Epilepsy Surgery

American Epilepsy Society
I. EPILEPSY PRESURGICAL EVALUATION

A. WHEN TO CONSIDER EPILEPSY SURGERY

Evaluation for epilepsy surgery is appropriate for anyone with seizures that are focal in origin, are continuing to occur despite treatment with antiepileptic drugs (AEDs), and cause a significant impairment in quality of life. Although the exact number of medication trials must be individualized, initial consideration is reasonable after two monotherapy trials with first line AEDs, and possibly one trial with dual therapy (combination of two AEDs). Many studies have shown the benefits of epilepsy surgery for seizure control, psychiatric symptoms, and overall quality of life, especially for temporal lobe epilepsy, the most common type of epilepsy in adults. There is even evidence that successful epilepsy surgery may increase life expectancy (Sperling).
B. GENERAL PRINCIPLE

The goal of the presurgical evaluation is to determine if the patient has a single epileptogenic focus that is not in 'eloquent' cortex and can therefore be resected without causing an unacceptable neurological deficit. The most common location of seizure onset in adults is the temporal lobe, especially the medial temporal lobe (hippocampus). This is also the seizure location most amenable to surgical cure.

C. VIDEO/EEG MONITORING OF TYPICAL EVENTS WITH SCALP EEG

This is the cornerstone of the epilepsy surgery evaluation. Continuous EEG with synchronous video monitoring is performed in an epilepsy monitoring unit until the patient’s typical spells occur. Supervised medication withdrawal and provocation procedures (e.g. sleep deprivation) are often necessary to help elicit spells more quickly.
The first step is to confirm that the patient’s habitual spells are indeed epileptic. A significant proportion of patients referred for epilepsy presurgical evaluation do not have epileptic seizures (in some studies, up to 50% of patients undergoing video/EEG monitoring have events other than epilepsy, mostly psychogenic non-epileptic seizures; PNES). Although a detailed history can be very helpful in this regard, video/EEG monitoring of a typical spell is required to make this diagnosis definitively.

**Seizure semiology:** The clinical manifestation of a seizure (seizure semiology) is also of localizing value. For example, a typical patient with TLE may have an epigastric aura, followed by a quiet period of unresponsiveness with staring, lip-smacking (oral automatisms), picking at sheets or clothes (manual automatisms), contralateral dystonic posturing, postictal confusion and lethargy, and postictal nose wiping with the ipsilateral hand. If seizures arise from the dominant hemisphere, there is usually delayed recovery of language, often with transient aphasia and paraphasic errors on language testing. A typical frontal lobe seizure will occur from sleep with no warning, may show restlessness, prominent bilateral limb movements (such as bicycling or asymmetric tonic posturing, or both, and will end quickly with immediate recovery. This may recur several times in one night. Some patients with frontal lobe seizures
may present with stereotypical bizarre and violent thrashing behaviors with prominent motor features. Caution needs to be exercised to not mistake these seizures for PNES. Occipital lobe seizures often have a visual aura, and may progress (due to electrical spread) into a temporal lobe or frontal lobe type of seizure. Parietal lobe seizures are the least common, may have a sensory aura, and tend to mimic frontal lobe seizures.

\textit{Scalp EEG:} Lateralization (left vs. right hemisphere) and localization (specific region within one hemisphere) begins with standard scalp EEG recordings. Many centers utilize additional electrodes that are particularly sensitive to medial temporal discharges, including inferior temporal and anterior temporal surface electrodes or sphenoidal electrodes (semi-invasive electrodes inserted through the mandibular notch at the bedside).

The presence of \textit{interictal} (between seizures) \textit{epileptiform discharges} (EDs: sharp waves or spikes) in a single location is highly suggestive of seizure onset in that region. Computer detection of EDs is usually performed during continuous video/EEG monitoring to assist in identifying these discharges. Lack of EDs does not rule out epilepsy, as a significant minority of patients with epilepsy will not have them on scalp EEG (up to 10%). Patients with medial temporal lobe epilepsy (MTLE) usually have EDs from the anterior-mid temporal lobe (electrodes F7/F8, T3/T4, as well as anterior temporal, sphenoidal, and inferior temporal electrodes, if used). Bilateral temporal lobe EDs are not unusual in patients with temporal lobe epilepsy (TLE), including in patients with unilateral seizures. Their presence may be a relative negative prognostic factor but it does not preclude successful epilepsy surgery.

\textit{Ictal scalp EEG} during complex partial or secondarily generalized seizures will usually show a lateralized rhythmic discharge that evolves in frequency, amplitude and location. Simple partial seizures (including auras) often have no scalp EEG correlate. The typical EEG correlate of a medial temporal lobe seizure is a rhythmic theta or alpha frequency discharge that begins in the anterior-mid temporal electrodes.
D. Imaging

MRI: The presence of a focal epileptogenic lesion on MRI significantly increases the chance of surgical cure. In patients with temporal lobe epilepsy (TLE), special views of the medial temporal lobes with thin oblique coronal cuts often show hippocampal atrophy and increased T2 signal. These findings strongly correlate with pathological evidence of hippocampal sclerosis (neuronal loss and gliosis, also called mesial temporal sclerosis, or MTS) and with seizure freedom after temporal lobectomy (approximately 80% likelihood).
Presurgical Evaluation - MRI

