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Inside This Issue

Craniofacial Resection for Skull Base Tumors

Richard S. Zimmerman, MD

The symptoms of anterior skull base tumors are often subtle. Most patients experience reduced sense of smell and feel a constant stuffiness in the nose. Some may have nosebleeds. Frontal lobe signs may be present but unrecognized. Patients may tolerate their symptoms for a considerable length of time before seeking medical care. In most cases, an endoscopic examination by an otorhinolaryngologist for suspected rhinitis or polyps reveals the tumor. If so, a biopsy can usually be performed in the physician's office. Tumors may be benign (schwannomas, meningiomas) or malignant. The most common causes of malignant skull base tumors are esthesioneuroblastoma, neuroendocrine carcinoma, sinonasal melanoma, sinonasal undifferentiated tumor (SNUC), and squamous cell carcinoma.

Because skull base tumors can involve the nose and nasal passages and can invade and compress the brain (Figure), they are best managed through a coordinated team approach. As Richard S. Zimmerman, MD, a neurosurgeon at Mayo Clinic Arizona, explains, "The reason that treatment must be highly integrated is that no one specialty crosses all the domains involved before, during, or after surgery."

Across Mayo Clinic's 3 campuses, the surgical teams always include a neurosurgeon and an otorhinolaryngologist. Depending on the case, an ophthalmologist and plastic surgeon also may be involved. When tumors cannot be fully removed by traditional surgery, stereotactic radiosurgery can be part of a staged approach. Neuroradiology is also integral. "We work hand in hand with neuroradiologists," says Ronald Reimer, MD, a neurosurgeon at Mayo Clinic Jacksonville. "They help in preoperative assessment of tumor burden, may perform embolization to lessen surgical blood loss, and help with intraoperative and postoperative MRI to ascertain degree of tumor resection." He adds, "Medical subspecialties help perioperatively as well. In patients with cancer, the oncologist and radiotherapist need to stage the patient and make sure no extensive tumor burden is present elsewhere in the body." Patients with malignant skull base tumors require lifelong follow-up, with imaging and endoscopic examinations approximately every 6 months.

At Mayo Clinic, surgical resection for skull base tumors typically involves a frontal craniotomy and a lateral rhinotomy. Sometimes neck dissection is necessary to remove involved lymph

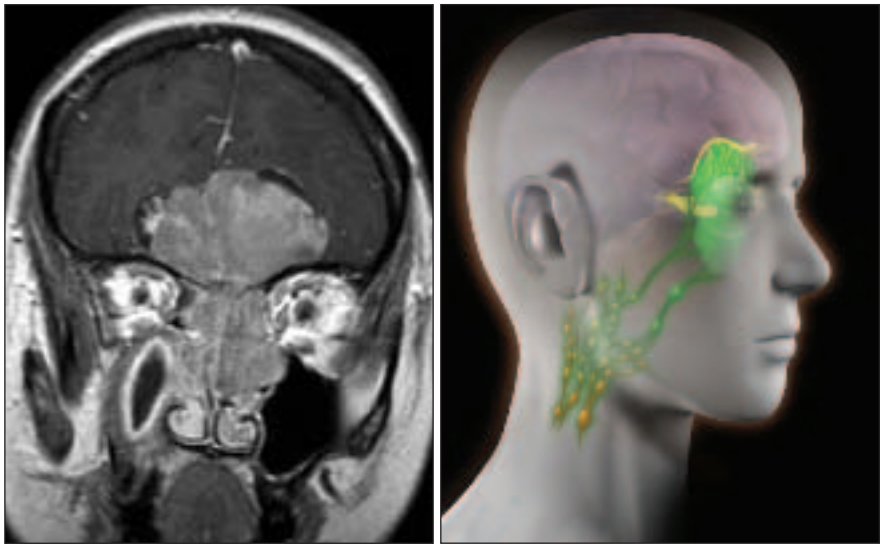

Figure. Esthesioneuroblastoma stage 4 tumor.

