REVIEW ARTICLE

SURGERY FOR SEIZURES

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Of the approximately 2 million Americans with a diagnosis of epilepsy who are treated with antiepileptic drugs, 20 percent continue to have seizures; this group of patients accounts for over 75 percent of the cost of epilepsy in the United States. For many of those with medically refractory epilepsy, their disability can be completely eliminated by surgical intervention. Only a small percentage of potential surgical candidates, however, are currently referred to epilepsy-surgery centers.

Overview

The classic 1886 paper of Victor Horsley heralded the modern era of epilepsy surgery, and the introduction of electroencephalography (EEG) in the first half of this century provided a practical means for localizing epileptogenic abnormalities for resection. Nevertheless, only a handful of epilepsy-surgery centers were created, treating relatively few patients — and only one book on the subject appeared — before 1986, when a series of international conferences and textbooks began to reflect an explosion of interest in the field. By 1992, over 100 epilepsy-surgery centers throughout the world offered a wide selection of surgical procedures (Table 1) to an increasing number of patients, ranging from infants to senior citizens, for the treatment of disabling partial, and even generalized, seizures refractory to medical therapy.

Modern epilepsy surgery, like heart-transplant surgery, requires a multidisciplinary team of highly trained and experienced specialists working together in an epilepsy center. A variety of surgical interventions are now performed, usually with the patient under general anesthesia, according to the location and nature of the epileptogenic abnormality. The majority of procedures require only a few hours in the operating room and a few days of postoperative hospital care. The most common surgery consists of removal of the amygdala and anterior part of the hippocampus and entorhinal cortex, as well as a small portion of the temporal pole, leaving the lateral temporal neocortex intact. New techniques for hemispherectomy and multilobar resection involve the partial removal and partial disconnection of affected tissue; these and related techniques are designed to reduce movement of the remaining portions of the brain within the cranial vault and to ensure resorption of cerebrospinal fluid. Corpuscallosotomies now usually involve only the anterior two thirds of the corpus callosum unless the patient has severe retardation. For some localized cortical resections, however, intraoperative testing may be necessary, which prolongs the operation and occasionally requires the patient to be briefly awakened from anesthesia. New techniques for treating epileptogenic regions within primary cortical areas, such as those controlling language and motor function, include the removal of a discrete lesion without disturbing the adjacent cortex (lesionectomy) and multiple subpial transections, which sever intracortical connections in a way that prevents the spread of epilepsy and still preserves the columnar structure necessary to maintain normal cortical function.

The current resurgence of interest in surgery for epilepsy can be attributed largely to technical advances in video EEG monitoring and neuroimaging, improvements in surgical technique, and a better understanding of the anatomical and pathophysiologic bases of the symptomatic epilepsies. Another factor is the correction of a variety of misconceptions that have discouraged primary care physicians from referring patients for surgery in the past. Finally, a clearer delineation of the natural history of certain catastrophic epileptic disorders of infants and young children and a new understanding of the plasticity of the developing brain and the damage that seizures do to it, as well as the improvements in diagnostic and surgical technique, have created a major new field, pediatric epilepsy surgery.

Presurgical Evaluation

The optimal surgical intervention for epilepsy should destroy just enough neuronal tissue to eliminate seizures and no more. Therefore, the objective of presurgical evaluation is to identify the area of brain most responsible for generating habitual seizures and to demonstrate that it can be removed without causing additional unacceptable neurologic or cognitive deficits. There is no simple test to delineate the epileptogenic zone, defined as the volume of brain tissue necessary and sufficient for the generation of seizures. The boundaries of the epileptogenic zone can only be approximated by identifying areas of the brain marked by persistent dysfunction, both epileptic and nonepileptic. A variety of diagnostic tests are used for this purpose (Table 2), but there is no consensus on how much information is actually needed before a particular surgical intervention can be recommended. In most cases, presurgical evaluation involves tests that localize epileptic excitability with interictal EEG as well as long-term video EEG monitoring designed to capture and characterize ictal electrical activity and clinical symptoms; imaging studies, usually magnetic resonance imaging (MRI), that indicate structural