Right hippocampal sclerosis (arrow)
Many patients with MTS have a history of febrile seizures in childhood. MRI may also show tumors (usually low grade), vascular malformations (usually arteriovenous or cavernous malformations), or cortical dysplasia. Detection of dysplasia often requires special views and careful examination for ectopic gray matter (heterotopias), cortical thickening, and blurring of the normal gray-white junction.
**PET:** Positron emission tomography (PET) utilizes an injection of radio-labeled glucose (18FDG) or other radio-labeled chemicals to measure brain metabolism or distribution of certain receptors. Interictal glucose PET usually shows hypometabolism in the seizure focus, especially in TLE. Ictal PET is not practical due to the extremely short half life of the radiotracers used. PET is most useful in MRI-negative TLE, though it may be helpful in extra-temporal epilepsy as well.

**SPECT:** Single photon emission computed tomography (SPECT) utilizes injection of a radio-labeled tracer of blood flow that binds on first-pass through the brain; thus, it is a snapshot of brain perfusion at the time of injection. The tracer is stable for several hours, allowing delayed imaging. The most useful study for presurgical evaluation is an ictal SPECT, in which the injection is performed as early as possible following ictal onset. The patient can then be scanned within the next few hours. Ictal studies usually demonstrate increased blood flow at the site of seizure onset. Interictal studies often show relative hypoperfusion at the site of seizure onset.
Comparing ictal and interictal studies, including quantitative subtraction and coregistration of the subtraction images with MRI can add additional information.
**Functional MRI (FMRI):** FMRI can be used for non-invasive motor, sensory and language mapping, and is most commonly used as part of surgical planning. FMRI can detect focal changes in blood flow and oxygenation levels that occur when an area of the brain is activated. Possible future applications of FMRI include localizing epileptiform discharges or seizures (EEG/fMRI), and lateralizing memory function.
Magnetoencephalography (MEG): MEG is a relatively new diagnostic technique. MEG is similar to EEG, but it detects magnetic rather than electric signals from the brain. MEG can sometimes detect epileptiform discharges in patients with normal scalp EEGs and can be considered complementary to EEG. It can also be used for functional mapping, including language mapping. Localization of extratemporal interictal EDs with MEG may be of particular importance in the evaluation of patients with extratemporal, neocortical epilepsies. Concordance between MEG and intracranial monitoring data has positive predictive value for epilepsy surgery outcome (Ramachandran, Nair).
E. WADA TEST:
(INTRACAROTID AMOBARBITAL PROCEDURE; IAP)

Named after Dr. Juhn Wada, this test was designed for language lateralization but it also helps in determining the risk of postoperative memory and language deficits, and in localization of the site of seizure onset. Amobarbital is a short-acting barbiturate that is injected into the internal carotid artery (via femoral artery puncture), resulting in unilateral hemispheric anesthesia for approximately 10 minutes. During this time, memory items are given to the patient and language is tested. After recovery, recall of the memory items is tested, and then the procedure is repeated on the other side. Language testing following injection permits language lateralization, or determination of mixed language dominance. A patient with unilateral TLE will usually have a significant memory asymmetry with this test, as the epileptogenic hippocampus is already dysfunctional. If the hippocampus to be resected is functioning normally on this test, the chance of a postoperative memory deficit is greater, especially in the dominant hemisphere. Most centers require demonstration of intact function of the contralateral hippocampus on this test prior to offering temporal lobectomy, in order to prevent a severe postoperative amnestic syndrome. Patients with extratemporal epilepsy usually have intact memory function bilaterally.
F. NEUROPSYCHOLOGICAL TESTING

Formal neuropsychological testing is important to establish a pre-operative baseline, as a predictor of possible cognitive loss with surgery, and as an additional aid for localization. For example, patients with temporal lobe epilepsy tend to have memory deficits. Those with TLE in the language-dominant (usually left) hemisphere have more prominent deficits in verbal memory compared with visual memory. Patients with average or above average memory function prior to temporal lobectomy have a higher risk of memory decline postoperatively, especially following left (dominant) temporal lobectomy.
Comprehensive Patient Care Conference for Surgical Candidates

- Epileptologist presents the patient
- Video-EEG studies are reviewed
  - Semiology
  - Interictal EEG morphology
  - Ictal EEG morphology
- Neuroradiologist discusses imaging studies
- Neuropsychology results are examined
- Neurosurgeon delineates surgical options
- Discussion of risks/benefits/outcomes
- Group consensus
If the seizure focus cannot be adequately localized and safely resected based on the above studies, recording seizures with intracranial EEG may be necessary. Intracranial electrodes are inserted surgically and include subdural (or epidural, though less common) strips or grids of electrodes, or intraparenchymal ‘depth’ electrodes. Depth electrodes are thin probes with multiple electrodes along their length and are most commonly used to record from the hippocampus. The exact location and type of electrodes is tailored to each individual patient. Intracranial electrodes, especially subdural grids, can also be used for identification of cortical areas that are important for language, movement, and/or sensation via cortical stimulation or recording of evoked potentials or both.
II. SURGICAL TREATMENT OF EPILEPSY