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nodes. "There is a trend to remove the tumor endoscopically," says Michael J. Link, MD, a neurosurgeon at Mayo Clinic Rochester. "At Mayo, we don't often prescribe endoscopic tumor removal because, while taking the tumor out can be fairly straightforward, the big issue is getting a good repair to prevent CSF leak and other potential problems. It may seem horrific to operate through the face, but in most patients, the scar is almost invisible in 3 months. The incision does not require a special type of closure and it heals well." Congenital deformities, trauma associated with facial fracture, encephalocele, and CSF leak are other conditions that, like anterior skull base tumors, may require craniofacial resection. "The multispecialty practice at Mayo Clinic is designed to function optimally for these patients," notes Dr Zimmerman. "Patients benefit not only from the integrated medical record but from systems and procedures that encourage communication across subspecialties and streamline the necessary detailed cross-specialty planning and collaboration. We have a system that allows the physicians involved to make their calendars available for planning and performing the primary procedure and also for any complications that may arise afterwards. It is a completely patient-centered approach."

Michael J. Link, MD

Surgical Management of Acromegaly

Acromegaly can distort physical appearance but is also life-threatening. Left untreated, it increases the risk of risk cardiovascular disease, diabetes, high blood pressure, lung disease, and colon cancer. In addition, the mass effect of large pituitary tumors can put pressure on optic nerves and cause loss of vision.

In approximately 99% of patients with acromegaly, the disease is caused by a growth hormone (GH)–producing pituitary adenoma (Figure 1). In the other 1%, the tumor is located elsewhere (eg, lungs, pancreas, or adrenal glands). Excess GH secreted in the bloodstream triggers the liver to produce insulin-like growth factor 1 (IGF-1), which stimulates growth of bones and soft tissue.

In adults who have reached their full height, the symptoms may occur gradually and remain unnoticed until the disease has progressed. Symptoms include enlargement of the jaw, forehead, hands, and feet as well as the tongue and other soft tissue. In children, because the skeleton is not yet fused, abnormal GH production also affects linear growth. The condition is referred to as gigantism, and accelerated linear growth often precedes weight gain in these children.

Physical changes are not the only route to diagnosis. Pituitary tumors may be discovered in patients with headaches or visual problems before external changes are evident. Diagnosis is made by an endocrinologist through imaging studies and a blood test for biochemical confirmation. The general appointment desk at Mayo Clinic automatically refers all patients with suspected pituitary disorders to a pituitary specialist in endocrinology who manages the case. From there, patients with tumors are sent for a neurosurgical consultation and to ophthalmology if the tumor is affecting vision.

A Multispecialty Team Approach to Treatment

"The overall treatment goals are to achieve normal GH and IGF-1," says Todd B. Nippoldt, MD,

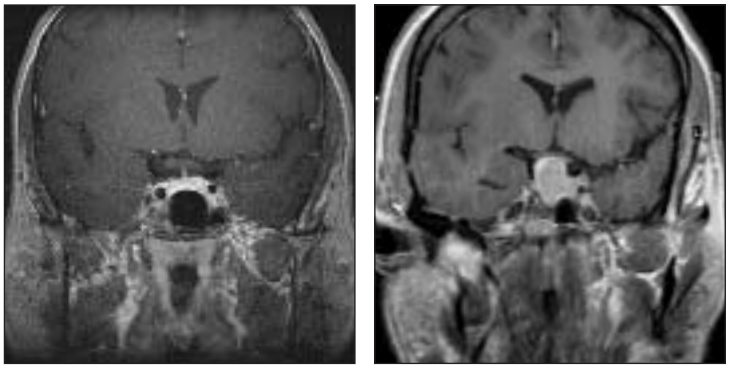

Figure 1. Left, MRI scan of normal pituitary gland. Right, MRI scan of pituitary macroadenoma with suprasellar extension.

