about 0.03 to 0.6 mm in diameter (cortical columns, $\sim 7,500$ neurons). Bottom, The frequency range of neuronal network oscillations.

or seizure initiation. When a critical volume of microdomain activity is reached, a large-scale seizure is generated. This explanation is sometimes referred to as the *sick column hypothesis*.

Clinical EEG recordings do not probe the spatial and temporal scales of microdomain activity, which makes early detection difficult. This hypothesis may explain why some patients do not respond to first-generation responsive stimulation devices designed to abort seizures.

Update on Implanted Devices to Detect and Abort Epileptic Seizures

Two new implantable epilepsy devices that use electrical stimulation are undergoing multicenter trials for treatment of medically refractory epilepsy. One device uses electrical stimulation of the anterior nucleus of the thalamus to modulate the brain activity and prevent seizures (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy Trial; Medtronic Inc, Minneapolis, Minnesota). Another device under investigation is the responsive neurostimulator system (RNS; NeuroPace, Inc, Mountain View, California). The initial results from these two pivotal multicenter trials have demonstrated evidence for reducing seizure frequency in patients with medically intractable partial epilepsy. Importantly, each of these trials investigating implantable devices has shown good safety.

Predicting Seizures: Devices on the Horizon

Not knowing when a seizure will occur is one of

the most debilitating aspects of epilepsy. As Dr Worrell notes, "Patients may only have four or five seizures a month, each lasting a few minutes. But those few minutes mean they can't drive, and they may be afraid to go out in public for fear of having a seizure. These effects can lead to social isolation."

The recent discovery that seizure-like events can occur in pathologic microdomains (ie, microseizures) in humans adds to a growing body of evidence that seizures may begin before they are evident clinically. In the future, devices may be able to provide patients with warnings that a seizure is about to occur or, possibly, to prevent a seizure.

Dr Marsh, a neurosurgeon who performs epilepsy surgery and stimulator implantation, points out that after the safety of a device is determined, the question of its efficacy and clinical benefit rests on the length of time between seizure warning and seizure onset. Dr Stead adds that if that period is reasonable (neither too long nor too short), fast-acting drugs or neurostimulation could be triggered to prevent seizures.

Future Applications

The future of seizure prevention rests on understanding the mechanisms underlying seizure generation. As knowledge in these areas advances, future clinical applications include improvements in epilepsy surgery, improvements in the devices delivering neurostimulation, and the possible development of algorithms that identify periods of increased probability of seizures.

Neuro-oncology at Mayo Clinic in Arizona: Collaboration and Continuity of Care

Collaboration and continuity of care are two aspects of the neuro-oncology practice at Mayo Clinic in Scottsdale, Arizona, that Alyx B. Porter, MD, particularly appreciates. Her work is supported by a team of neurosurgeons, neuroradiologists, radiation oncologists, medical oncologists, neuropathologists, and rehabilitation specialists. Together, they manage the spectrum of confirmed and suspected brain cancers—from glioblastomas to undiagnosed abnormalities found on MRI.

Their collaboration extends beyond neurologic specialties. Dr Porter and the team work closely with endocrinologists in treating pituitary adenomas and with otolaryngologists in treating acoustic neuromas. They also work with the division of medical oncology in managing neurologic symptoms (eg, seizures, numbness, weakness, cognitive impairment) that result from systemic

cancers or their treatment. As Dr Porter explains, "If the community oncologist has a patient who develops neurologic symptoms apart from pain, we can manage the neurologic diagnosis and provide treatment options." Supporting these efforts are rehabilitation specialists. Occupational and physical therapy, speech-language pathologic treatment, and neuropsychological therapy are offered in Mayo's inpatient and outpatient rehabilitation facilities.

Continuity of Care Within and Across Mayo's Sites

Many patients come to Arizona in the winter months. For patients seen at either of Mayo's other two campuses, in Rochester, Minnesota, and Jacksonville, Florida, the unified medical record and close relationship between Mayo's



Alyx B. Porter, MD

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neuro-oncology division members translate into uninterrupted care.

Neuro-oncology patients can be seen in an expedited time line. At all three Mayo Clinic locations, neurosurgery, neuro-oncology, and radiation therapy are housed in the same building, which facilitates face-to-face consultation among team members.

National Clinical Cancer Trials at Mayo Clinic in Arizona

Mayo Clinic in Arizona is part of Mayo's National Cancer Institute (NCI)-funded Cancer Center and the Mayo-led North Central Cancer Treatment Group, a cooperative clinical research group that helps develop and expedite high-priority NCI-funded trials. Cancer treatment trials generated through these sources are conducted at all three Mayo Clinic sites.

Many of the new chemotherapy drugs, including the immune-based therapies for glioblastomas, are combined with radiation therapy. Radiation oncology researchers at Mayo are continuously developing new protocols to complement advances in chemotherapy.

Currently, four clinical trials for glioblastoma are being conducted at Mayo Clinic, each testing novel drug combinations developed at Mayo (see *NeurosciencesUpdate*, Volume 6, No. 3, for information on development, targets, and mechanisms). Two trials are for patients with newly diagnosed glioblastoma and two are for patients with recurrent glioblastoma. In addition, there is a phase 3 trial that is testing the effects of memantine hydrochloride (Namenda; Forest Pharmaceuticals Inc, New York, New York) in counteracting cognitive dysfunction after whole-brain radiation therapy.

As Joon H. Uhm, MD, a neuro-oncologist at Mayo Clinic in Rochester, says, "The dictum 'one cancer center, three front doors' is a very apt description of Mayo's cancer treatment and research integration."

Dr Porter adds that neuro-oncology on Mayo's Arizona campus provides patients with an interdisciplinary team approach that takes full advantage of all the clinical and research resources provided throughout Mayo. No effort is spared to translate those considerable resources into focused, patient-centered care.



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While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

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