A. INTRODUCTION

Epilepsy surgery can be divided, based on the goals of the operation, into curative and palliative procedures. Curative procedures include lesion resection, lobectomy, corticectomy, and some cases of hemispheric surgery and multiple subpial transections. The primary goal of curative surgery is to stop seizures and permit the patient to be able to lead normal life, preferably off all antiepileptic medications. There is gathering evidence that early surgical intervention is favorable for a variety of reasons. Becoming seizure-free at a younger age may lessen the cognitive, behavioral, and psychosocial problems experienced by epilepsy patients, potentially improving societal integration. Additionally, because it is possible that continued seizures may result in progressive neurological damage over time, surgery has the potential to be neuroprotective in contrast to the effect of continued medically refractory seizures. Also, if a hemispheric procedure is required or if ‘eloquent’ areas of brain are within the epileptogenic zone, the potential for recovery of language and sensorimotor function is better when patients are younger.

Types of Surgical Procedures

- Resective Surgery:
  - Lesionectomy
  - Selective amygdalohippocampectomy
  - Corticectomy
  - Lobectomy (e.g. temporal lobectomy)
  - Multilobar resection
By definition, palliative procedures seldom result in cessation of seizures. These surgeries may prevent the occurrence of a particularly morbid type of seizure such as drop attacks, or lessen the frequency or severity of seizures. Palliation may be a desirable result in patients with seizure-related injuries or with a predominance of one seizure type that can be eliminated with surgery. Examples of palliative surgery include some cases of hemispheric surgery, multiple subpial transections, and disconnection procedures, including corpus callosotomy. There is a continuum between likely curative and likely palliative procedures, and patient and family expectations should be adjusted accordingly. For example, the procedure of choice for a patient with invasive monitoring-documented medial temporal lobe epilepsy (TLE) who has no magnetic resonance imaging evidence of medial temporal sclerosis (MTS) is resection of the anteromedial temporal lobe through one of a variety of surgical methods (see below). The likelihood of seizure freedom in these patients is approximately 60%, in contrast to 80-90% seizure freedom if MTS is present on MRI.

The goal of epilepsy surgery is either to define and resect an area of epileptogenesis (seizure focus) or to disrupt spread of seizure activity and thus reduce the likelihood of seizures or prevent certain seizure types. Most surgical candidates suffer from partial seizures, and many have epilepsy due to definable structural abnormalities. The location and nature of these lesions dictates the type of surgery performed and the expected outcome.
The concept of surgically remediable syndromes is important when considering patients for surgical evaluation. These are syndromes that respond poorly to medical therapy and well to surgical treatment. Patients with these problems may be considered for surgical intervention earlier than with some other cases of partial epilepsy. Medial temporal lobe epilepsy is the most common of these syndromes. Classically, it consists of a history of a complex or atypical febrile seizure in early childhood, onset of recurrent seizures in late childhood or adolescence, complex partial seizures, and evidence of hippocampal sclerosis on MRI. Lesional epilepsy, caused by lesions such as vascular malformations, low grade glial tumors, or cortical dysplasia, also responds well to surgical therapy in most cases.
B. INVASIVE DIAGNOSTIC PROCEDURES

Invasive procedures are used when the noninvasive presurgical evaluation (detailed previously) is inadequate to define the epileptogenic zone reliably enough for surgery.

Depth Electrodes

Depth electrodes are used primarily in cases of suspected medial temporal lobe epilepsy. They are thin cables with 4 to 12 cylindrical contacts (separated by 5-10 mm) lying along their distal ends. They are placed within the brain parenchyma, usually in the hippocampus, amygdala, and cingulate cortex. Sometimes, these electrodes are also used for evaluation of other lesions, e.g. cortical dysplasias. These electrodes are usually used when medial temporal lobe epilepsy is suspected but cannot be reliably lateralized (possibly due to rapid propagation from one medial temporal lobe to the other), and to distinguish medial from lateral (neocortical) temporal lobe seizure onset. They are usually placed stereotactically through burr holes along the long axis of the hippocampus (entering from the occipital lobe), or orthogonal to the long axis of the hippocampus (entering through the lateral temporal lobe). They may be used in combination with subdural strip electrodes to record from the lateral temporal cortex as well. The major drawback of depth electrodes is very limited spatial sampling. One can never be sure
whether the electrodes are in the center of the epileptogenic zone and whether the seizures truly originate from the detected area. Sometimes, concurrent scalp EEG is used to ameliorate this limitation.