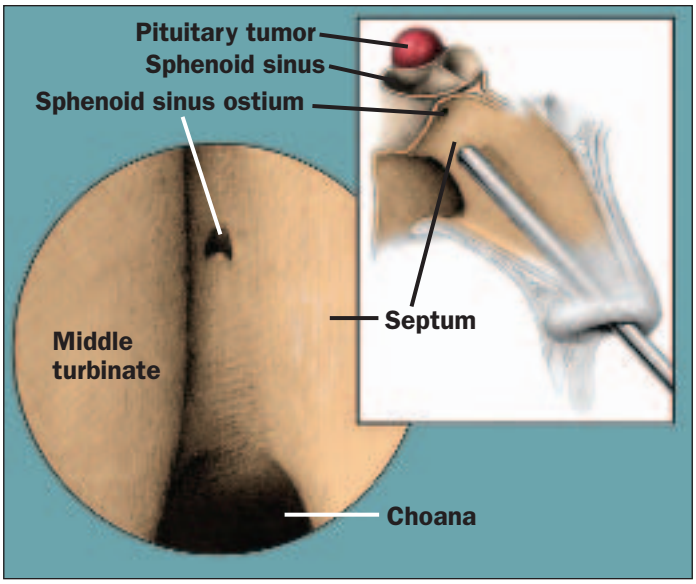

Figure 2. Illustration of the transnasal surgical approach.

in the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic Rochester. John Atkinson, MD, a Mayo Clinic neurosurgeon, adds, "The question in each case is how best to get the tumor under control. It may be through surgical resection, radiotherapy, stereotactic radiosurgery, medical therapy, or some combination. This is a complex disease that overlaps many subspecialties and absolutely requires a team approach."

At Mayo Clinic, the team includes physicians from endocrinology, neurosurgery, radiology, anesthesiology, radiosurgery, otorhinolaryngology, and ophthalmology. A pituitary specialist in endocrinology is always the team leader.

Surgical Resection

Unless surgery poses risks for the patient, tumor resection is considered the first-line treatment. Medical therapies are available—those that block and those that suppress GH. However, they are expensive and do not affect the tumor itself. They may be used in conjunction with staged surgery for large tumors.

Transsphenoidal surgical resection can rapidly normalize GH levels in approximately 65% of patients with acromegaly. More than 120 such procedures are performed each year at Mayo Clinic Rochester. Surgical issues particular to acromegaly must be considered. For example, intubation and maintaining the airway can be difficult in patients with enlarged tongues and thickened oral airways. Mayo Clinic anesthesiologists typically use a fiberoptic endoscope as they intubate the patient, and they keep the airway open for longer than usual after surgery.

At Mayo, the transsphenoidal surgery to resect the tumor is performed by an otorhinolaryngologist and a neurosurgeon. Since the late 1990s, they have used a transnasal endoscopic approach (Figure 2), which shortens operating time, reduces postoperative discomfort, and is as effective as transseptal or sublabial endoscopic approaches (see *Mayo Clinic Proceedings* 1999;74:661-670). The surgeons typically use the nasal endoscope only for access to the sella turcica. An operating microscope is used for tumor removal. This approach has the additional advantages of endoscopic visualization and eliminating the need for an external incision and postoperative nasal packing.

In this procedure, the diameter of the working channel to the sella turcica is reduced by 50% and the view of the sella is 10˚ off center. These limitations are best managed in a large-volume pituitary practice in which experience enhances expertise.

Stereotactic Radiosurgery

The advantage of radiosurgery is highly focused delivery to the tumor with little radiation exposure to surrounding tissue. With nearly 4,000 patients treated to date, Mayo Clinic has one of the busiest radiosurgery practices in the world, successfully treating about 95% of pituitary adenomas. Recent acquisition of the new Leksell Gamma Knife Perfexion is expected to increase accuracy and precision in radiation delivery, to improve patient comfort, and to reduce treatment time by as much as 40% to 60%.

Radiosurgery may be an adjunct or alternative to surgical resection in selected patients. Patients with macroadenomas and considerable suprasellar extension usually are not considered good candidates. In patients with large tumors that extend into the cavernous sinus and are not fully removed by surgery, radiosurgery can be part of a staged approach. The tumor can initially be debulked, separating its superior surface from the optic nerves. Radiosurgery can then address the remaining tumor with little risk to cranial nerves.