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abnormalities; tests for nonepileptic dysfunction, including positron-emission tomography to reveal areas of abnormal glucose use, single-photon-emission computed tomography to reveal areas of abnormal blood flow, and neuropsychological testing; and studies of normal cortical function to determine areas that must be preserved during surgery. This last category includes cortical mapping and intracarotid injection of amobarbital (the Wada test) to identify the language-dominant hemisphere and the laterality of memory function.

Diagnostic strategy is currently tailored to the specific surgical intervention to be used. For standardized temporal-lobe resections, the presurgical evaluation need only determine that habitual seizures are originating within the boundaries of the intended excision and that the structures of the contralateral mesial temporal lobe can support memory. For specific neocortical resections and multiple subpial cortical transections, more detailed investigation is required to identify the boundaries of the epileptogenic zone, as well as of adjacent areas of essential primary cortex. For hemispherectomies and large multilobar resections, the goal of the presurgical evaluation is to determine the extent of the functional and structural disturbance of the involved hemisphere and whether the contralateral hemisphere is reasonably intact. If section of the corpus callosum is contemplated, there must be a documented history of disabling drop attacks as the principal type of seizure; it is also important to determine that the patients are not candidates for a more definitive resection. Before lesionectomy is performed, it is necessary only to demonstrate that seizures are originating at the site of the structural lesion and that the lesion is in an essential cortical area that cannot be resected.

Long-term video EEG monitoring is generally per-

Table 1. Surgical Procedures Commonly Performed to Treat Epilepsy.*

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>NO. PERFORMED WORLDWIDE</th>
<th>INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior temporal lobectomy</td>
<td>2336</td>
<td>4682</td>
</tr>
<tr>
<td>Amygdalohippocampectomy</td>
<td>—</td>
<td>568</td>
</tr>
<tr>
<td>Neocortical resection</td>
<td>825</td>
<td>1073</td>
</tr>
<tr>
<td>Lesionectomy</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Multiple subpial transections</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hemispherectomy and large multilobar resections</td>
<td>88</td>
<td>448</td>
</tr>
<tr>
<td>Corpuscallosotomy</td>
<td>197</td>
<td>843</td>
</tr>
<tr>
<td>Total</td>
<td>3446</td>
<td>8234</td>
</tr>
</tbody>
</table>

*Data were obtained from Engel et al. Dashes indicate that no data are available.

Table 2. Diagnostic Tests Used in Evaluation for Surgery for Epilepsy.

Tests of epileptic excitability
Noninvasive EEG
Routine interictal EEG
Video EEG, long-term monitoring
Outpatient long-term monitoring
Invasive EEG
Intraoperative electrocorticography
Stereotactic-depth-electrode, long-term recording
Subdural grid or strip, long-term recording
Ictal single-photon-emission computed tomography
Intracranial and ictal magnetoencephalography*
Functional MRI*

Tests for structural abnormalities
X-ray films, computed tomography, and other radiographic studies
MRI
Magnetic resonance spectroscopy*

Tests of functional deficit
Interictal positron-emission tomography
Interictal single-photon-emission computed tomography
Neuropsychological batteries
Intracarotid amobarbital (the Wada test)
Intracranial EEG
Intracranial magnetoencephalography*
Magnetic resonance spectroscopy*

Tests of normal cortical function (cortical mapping)
Intraoperative electrocorticography
Extraoperative subdural-grid recording
Intracarotid amobarbital (the Wada test)
Positron-emission tomography*
Magnetoencephalography*
Functional MRI*

*Still considered experimental.
focal, dysplastic, cortical lesions in many patients previously given a diagnosis of cryptogenic neocortical epilepsy. Positron-emission tomography and MRI have also helped to identify localized, resectable, cortical abnormalities in infants and young children with cryptogenic forms of catastrophic secondary generalized epilepsy, such as infantile spasms, who otherwise would not have been considered for surgery. Presurgical evaluation may become cheaper because of new techniques for outpatient ictal EEG recording with digital home-monitoring systems, advances in the identification of ictal, as well as interictal, spike sources by magnetoencephalography, and the more widespread use of magnetic resonance spectroscopy and functional MRI.