Subdural electrodes

Subdural electrodes (strips, grids or both) are used to record from the surface of the brain. They are most commonly used to delineate a region of seizure onset in neocortical epilepsy, although subdural electrodes that record from the parahippocampal gyrus may be used in suspected medial temporal lobe epilepsy. The electrodes are thin discs of platinum or stainless steel embedded in a thin sheet of plastic. Unless they are configured in thin strips, they require a craniotomy for placement. The number and configuration of the strips or grids, or both, depends on the location of the seizure onset on scalp EEG and is tailored for each individual patient. In addition to their utility in localizing the epileptogenic zone, these electrodes can be also be used to perform extra- or intraoperative stimulation mapping of cortical function in the brain tissue beneath the electrodes. As with depth electrodes, the drawback of subdural electrodes is limited EEG sampling. This may be improved by adding electrodes or designing a combination of strip and grid electrodes. Placement of subdural electrodes may be difficult because of adhesions or nearby vascular structures, and in such cases epidural electrodes may be used, although they usually provide EEG of lower quality than subdural electrodes.
C: RESECTIVE PROCEDURES

Anteromedial temporal lobectomy

Anteromedial temporal lobectomy (ATL) is used to treat medial temporal lobe epilepsy, the most common form of intractable epilepsy in adolescents and adults. Seizures usually arise in the hippocampus, although they may arise from the amygdala or parahippocampal gyrus. Medial temporal sclerosis (MTS) is the pathological hallmark of medial temporal lobe epilepsy. It is characterized by loss of hippocampal neurons in a particular pattern (area CA1 is most severely involved), gliosis, and synaptic reorganization in the inner molecular layer of the dentate gyrus (mossy fiber sprouting). In the majority of cases, MTS can be detected non-invasively using magnetic resonance imaging. In the case of typical medial temporal lobe epilepsy, a standardized ATL is commonly performed. As described by Spencer and colleagues (1984), this resection includes a small amount of the anterolateral temporal lobe (usually 3-4 centimeters from the tip of the temporal lobe on the dominant side and 6-6.5 centimeters on the non-dominant side), the majority of the amygdala, the uncus, and the hippocampus and parahippocampal gyrus back to the level of the collicular plate. An alternate approach is to define the limits of the resection using physiologic criteria for each individual patient. This requires implantation of chronic subdural electrodes if determination of the ictal onset is desired (most useful) or intraoperative electrocorticography (ECoG) if interictal abnormalities are used.
(less reliable). This approach is used if there are concerns that the seizure focus may extend beyond the medial temporal lobe.

Typical complications of ATL may include visual field defects in the contralateral superior quadrant due to damage to the fibers of Meyer’s loop, and memory deficits. Functionally significant visual field deficits are uncommon using the various techniques that spare all but the anterior 3-4 cm of the lateral temporal lobe; such deficits are more frequent after more extensive ATL on the non-dominant side. Measurable worsening of verbal memory can result after language-dominant ATL. In most cases, this risk is determined by preoperative functioning. If verbal memory is intact preoperatively (based on neuropsychological testing) and the Wada test shows intact memory function in the affected hippocampus and medial temporal structures, a more pronounced decrement can be expected after resection of the dominant medial temporal lobe. If preoperative verbal memory is impaired in the affected medial temporal structures, as suggested by neuropsychological and Wada testing, then little or no decrement is usually seen. In most cases, because MTS is associated with preoperative verbal memory deficits, patients who undergo ATL show little or no significant deterioration of memory.

The utility of temporal lobe surgery for intractable epilepsy (compared to continued treatment with antiepileptic drugs) was recently demonstrated in a prospective, randomized, controlled trial (Wiebe). Eighty patients were randomized to surgery or medical treatment for one year. At one year, those undergoing surgery had a much higher rate of seizure freedom (58% versus 8%) and a significantly better quality of life.

Lesionectomy

Lesionectomy refers to surgical resections aimed at curing epilepsy by removing structural brain lesions, most commonly malformations of cortical development, low-grade neoplasms, or vascular malformations. The surgical approach depends on the location of the lesion. Intraoperative frameless stereotaxy has been a major technological improvement in the intraoperative localization of subtle cortical lesions and in correlating the location of lesions with physiologic data acquired through subdural electrodes [Slide 18]. For example, in the previous slide, magnetic resonance images used in frameless stereotactic localization of an area of focal cortical dysplasia at the base of the central sulcus (center of cross-hairs) enabled adequate coverage with subdural electrodes of a lesion that was not visible from the surface of the brain.

There is ongoing debate over when the resection should be limited to the lesion itself and when additional adjacent cortex should be removed along with the lesion. The specific pathology involved, eloquence of the adjacent cortex, and duration of the epilepsy determine the best approach for each patient. Cavernous malformations are examples of well circumscribed lesions where the region of epileptogenesis is often limited to the immediately adjacent cortex, especially in those who have not had long-term intractable seizures. In contrast, cortical dysplasia stands out as a pathological entity that may pose problems in determining resection boundaries. A combination of structural, metabolic, and physiologic data may need to be employed in these cases.
Neocortical Resection

Resection of cortex outside the medial temporal lobe is referred to as a topectomy, a corticectomy, or a neocortical resection. The boundaries of these resections are typically determined by recording the area of seizure onset with implanted subdural electrodes. Again, the surgical approach depends on the location of the focus. In the absence of pathological abnormalities, extratemporal resections result in poorer outcomes than other epilepsy surgery procedures. Because suspected regions of epileptogenesis may involve eloquent cortex, in these cases, mapping of cortical function is often an important part of the diagnostic work-up.