Todd B. Nippoldt, MD, and John Atkinson, MD

Since 1990, 221 patients have undergone stereotactic radiosurgery for pituitary adenomas at Mayo

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Clinic Rochester. Of these patients, 90% had prior surgery, and 80% had tumors extending into the cavernous sinus. Radiosurgery stops tumor growth but is slow to reduce excess GH production. "We often use medical therapy while waiting for the effects of radiosurgery to work," explains Dr Nippoldt. Biochemical remission with radiosurgery is 3 times more likely in patients whose IGF-1 levels are less than 2.25 times the upper limit of normal. Biochemical remission, defined as a fasting GH level less than 2 ng/mL and normal IGF-1 adjusted for age and sex without suppressive medication, has occurred in approximately 80% to 90% of properly selected patients with acromegaly at Mayo Clinic. As Dr Nippoldt notes, biochemical remission is adversely affected by taking pituitary suppressive drugs before radiosurgery so patients are advised to discontinue these medications 8 weeks before the procedure.

Normalizing GH secretion in acromegaly can reduce swelling in soft tissue, but it cannot effect changes in the bone and general appearance. It can, however, improve mortality and prevent further organ damage.

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Chronic Neuropathic Pain: Management Through Neurostimulation

Mayo Clinic offers numerous approaches to managing chronic pain (Table). Refractory neuropathic pain, one of the most intractable and difficult types of pain to treat, often can be reduced or alleviated through neuromodulation or stimulation techniques. Most prominent among them is spinal cord stimulation (SCS), previously called dorsal column stimulation. The goal of SCS and other stimulation techniques for pain such as peripheral nerve stimulation (PNS) is to cover the affected area with pleasant paresthesias (often experienced as light tingling or buzzing). SCS is most commonly used to treat lower extremity pain from spinal pathology such as recurrent disk herniation or failed back surgery syndrome. Other indications include upper extremity neuropathic pain, phantom limb pain, arachnoiditis, and complex regional pain syndromes I and II.

The American College of Cardiology/American Heart Association now recommends SCS as a treatment for inoperable, stable angina due to ischemia. Mayo Clinic Rochester has had extensive experience with this procedure and was part of a clinical trial testing the use of SCS for angina. Mayo Clinic Arizona is currently participating in a similar clinical trial. Other new applications of stimulation techniques include treatment of headache, head pain, facial pain, pelvic pain, and, more recently, SCS for low back or axial pain. Mayo Clinic Jacksonville was among the first in the nation to use SCS for visceral pain.

Marc A. Huntoon, MD

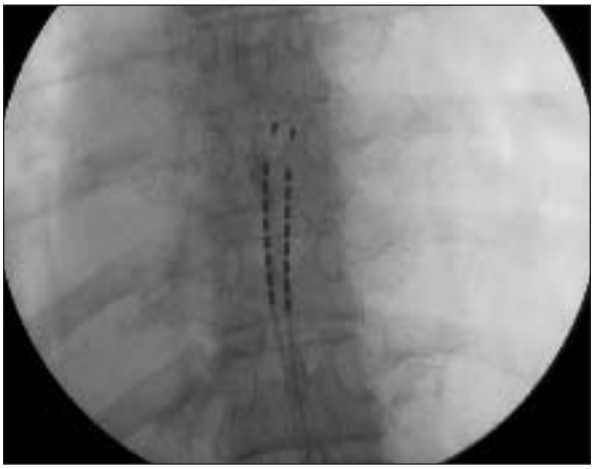

Figure. A dual-lead spinal cord stimulation system.

Implantation

SCS implantation is an outpatient surgical procedure. Leads (wires) with metallic contact points (electrodes) are positioned in the appropriate epidural space. The electrodes create an electrical field adjacent to the spinal cord that produces the pleasant paresthesias experienced by the patient. The leads are powered by current from a battery-driven implantable pulse generator (IPG). The IPG is connected to the leads by a thin wire. A remote, handheld programmer allows the patient to control the rate and intensity of the pulses.