### EARLY INTERVENTION

Timely identification of potential candidates for surgery has suffered from the imprecise definition of medically refractory epilepsy. In practice, most patients referred to epilepsy-surgery centers still have several seizures a month — and sometimes several a day — despite treatment with standard antiepileptic drugs, alone and in combination, at adequate doses. However, patients with disabling but infrequent seizures can also benefit greatly from surgery, as can those for whom a doctor’s insistence on yet another drug regimen only delays a definitive surgical procedure and creates a risk that irreversible psychosocial consequences of prolonged illness will develop. Surgical intervention need not be considered only as a last resort. There are surgically remediable syndromes (Fig. 1) — conditions with a known pathophysiology and natural history that have a poor prognosis with purely medical treatment, but that respond well to surgical treatment. Because patients with these conditions can be readily identified by noninvasive studies, and because these disorders can have progressive fea-

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**Figure 1. Surgically Remediable Epileptic Syndromes**

Important diagnostic features of three surgically remediable syndromes are shown. Mesial temporal-lobe epilepsy (top panel) is characterized on EEG by focal interictal sphenoidal spikes (small arrows) and ictal onset (large arrow). Unilateral hippocampal atrophy (arrow) is apparent on a T1-weighted coronal MRI. Axial positron-emission tomography (PET) reveals extensive unilateral temporal glucose hypometabolism (arrow).

In the middle panel, EEG in a 23-year-old woman with a low-grade glioma (a discrete neocortical lesion) in the right inferior temporal—occipital junction showed focal interictal spikes (small arrow) and ictal onset (large arrow) in the right posterior temporal area. The structural lesion is evident on a T2-weighted coronal MRI through the temporal—occipital junction (arrow). Functional MRI of the response to visual stimulation indicated that the lesion did not encroach on primary visual cortex (an axial image is shown).

In the bottom panel, EEG in a two-year-old child with catastrophic secondarily generalized seizures and unilateral seizures due to a left-sided hemimegalencephaly (diffuse hemispheric disturbance) revealed attenuation over the left hemisphere (lower channels), widespread interictal spikes most prominent on the left side (small arrows), and a variety of ictal discharges emanating from the left side (a tonic seizure is shown, beginning at the large arrow). The patient also had a markedly dysplastic left hemisphere on MRI (the right side of the T1-weighted axial image) and, on functional PET, profound hypometabolism of glucose in the left hemisphere (right side of axial image), but an apparently normal pattern of glucose metabolism in the right hemisphere (left side of image). Illustration by Lynne Olson from material provided by Drs. John Curran, John Mazziotta, Michael Phelps, Raman Sankar, and Arthur Toga.
tures, referral to an epilepsy-surgery center ought to be considered as soon as first-line antiepileptic medications fail to be effective. For most conditions, this means high-dose carbamazepine and phenytoin. Continued attempts to treat patients with second-line drugs, or combinations of drugs, may not be in the best interest of those with surgically remediable syndromes.

The prototype of a surgically remediable syndrome is mesial temporal-lobe epilepsy, which has a characteristic presentation and a specific pathophysiologic basis: hippocampal sclerosis (Table 3). This disorder is possibly the most common form of epilepsy and one of the most refractory to medical treatment. Seizures usually begin in the first decade of life and characteristically become intractable as early as adolescence. The risk of irreversible psychosocial consequences for patients with intractable seizures is great. Most patients with this condition, however, can be easily identified as likely candidates for surgery by anterior temporal interictal spikes on EEG, hippocampal atrophy on high-resolution MRI, and temporal-lobe hypometabolism noted on interictal positron-emission tomography. Ictal EEG, neuropsychological tests, and if necessary, ictal single-photon-emission computed tomography can confirm the diagnosis, and anterior mesial temporal-lobe resection offers a 70 to 80 percent chance of cure.