This may include extra-operative techniques such as functional MRI, magnetoencephalography, and invasive mapping procedures such as cortical stimulation and somatosensory evoked potentials (SSEPs) mapping through subdural electrodes, as well as intra-operative cortical stimulation and SSEPs.
Selective Amygdalohippocampectomy

- Idea is to remove mesial structures (hippocampus, amygdala, parahippocampal gyrus) leaving lateral temporal cortex intact

- Distinct surgical approaches include:
  - Transsylvian
  - Transcortical
  - Subtemporal
Hemispherectomy

Hemispherectomy is used for patients in whom seizures arise over most or all of one cerebral hemisphere. Processes causing this condition usually also produce severe damage to the involved hemisphere early in development. They include diffuse cortical dysplasia, pan-hemispheric Sturge-Weber syndrome, large perinatal infarcts, hemimegalencephaly [Slide 24], and Rasmussen's encephalitis. The goal of hemispherectomy is to remove or disconnect all the cortex of one hemisphere from the rest of the brain. Anatomical hemispherectomy resects the hemispheric cortex in its entirety, whereas a functional hemispherectomy (Tinuper) removes the temporal lobe and central cortex but preserves some of the frontal and occipital cortex.
The upper image shows a hemisphere that had been severely injured by an infection early in childhood. The lower image shows the extent of the cortical resections in the temporal lobe and central cortex. Disconnection of the residual frontal and occipital cortex is accomplished by transecting the fibers of the white matter, approached from within the lateral ventricle (not shown). The white matter connections to the residual cortex are completely divided so that, even though it is still viable, that cortex has no functional effect on the rest of the brain. More recent modifications of the technique involve removing only enough cortex to gain access to the lateral ventricle, and then performing a complete disconnection of the hemisphere, working from within the ventricle.
Although it may sound surprising, new deficits after hemispherectomy are relatively rare. This is because most of the conditions treated with this surgery have caused major injury to the hemisphere early in development. The patient's brain then appears to develop by relying on the 'good' hemisphere. Following major childhood injuries, the pediatric brain can often achieve substantial recovery of function due to the increased plasticity of the young brain. A notable exception is Rasmussen's encephalitis in an older (e.g. adolescent) patient, where a progressive and relentless loss of function of the hemisphere may be seen. Even in early injuries there are limits to transfer of function to the contralateral hemisphere, and loss of fine motor control in the contralateral hand and some degree of contralateral visual field defect are to be expected.
D. Disconnection Procedures

Multiple Subpial Transections

The multiple subpial transections (MST) procedure was developed to treat epilepsy arising from areas that cannot be resected because of the importance of the underlying eloquent cortex (Morrell, 1989). The underlying rationale is that disruption of horizontal connections that run within the cortex and which are vital for synchronizing neural activity (a key feature of seizures) can be accomplished without affecting the ascending and descending fibers that are critical for the normal functioning of the cortex. The technique involves the use of a small hook that cuts through the gray matter while leaving the overlying pia and surface blood vessels intact. Modification of this technique with the use of a knifelike device that points away from the pial surface has also been used. These transections are made at right angles to the long axis of the gyrus at 5 mm intervals. Because all of these patients have extratemporal epilepsy, most centers determine the boundaries of the area to be transected from ictal onsets recorded with chronically implanted subdural electrodes. Centers vary on whether they use intraoperative ECoG and cessation of interictal spiking in the area as a physiological end-point of the procedure.
Several reports have documented that MST can be performed in primary motor, sensory and language cortices without producing a significant permanent new deficit. In most cases, MST is combined with some cortical resection. In a meta-analysis of patients who underwent combined MST and cortical resection, responses in terms of excellent seizure control (> 95% seizure reduction) varied widely according to seizure type (67% for complex partial seizures and 87% for secondarily generalized seizures); responses were somewhat poorer for MST only (Spencer, 2002). Approximately 20% of patients develop new neurologic deficits after MST. Efficacy for treatment of Landau-Kleffner Syndrome (acquired epileptic aphasia) has been promising in a small number of patients (Morrell, 1995), but this is difficult to assess fully as MSTs are often combined with adjacent cortical resections.
Callosotomy

Transection of the corpus callosum is intended to disrupt the rapid spread of certain seizures from one hemisphere to the other. Although indications for the procedure vary among centers, callosotomy is most commonly performed for drop attacks (Spencer, 1988). These seizures can be extremely injurious because of their rapid onset and often produce multiple injuries over time due to unprotected falls. They are most commonly seen in the setting of Lennox-Gastaut Syndrome, a severe symptomatic generalized epilepsy syndrome with multiple seizure types. Because of complications with complete callosotomy, the initial surgery usually sections the anterior 66-75% of the corpus callosum. If seizure response is less than expected or transient, a second procedure is sometimes performed to complete the callosal section. Complete callosotomy at the initial surgery is usually reserved for patients whose baseline neurologic function is so impaired that major disconnection syndromes would not affect their quality of life.

Complications of callosal sectioning can be divided into early (or transient) and permanent effects. The early disconnection syndrome can include mutism and inability to initiate movement of one or more limbs. This can occur after partial or complete callosotomy, lasts one to several weeks, and then resolves. The more severe, complete disconnection syndrome is rare after partial callosotomy but more common after complete sectioning. It
includes complete inability to transfer sensory information from one hemisphere to the other and major problems with coordination and motor control of the nondominant limbs. In some cases the non-dominant arm may even act in an autonomous fashion and antagonize the actions of the dominant arm.