Placement of the leads and the IPG depends on the source of the pain and the area affected. In PNS, percutaneous leads are implanted near the affected nerve. In SCS, leads are placed in the epidural space near the spinal cord. The leads may be cylindrical or paddle shaped. The advantage of percutaneous leads is that they can be placed with a minimally invasive procedure. The disadvantage is that they may migrate over time and need to be


Terrence L. Trentman, MD

repositioned. Paddle leads in the epidural space are more stable but require a minilaminectomy. Bilateral lower extremity pain, more challenging to treat, may require 2 leads (Figure).

Mayo Clinic is also using tripolar stimulation, which enables deeper penetration of SCS without spreading stimulation to the peripheral nerve roots. As Marc A. Huntoon, MD, an anesthesiologist and head of the Pain Clinic at Mayo Clinic Rochester, notes, "Tripolar stimulation enables us to steer the charge. The technology to do that is improving all the time and is going to enhance treatment of lower back pain and possibly lower extremity pain as well. It's an alternative measure to treat patients with a mixed pain syndrome of both low back and leg pain."

The IPG is implanted in the lower abdomen or buttocks or under the clavicle, depending on where the leads are placed. Other sites that can be treated with PNS include the forehead for pain in the ophthalmic branch of the trigeminal nerve, the occipital region for controlling migraine and cluster headache, and other sites in the head and neck area, depending on the source of the pain.

Table. Approaches to Chronic Pain Offered at Mayo Clinic

- Acupuncture
- Behavioral pain therapies
- Chemical denervation
- Counseling
- Epidural therapies
- Implanted pumps
- Joint injections
- Medication management
- Nerve blocks
- Neuromodulation
- Physical therapy
- Radiofrequency ablation
- Peripheral nerve or spinal cord stimulation

Trial Run

At Mayo Clinic, all SCS candidates undergo a psychological evaluation before surgery. As Terrence L. Trentman, MD, an anesthesiologist and head of the Pain Clinic at Mayo Clinic Arizona explains, "Among our goals are determining whether the patient is cognitively competent to provide informed consent and run the stimulator and identifying undertreated psychological disorders such as depression or anxiety that may accompany long-term pain."

During insertion of the trial leads, the patient is lightly sedated, and an anesthesiologist inserts the leads percutaneously using fluoroscopic guidance. The stimulator is turned on, and the patient provides feedback about the pain coverage. The goal is to cover all of the patient's painful areas with pleasant paresthesias. The leads are then anchored to the skin, and the patient goes home with an external power source for the 3- to 7-day trial.

At the end of the trial, the patient's response is reviewed relative to pain level, improved sleep, increased activity, decreased use of pain medications, and satisfaction with exchanging pain for paresthesias. The standard threshold for permanent implantation is more than 50% improvement across all measures. A successful trial run is the best predictor of long-term success with SCS.

Recent Advances

Mechanical Improvements

Advances in stimulator technology now allow patients more individualized control. They can preprogram the device to turn on and off at a certain time of day and to vary the pattern of stimulation, choosing, for example, to stimulate the thigh while they are sitting or the calf while walking. Batteries generally last 2 to 5 years, depending on use. Long-life rechargeable batteries are also available, although they, too, eventually must be replaced.

Minimally Invasive Peripheral Nerve Stimulation

In 2007, Dr Huntoon pioneered a noninvasive trial technique for stimulating peripheral nerves so that placement percutaneously is possible. As he notes, "In the past, we had to dissect down to the nerve to place the stimulators next to it. This new method uses ultrasound to guide the needle and placement of the leads right next to the target nerve."

Outcomes

Approximately 50% to 70% of patients report at least 50% long-term relief with neuromodulation. As Dr Trentman notes, "Between 30% and 50% of patients get less than 50% relief. However, patients who have SCS have invariably been through many other treatments, so the success rate should be viewed accordingly."

Outcomes are optimized through a team approach. Salim M. Ghazi, MD, an anesthesiologist and head of the Pain Clinic at Mayo Clinic Jacksonville, emphasizes that, as is true of all forms of pain management, neurostimulation requires multispecialty coordination. He notes that the concept of teamwork is built into the name of their Independent Multidisciplinary Pain Clinic. Drs Huntoon and Trentman agree, stating that in neurostimulation, "surgical implantation is only 1 aspect of the picture. All patients need physical therapy and counseling before and after treatment."