Patients with medically refractory partial seizures that are due to discrete structural lesions, such as glial tumors or congenital malformations, also have a surgically remediable syndrome. Caution should be exercised, however, because some structural lesions are not clinically important and others are part of a multifocal process in which another lesion that cannot be visualized is actually responsible for the epileptic condition. Consequently, surgical treatment should not be undertaken on the basis of structural imaging alone; confirmation of epileptogenicity is necessary, and this usually requires ictal EEG. Surgical outcomes in properly evaluated patients with discrete epileptogenic lesions are equivalent to those in patients treated for mesial temporal-lobe epilepsy.

Catastrophic seizures, either generalized or unilateral, in infants and young children can result from a number of brain disturbances that are confined to one, or part of one, hemisphere; these include hemimegalencephaly and other diffuse cortical dysplasias, Sturge–Weber syndrome, large porencephalic cysts, and the usually unilateral inflammatory process of Rasmussen’s encephalitis. Medically refractory seizures in these conditions often occur many times a day, are associated with profound developmental delay, and can be life-threatening. The pathologic region is easily identified with MRI or, in some cases, positron-emission tomography. Ictal EEG can demonstrate that the epileptogenic abnormalities are restricted to the structurally abnormal hemisphere, and both EEG and positron-emission tomography can be useful in confirming that the contralateral hemisphere is functionally intact. In these situations, hemispherectomy or a large multilobar resection can end habitual seizures and reverse the inevitable developmental delay. Because removal of the perihalamic area is usually considered only for patients who already have hemiparesis with a useless hand, this surgical procedure introduces no new motor deficit; in fact, function of the affected limbs often improves. Without surgery such children might be condemned to life in an institution, but with appropriate surgical intervention they have a 60 to 80 percent chance of living a nearly normal life.

Patients with secondary generalized epilepsy, such as the Lennox–Gastaut syndrome, have diffuse brain damage and often have disabling drop attacks that cause frequent severe injury. Antiepileptic drugs are usually ineffective against such seizures, and patients must therefore wear protective helmets and greatly limit their activities. If drop attacks are the most disabling type of seizure experienced by a patient with secondary generalized epilepsy, corpuscallosotomy should be considered. Corpuscallosotomy can completely end drop attacks for a large proportion of patients, but it is a palliative, not a curative, procedure; it is not likely to affect other types of seizures or to alter the mental retardation or other neurologic abnormalities usually associated with secondary generalized epilepsy. Nevertheless, the tremendous positive effect of this surgical intervention on the quality of life of patients with disabling drop attacks justifies regarding this condition as surgically remediable.

Advances in diagnostic technology and surgical procedures will undoubtedly result in the identification of more surgically remediable syndromes in the future.
instance, studies are under way to determine whether the progressive verbal agnosia that develops in children with the Landau–Kleffner syndrome, presumably due to cryptogenic epileptic activity involving language cortex, can be reversed by multiple subpial transection that eliminates epileptogenic activity in that area without introducing additional language disturbances.

Patients with medically refractory seizures who clearly do not have one of the surgically remediable syndromes mentioned here should be given more aggressive therapy with antiepileptic drugs, alone or in combination. They should not, however, be discounted as possible candidates for surgery, and at some point referral to an epilepsy-surgery center is appropriate. Although these patients often require prolonged and expensive invasive monitoring with depth electrodes or subdural electrodes, and although fewer than 50 percent of patients who do not have a surgically remediable syndrome become seizure-free postoperatively, most obtain some benefit. It is important to make sure that patients do not have a surgically remediable syndrome before delaying referral for surgery and proceeding with numerous, prolonged manipulations of medical therapy.