Seizure response is best for drop attacks, although some centers use callosotomy for a wider range of seizure types. Some series have shown an increase in partial seizures after callosotomy, presumably due to a loss of inhibitory input to a cortical focus from the contralateral hemisphere via the callosum. A recent study showed corpus callosotomy to be more efficacious in decreasing the frequency of disabling generalized tonic-clonic seizures when compared to vagus nerve stimulation, but the risk of complications was also higher in the callosotomy group (Nei). The potential benefits of corpus callosotomy need to be weighed against the potential risks.
III. VAGUS NERVE STIMULATION AS A TREATMENT FOR EPILEPTIC SEIZURES

A. INTRODUCTION

Antiepileptic drugs (AEDs) are the primary treatment for epileptic seizures, and 60-80% of newly diagnosed patients achieve seizure control with AED therapy. The sizable group of remaining patients is defined as having refractory or intractable epilepsy. These patients are not evenly distributed within the epilepsy population. Patients with refractory partial seizures are quantitatively the largest group, representing 72% of those with chronic epilepsy in a population survey from the United Kingdom (Hart). Young children with catastrophic epilepsies such as Lennox-Gastaut syndrome are also disproportionately represented. Vagus nerve stimulation (VNS) was developed as a treatment for medically refractory epileptic seizures.
B. TECHNICAL FACTORS

The device is similar to a standard pacemaker and consists of a generator (housing a lithium battery and electronics) and two lead wires. The generator is implanted in a subclavicular pocket. The lead wires are tunneled into the left carotid sheath via a transverse or longitudinal neck incision, and the spiral electrodes are applied to the left vagus nerve. The left vagus is used due to a lower percentage of efferent fibers to the atrioventricular node. The device is programmed with a telemetry ‘wand’ held over the skin overlying the generator and connected to a portable computer. Settings for current, frequency, duty cycle, etc. are selected in software. A typical cycle includes 30 seconds of 30 Hz stimulation followed by a 3 to 5 minute off period, 24 hours per day. The device can also be activated manually by the patient or caregiver, using a pocket magnet.

C. EFFICACY

Two multi-center controlled clinical trials (VNS Study Group; Handforth) led to FDA approval of VNS in 1997 as adjunctive therapy for the treatment of partial seizures in patients 12 years of age and older. The design of these trials was similar to those used in recent AED trials. In both studies, high level stimulation produced a significantly greater reduction in seizures than did low level stimulation. Only one patient became completely seizure-free. VNS is therefore considered a palliative therapy and is not curative.

D. SIDE EFFECTS

Most patients experience some hoarseness when the stimulator is firing (due to recurrent laryngeal nerve activation). This is usually mild, current dependent, and decreases with time. No cardiac, respiratory or gastrointestinal effects were seen during the controlled trials. Wound infections were encountered in ~1% of cases. Investigation of the syndrome of sudden unexpected death in epilepsy (SUDEP) showed that this syndrome is no more frequent in patients receiving VNS than would be expected in a similar population of patients with medically refractory epilepsy (Annegers, Epilepsia, 1998).

E. CONCLUSION

VNS provides an alternative for patients with localization-related epilepsy whose seizures have failed to respond to AED therapy (or who are intolerant of AEDs) and who are not optimal candidates for curative epilepsy surgery. The appropriate use of VNS for other epilepsies will become clear as additional controlled clinical data are accumulated. Open label studies of VNS in patients with Lennox-Gastaut syndrome and frequent drop attacks have shown seizure reductions similar to those of callosotomy. Given the morbidity associated with callosotomy, it may be reasonable to use VNS first, reserving callosotomy for VNS failures (Salinsky). Just as AEDs are often used to treat disorders other than epilepsy (mania, headache, neuropathic pain), VNS may also have such a role. In 2005 the FDA approved VNS as a treatment for medically-refractory depression.
E. EMERGING SURGICAL STRATEGIES

There are currently several novel approaches to surgical treatment of epilepsy undergoing multi-center clinical trials.

Deep brain stimulation

Deep brain stimulation has been studied for treatment of medication-resistant seizures. The notion is that stimulation of deep brain structures, e.g., certain thalamic nuclei, may increase inhibition and, in turn, disrupt seizure generation, propagation, or both. The surgical procedure involves insertion of the electrode in either the anterior or centro-median nucleus of the thalamus followed by cyclic or continuous stimulation. In one study, chronic centro-median nucleus stimulation decreased the frequency of generalized seizures but did not affect the frequency of complex partial seizures (Velasco, 1987). In another study, patients with anterior nucleus stimulation fared better than patients with centro-median nucleus stimulation, but the anti-seizure effect was delayed for a number of years after the surgery (Andrade). A prospective, randomized study of anterior thalamic stimulation is underway.
**Cortical stimulation**

Preliminary evidence suggests that continuous scheduled or ‘responsive’ cortical stimulation for the treatment of epilepsy may be efficacious. The use of such devices depends on the placement of the stimulation electrodes (depth or strip) in the epileptogenic zone. One trial of continuous scheduled stimulation showed significant improvement in the frequency of seizures and interictal epileptiform discharges (Velasco, 2000). The responsive cortical stimulation method depends on a continuous interictal and ictal EEG analysis by a computer which can trigger direct cortical stimulation in response to specific ictal EEG changes. A blinded trial of responsive cortical stimulation for the treatment of focal onset epilepsy is underway.