Salim M. Ghazi, MD

High Spatial Resolution and Expanded Frequencies: The Search for Ictogenesis

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Gregory A. Worrell, MD, PhD

Understanding the where and when of seizure initiation, or ictogenesis, is as important to epilepsy research and patient care as discovering the why. A single neuron cannot have a seizure; a seizure requires populations of neurons firing in synchrony. The question asked by 2 Mayo Clinic neurologists is how many neurons does it take—what is the smallest anatomic unit that gives rise to a seizure? The smallest unit could translate into the earliest possible moment of detection, and that could be the key to seizure suppression.

Squire M. (Matt) Stead, MD, PhD, Gregory A. Worrell, MD, PhD, and W. Richard Marsh, MD

High Spatial Resolution: Microelectrodes and Microseizures

The smallest functional unit of the cortex is the cortical column. Identified in the 1950s by Vernon B. Mountcastle, cortical columns are stacked arrangements of cells, each dedicated to a specific function. Each column comprises approximately 1,000 to 7,500 neurons that serve as their own network. It is cortical columns that Squire M. (Matt) Stead, MD, PhD, and Gregory A. Worrell, MD, PhD, neurologists at Mayo Clinic Rochester, chose as the focus of their research into ictogenesis.

Cortical columns measure just 300 microns across. To understand how small that is, it is worth noting that the standard clinical intracranial EEG electrode records from an area approximately 20 mm square. Each EEG electrode captures the activity of millions of neurons and hundreds of cortical columns. Using microelectrodes just 40 microns in diameter, thinner than human hair, Drs Stead and Worrell are able to record brain activity in humans from individual cortical columns (Figure).

Their eureka moment came when they found evidence of seizure activity in a given column, while, as Dr Stead explains, "a millimeter away in any direction, in all the microelectrodes surrounding that column, it was quiet. There was no seizure activity." These "microseizures" were the first evidence that seizure activity occurs in the smallest unit of functional brain organization.

Microseizures are subclinical, and Drs Stead and Worrell have recorded them in the brains of people with and without epilepsy. Their hypothesis predicts that as a clinical seizure approaches, individual columns have more frequent seizures and recruit other columns of neurons. "The occasional synchronous oscillation within a column may be a normal phenomenon," explains Dr Stead, "but we might be looking at the basis of the seizure threshold. In people with epilepsy, whose seizure thresholds are lower, the frequency and density of these microseizures may be greater."

Another critical factor is timing. When do seizures start? "What we've found is that hours before a clinical seizure occurs, there is increased columnar activity," says Dr Worrell. "Capturing this increased activity may translate eventually into a brain stimulation device that could identify microseizure activity, long before a clinical seizure begins." The earlier seizure activity is detected and the more precise the location, the better the chances are to prevent or abort it.

Expanded Frequencies

Sometimes old ways persist. When brain waves were first recorded for clinical purposes, the frequency range was set at 1 to 70 Hz because those frequencies represented the mechanical and spatial limits of the recording pens. Today, despite the advent of computerized technology, clinical EEG recording frequencies remain at 1 to 70 Hz.

Drs Stead and Worrell theorized that ultraslow or extremely fast oscillations up to 1,000 Hz might be relevant to ictogenesis and designed their recording equipment accordingly. They have now demonstrated that both high- and low-frequency oscillations are clinically relevant signatures or biomarkers of the epileptogenic zone, the region surrounding the area from which seizures arise.

Implantation and EEG Analysis

W. Richard Marsh, MD, one of the neurosurgeons at Mayo Clinic Rochester who performs epilepsy surgery and stimulator implantation, explains that patients who are undergoing intracranial monitoring using depth electrodes are given the option of including microelectrodes for research purposes along with the standard leads. Recording from microelectrodes on the surface of the brain is under development. "The techniques for electrode

implantation are well established," Dr Marsh explains. "There's nothing innovative about it. The innovative part is the recording—both the frequencies recorded and the narrowness of the sites. There is substantial computational power behind the analysis because of the tremendous volume of data—terabytes of data—beyond the human capacity to analyze. The research team has developed programs to make sense of it."