**Surgical Outcome**

Table 4 shows data on the results of surgical treatment for epileptic seizures, during the period 1986 to 1990, as obtained from an international survey of 100 epilepsy-surgery centers. These data do not fully reflect the success of current surgical techniques for two reasons: some reporting centers were in developing countries that did not have access to the most modern approaches, and results in general have improved considerably in the past five years. Although no comparable worldwide data on outcomes are available for surgical procedures performed since 1990, the results reported in the more recent literature from individual centers, as well as data presented at professional meetings, indicate steady progress. In attempting to gauge the cost-effectiveness of surgery, however, the translation of the successful elimination of seizures into psychosocial rehabilitation, elimination of disability, and improved quality of life becomes important. Although patients who no longer have seizures represent an important savings in direct costs for medical care, they may still remain dependent on family and the social-welfare system and have many indirect costs associated with their disability. Patients are most likely to be able to work and to live relatively normal, productive lives if surgical intervention takes place early in the course of their epileptic disorders.

Operative complications of surgery for epileptic seizures are rare and account for minimal disability. In localized resective surgery, less than 3 percent of patients have some postoperative neurologic deficit due to unintended vascular compromise or accidental damage to essential neural tissue; the great majority of these disturbances are transient and resolve within a period of months. Mesial temporal-lobe resections are often associated with defects in the contralateral superior quadrant of the visual field that are identifiable by formal testing but almost never noticed by patients themselves. Because memory function specific to the involved temporal lobe is usually depressed preoperatively, hippocampal resection is unlikely to introduce a new deficit, and in fact, often results in an improvement in memory function specific to the contralateral temporal lobe. However, anterior mesial temporal lobectomy in the dominant hemisphere of patients with normal memory will produce a deficit in verbal memory that could pose a problem for those who need to function at a high intellectual level. Functional mapping techniques, including the intracarotid amobarbital procedure, can be used to predict when surgical intervention is likely to cause further language, memory, or other neurologic disturbances and can enable surgical strategy to be altered in order to avoid unacceptable consequences. In some circumstances, however, new neurologic deficits are unavoidable and must be accepted by patient and physician as a tolerable trade-off before any surgery is undertaken.

Microsurgical techniques and other improvements in surgical methods have not only increased the safety and efficacy of routine surgical procedures for epileptic seizures, but also made even hemispherectomy and corpuscallosotomy more attractive alternatives. Modifications of hemispherectomy have almost eliminated the devastating delayed complications previously associated with the procedure. The ability to sever the corpus callosum without entering the third ventricle has greatly improved the early postoperative course of patients treated with that technique; section of only the anterior two thirds of the corpus callosum can avert the some-
but pharmacologic advances are unlikely to decrease the large number of potential candidates for surgery in the near future. Stimulation of the vagus nerve and the thalamus may reduce the frequency and severity of some forms of epileptic seizures, but these techniques remain experimental and the indications for their use are uncertain. The accurate identification of surgically remediable syndromes, the application of advanced diagnostic tools that eliminate the need for invasive monitoring, and the potential for early intervention already make safe and effective surgical treatment possible for a great many patients who now suffer from disabling epileptic seizures. Surgery for epilepsy, however, will be considered for only a relatively small proportion of the patients who could benefit from such treatment, unless it gains more widespread acceptance. We have a moral obligation to make this potentially curative therapy available to people disabled by epilepsy. To take a global perspective, 90 percent of the world's population lives in the developing countries; they bear the brunt of the overwhelming burden of epilepsy. Supporting and disseminating advances that make epilepsy surgery more cost effective not only will eventually help tens of thousands of patients in the United States, but also will aid millions of people in developing countries who need not suffer the consequences of medically refractory epileptic seizures.

REFERENCES