**Gamma knife**

There is preliminary evidence that gamma knife radiosurgery may have a role in the treatment of temporal lobe epilepsy and for management of cavernous malformations, arteriovenous malformations, and thalamic hamartomas associated with epilepsy.

**F. SUMMARY**

Surgical therapy offers hope for improved quality of life for a wide variety of patients with intractable epilepsy. Expected outcome depends on the type of surgery performed and the location and nature of the pathological substrate. Advances in structural, functional and metabolic imaging are greatly enhancing our ability to define the extent and nature of epileptogenic lesions prior to surgery and, therefore, allowing us to make better decisions on surgical candidacy and operative planning.
IV. HEAD INJURY AND SEIZURES

Head injury is a major cause of neurologic morbidity and mortality throughout the world. It is one of the main causes of ‘remote symptomatic epilepsy,’ possibly causing 20% of such epilepsy and 5% of all epilepsy.

Traumatic Brain Injury (TBI) accounts for over one million emergency department visits each year in the United States and over ¼ of a million hospitalizations (Thurman). About 2% of patients who come to medical attention for head injury develop post-traumatic seizures. The risk varies primarily with the severity of injury. Seizures can complicate recovery from head injury and pose an additional burden for the patient and family. They can prolong rehabilitation and increase its cost.

There have been several studies of the use of antiepileptic drugs (AEDs) to prevent seizures after head injury. Anticonvulsants are often used prophylactically after head injury, but not always with good evidence to support their use. If recurrent unprovoked seizures (i.e. epilepsy) develop, there is usually no question about treatment with AEDs, but before seizures
occur or epilepsy develops, the risk of seizures must be balanced against the risk of adverse effects of medications.

Seizures occurring early after injury (generally considered as within seven days) are labeled 'acute symptomatic seizures' and are not considered indicative of epilepsy, at least at that point. Seizures occurring later are considered 'remote symptomatic seizures' and, if recurrent and unprovoked, are considered 'remote symptomatic epilepsy'. Head injury, at least in some cases, establishes a process of epileptogenesis such that epilepsy results eventually. Some studies have addressed whether AEDs after injury can prevent this epileptogenesis.
A. RISK FACTORS FOR SEIZURES AFTER HEAD INJURY

Acute symptomatic seizures and remote symptomatic epilepsy can follow head injury. About 2% of patients with injuries severe enough to cause loss of consciousness, and 7 to 15% of those injured seriously enough to be admitted to a hospital, go on to develop later recurrent unprovoked seizures, i.e. epilepsy. Series describing higher risks are usually those in which patients were selected for more severe trauma. Early seizures (within the first seven days of injury) appear to occur more frequently in children, but early seizures are more often associated with later epilepsy in adults. Fortunately, only a minority of patients with early seizures goes on to develop epilepsy.

The severity of injury is the primary risk factor. Among the highest reported risks were in soldiers injured in the Vietnam War in whom penetrating head injuries led to epilepsy in up to 53% (Salazar). Persistent focal neurologic deficits were particularly ominous, and 90% of patients with residual aphasia had epilepsy. Military series are naturally subject to selection bias because patients with more severe seizures and other disabilities are more likely to require late and prolonged treatment and thus be ascertained better in series based on subsequent medical care. Other reported risk factors for the development of seizures and later epilepsy include parenchymal hemorrhage or subdural hematoma and a low Glasgow Coma Scale score (of 3 to
8). Some studies find cortical injuries, larger volume of tissue loss, depressed skull fractures, retained metal fragments, and longer duration of lost consciousness as risks for seizures and epilepsy. At least 20% of adults will have an unprovoked seizure within two years of TBI when there has been a penetrating injury, intracranial hematoma, cortical contusion, depressed skull fracture, or immediate provoked seizure at the time of the injury (Temkin 1996). In general, EEGs have not been particularly informative in predicting risks, but in one series, development of an epileptiform focus a month after injury predicted later epilepsy in 50% of cases (Angeleri).

In the Mayo Clinic study by Annegers and colleagues, patients with severe injuries (with parenchymal brain contusion, intracranial or subdural hematomas, or amnesia or loss of consciousness for over 24 hours) had a 10% cumulative incidence of subsequent unprovoked seizures over five years of follow up (Annegers, NEJM, 98). Those with moderate injuries (loss of consciousness for 30 minutes to 24 hours or a skull fracture) had a 1.2% incidence over the same period (still increased from that in the general population), and those with mild injuries (loss of consciousness or amnesia lasting under 30 minutes) had a 0.7% incidence of seizures-no greater than in the general population. Patients with severe injury and early seizures had a 36% chance of developing epilepsy. About 80% of patients who develop late seizures do so within two years (60% in the first year), but 12% of all epilepsy due to head injury presents more than 10 years after the injury, and some increased risk extends to at least 20 years after the injury.
B. TREATMENT: CAN AEDs PREVENT POST-TRAUMATIC SEIZURES AND EPILEPSY?