From Theory to Practice

The Next Generation of EEG Machines

Drs Stead, Worrell, and colleagues have been awarded a Mayo Discovery Translational grant. Combined with funding from the Epilepsy Foundation of America, it will be used to build the first prototype of a new multiscale EEG machine—the next-generation EEG recording system. The new system will improve sensitivity through increased spatial sampling (microelectrode arrays) and wide frequency bandwidth recording.

Pinpointing the Epileptogenic Zone

Microseizure recording might also aid in a more precise delineation of the epileptogenic zone. It is standard practice during epilepsy surgery to remove the epileptogenic zone. Identifying columnar seizure activity may more precisely establish and individualize its margins.

Implantable Devices

Dr Worrell notes, "This work is motivated by the fact that many patients with epilepsy do not have successful treatment and require surgery or an implantable stimulation device." Patients with intractable epilepsy might only have 4 or 5 seizures a month, each lasting a minute or so. But, as he explains, "those 4 minutes mean they can't drive, can't swim, and may be afraid to go out in public for fear of becoming unconscious or incontinent and could even end up socially isolated. The importance of those 4 minutes is their unpredictability."

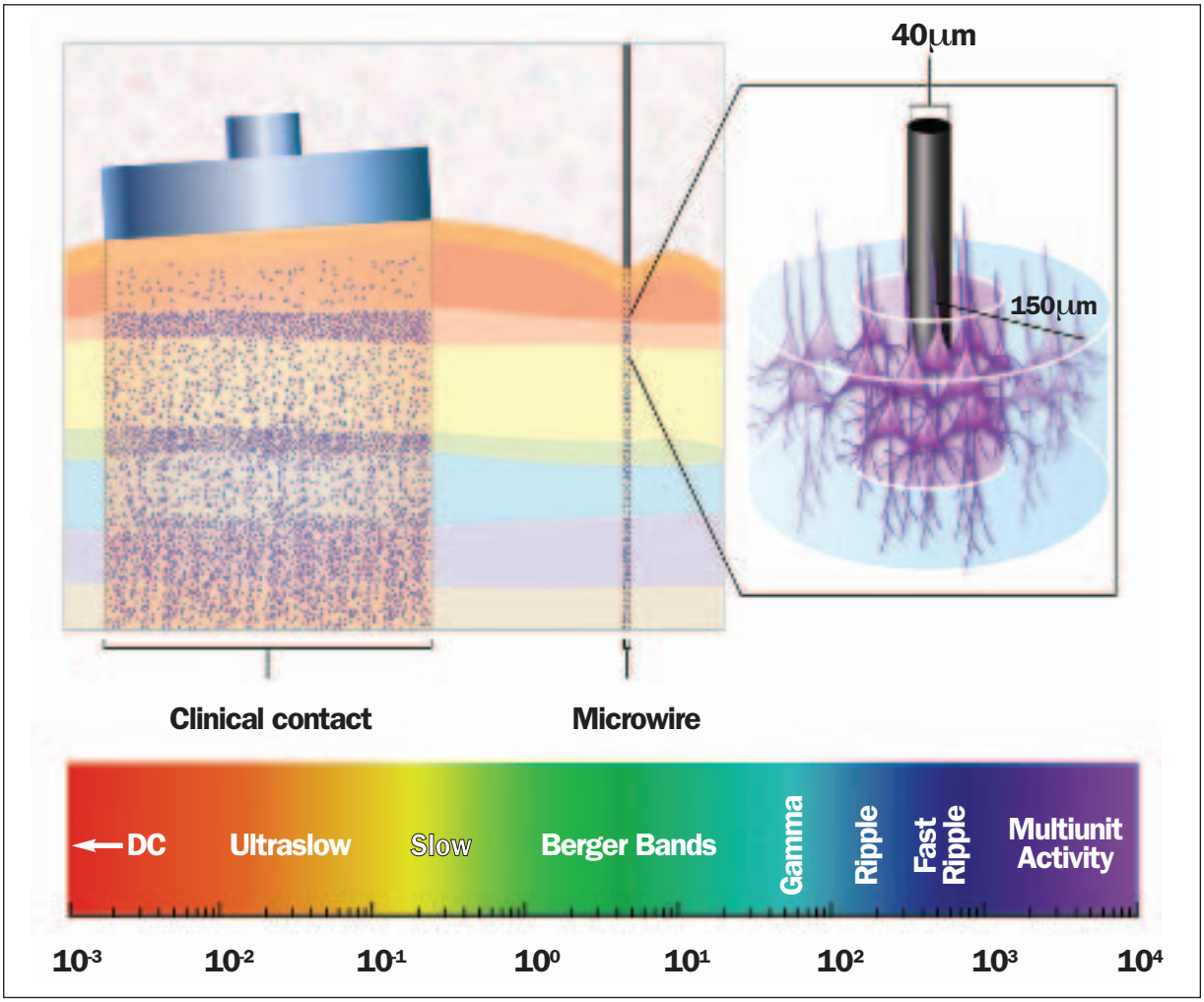

Figure. Top, The large volume sampled by the millimeter scale clinical electrode (~10^6 neurons) versus a 0.04-mm microwire. The cortex is organized into columns of neuronal clusters, about 0.03 to 0.6 mm in diameter (cortical columns: ~7,500 neurons). Bottom, The frequency range of neuronal network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

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Neurosciences Update