The use of AEDs in the setting of head injury depends on the anticipated likelihood of seizures and their harmful consequences balanced against the likely effects of AEDs. AEDs can prevent seizure recurrences in patients who have had seizures. Prophylactic AEDs attempt to prevent seizures or prevent or retard the development of epilepsy.

Early seizures
- Prophylactic AEDs prevent early post-traumatic seizures, at least after severe head injury. After milder injury, without an early post-traumatic seizure, the likelihood of seizures is low enough that, for the most part, the value of prophylactic AEDs has not been studied.

Early studies of AEDs after head injury were usually favorable - but usually uncontrolled. In a prospective, randomized trial of over 400 patients given placebo or phenytoin (adjusted to therapeutic levels) within 24 hours of a severe injury, Temkin and colleagues (1990) found that seizures occurred within the first week in 14% of patients on placebo and 4% on phenytoin, establishing the efficacy of phenytoin in preventing early seizures after serious
head injury. Severe injury included contusion or hematoma on CT scan, depressed skull fracture, penetrating wound, an early seizure (within the first 24 hours), or a Glasgow coma score under 10. Nevertheless, there was no significant difference in the incidence of later seizures or overall outcome at one or two years. This argues that longer treatment is of no benefit, and adverse effects of medications accumulate with time. Though cognitive and other side effects were relatively minor, the absence of benefit precludes their use.

It is reasonable to begin an intravenous loading dose of phenytoin as soon as possible after a severe head injury to reduce the risk of seizures within the first week. Two studies support the value of phenytoin in the same situation, and adverse effects were very few over the study period of just a week. A meta-analysis of controlled trials by Temkin (2001) found good evidence for the use of either phenytoin or carbamazepine in the first week after severe TBI. Phenobarbital was not as clearly reliable and of note, no AEDs approved in the United States after 1980 have been studied in detail for this purpose.

Another meta-analysis (Schierhout) concluded that the definite benefit of treating 100 patients would be seizure prevention during the acute phase in ten of those patients, but a few patients will develop a skin rash. Also, the reduction in early seizures was unaccompanied by any reduction in mortality or neurologic disability.

A review of studies by Chang and Lowenstein (Chang) was the basis for a practice parameter from the Quality Standards Committee of the American Academy of Neurology. It recommended short term prophylactic use of AEDs within the first week after severe head injury, but not for longer.

Late seizures
The use of AEDs for a longer period after TBI is nowhere near as promising. The risk of seizures is clearly increased with moderate or severe head injury, but the prolonged use of AEDs does not appear to alter the likelihood of seizures. Indeed, the AAN practice parameter and the meta-analysis from Temkin found no studies with reliable evidence that anticonvulsants prevented later seizures. Phenytoin, carbamazepine, and valproate have all been studied for prophylaxis and found wanting, and adverse effects increased with longer AED use.

Once a late post-traumatic seizure has occurred, however, patients are likely to go on to have epilepsy and generally warrant treatment. In the continuation of the phenytoin prophylaxis trial, 86% of patients who had a single seizure later than seven days after the injury went on to have at least one additional seizure, half within the next month. Most of these patients were on AEDs, suggesting that even this number underestimates the risk of recurrence. Consequently, patients with late post-traumatic seizures should usually take AEDs, although there is no good information on how long the medications should be continued.

Epileptogenesis
In some cases, head injury clearly initiates a process leading to later recurrent seizures. Long term prophylactic treatment assumes that recurrent seizures (epilepsy) are likely to develop and that inhibiting that development with AEDs is possible and justifies potential side
effects. Prophylactic treatment after head injury (or after a single provoked seizure in the setting of head injury) was at one point hoped to interrupt the process of epileptogenesis. Such interruption would constitute true antiepileptogenesis, i.e. prevention of the process leading to epilepsy, rather than just suppressing individual seizures. If AEDs were truly antiepileptogenic in this case, seizures would be less likely to occur even after the medications were discontinued. Several studies of prophylactic treatment have been carried out in patients with severe head injuries, but the definitions of severity have varied among studies. Those studies and meta-analyses have found no evidence that such antiepileptogenesis has been afforded by any of the medications yet tested. Because AEDs do not appear to prevent late seizures following head injury (and even severe head injury) the AAN practice parameter, and other experts, do not recommend prolonged AED use after head injury for the purpose of prophylaxis. In terms of true antiepileptogenesis, it is important to note that newer AEDs have not been studied and might offer some benefit. Also, most studies were in adults, and the same questions have not been studied as thoroughly in children.

In summary, AED use is appropriate prophylactically or after individual seizures within the first week of a severe head injury, i.e. those with coma, penetrating injury, or hemorrhage. After the first week, however, most experts (and the AAN practice parameter) agree that the medication should be tapered and discontinued. With later post-traumatic seizures, however, epilepsy is likely, and AEDs are appropriate though with an uncertain duration of treatment. Of course, a single seizure developing long after head injury might be unrelated to the injury and warrants a thorough clinical evaluation to help decide on the value of treatment.
Conclusion

- Many patients with medically-intractable epilepsy are surgical candidates
- All patients with epilepsy should undergo epilepsy protocol imaging
- Many modern epilepsy surgery options exist, including resection, disconnection and palliation