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Because microseizures may occur hours before a clinical seizure in patients with epilepsy, a possible application of this research is an implantable device that would detect subclinical microseizure activity and use continuous feedback stimulation to prevent microseizures from turning into large-scale clinical seizures. Another advantage would be the ability to alert patients not only of seizure onset but also of periods when they will be seizure free.

Microrecording sites and broader recording frequencies are improving understanding of the where and when of ictogenesis. "If the hypothesis that seizures in patients with epilepsy stem from cortical columns proves true, the practical applications will follow," says Dr Marsh.

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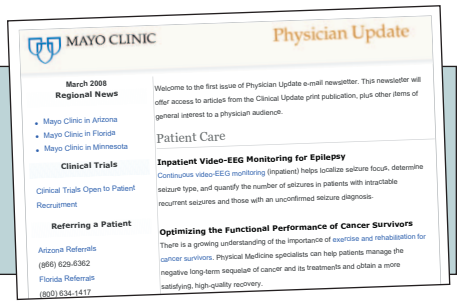
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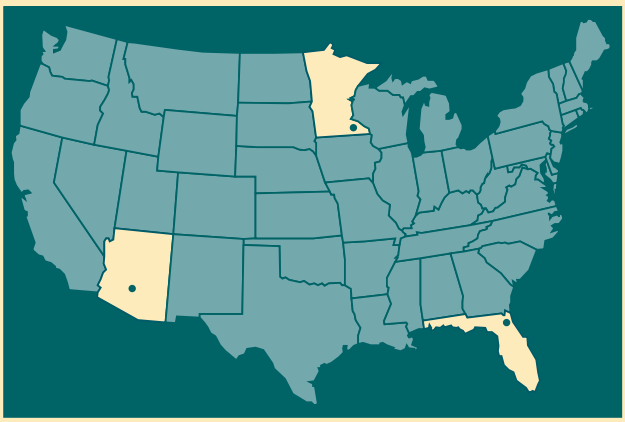
Inpatient Video-EEG Monitoring for Epilepsy
Continuous video-EEG monitoring (inpatient) helps localize seizure focus, determine seizure type, and quantify the number of seizures in patients with intractable recurrent seizures and those with an unconfirmed seizure diagnosis.
Optimizing the Functional Performance of Cancer Survivors
There is a growing understanding of the importance of exercise and rehabilitation for cancer survivors. Physical Medicine specialists can help patients manage the negative long-term sequelae of cancer and its treatments and obtain a more satisfying, high-quality recovery.

Expedited Patient Referrals to Mayo Clinic Departments of Neurology and Neurologic Surgery

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

1. **Cerebral aneurysms**
2. **Cerebral or spinal arteriovenous malformations**
3. **Brain, spinal cord, or peripheral nerve tumors**
4. **Epilepsy with indications for surgery**
5. **Carotid disease**



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