

# Epilepsy Surgery: Outcome and Complications

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The past 25 years has witnessed the evolution of epilepsy monitoring and surgery into a mature neuroscience subspecialty.<sup>1,2</sup> The proliferation of multidisciplinary epilepsy centers has increased our capacity to provide multidisciplinary evaluations of patients with intractable epilepsy, thereby leading to greater numbers of patients being offered surgical treatment (Table 70-1). A robust clinical literature has documented both improvements in surgical approaches and a set of measures of surgical outcomes that has stimulated changes in our approach to these patients. In addition, the emergence of a nosologic context of “surgically remediable syndromes” has been spurred by advances in brain imaging and studies of the neurobiologic underpinnings of epileptogenesis.

Traditional en bloc resective approaches, which predominated during the first 60 years of epilepsy surgery, have been supplemented by more focused, minimalistic approaches, including selective amygdalohippocampectomy (SAH), multiple subpial transection (MST), keyhole deafferentation hemispherotomy, radiosurgery, and neuromodulatory approaches such as deep brain stimulation (DBS), vagal nerve stimulation (VNS), and the NeuroPace device (Table 70-2).

Advances in our understanding of the intractable epilepsies have facilitated a discrete taxonomy of “surgically remediable syndromes” (Table 70-3).<sup>1</sup> Each syndrome and each new treatment approach engender a new data set with regard to (1) seizure, neurobehavioral, and psychosocial outcomes; (2) complications (surgical, neurological, neuropsychological, and psychobehavioral); (3) “health outcomes” expressed in terms of alterations in quality of life (QOL); and (4) “cost-effectiveness” in comparison to alternative therapeutic interventions.

## EPIDEMIOLOGY AND HEALTH CARE COSTS OF INTRACTABLE EPILEPSY

Epilepsy is a relatively common disorder, with more than 2 million Americans (1.3%) afflicted and approximately 1 in 10 Americans having a minimum of one seizure over the course of a lifetime.<sup>3</sup> Up to a third of all individuals with epilepsy are refractory to medical therapy.<sup>4</sup> Medically intractable epilepsy is costly. Estimates of the lifetime cost of intractable epilepsy incorporate both *direct cost* (cost of medical care) and *indirect cost* (i.e., productivity, lost earnings). In a 2000 study, patients with medically intractable epilepsy in the United States were found to account for 42% of the estimated \$1.7 billion in annual direct medical costs for epilepsy and 86% of the \$10.8 billion in indirect costs.<sup>5</sup> Beyond these estimates, the burden of epilepsy incorporates additional, unmeasurable indirect costs that encompass pain, suffering, and reduction in the QOL of epileptic patients and their caretakers.<sup>6,7</sup>

## ADVANCES IN OUTCOME ASSESSMENT OF EPILEPSY SURGERY

Seizure frequency, previously considered the “gold standard” of outcome measures, is an inadequate measure of surgical outcome for many reasons. Persistent epileptic seizures are often

associated with significant psychosocial, psychiatric, and neuropsychological impairments, as well as medication toxicity and excess mortality rates (Fig. 70-1).<sup>8</sup> These disabilities may persist despite relief of seizures after “successful” surgery. Therefore, contemporary studies of postoperative outcome emphasize neuropsychological and psychosocial functions and “health outcomes” commensurate with the World Health Organization’s definition of health as “... a state of complete physical, mental and social well-being ...”.<sup>3,8</sup>

## Classification of Seizure Outcomes

Studies have demonstrated that “health-related quality of life” (HRQOL) and psychosocial measures may not improve significantly with as much as a 70% reduction in seizure frequency after surgery.<sup>9</sup> In recognition of the benefits of postoperative freedom or near freedom from seizures, contemporary seizure outcome classification schemes have emphasized patterns of seizure reduction that are likely to have an impact on QOL.<sup>10-12</sup> The Engel classification scheme (Table 70-4) provides four categories of seizure outcome: I, seizure free; II, “rare” seizures (two to three per year); III, “worthwhile improvement” (>90% reduction); and IV, “no worthwhile improvement” (<90% reduction).<sup>8,11</sup> That a class IV (“no worthwhile improvement”) outcome may be associated with a 70% reduction in frequency is emphasized by HRQOL studies showing that epilepsy-specific measures are affected even by a few seizures per year.

## Neuropsychological Outcomes

Neuropsychological assessment is useful both during the surgical patient selection process and as a tool to assess outcomes after surgery. The aim of the evaluation is to establish a profile of the patient’s strengths and weaknesses in multiple domains on a variety of standardized tests and questionnaires (Table 70-5) in relation to normative values derived from the general population.<sup>13</sup>

Of particular concern in temporal lobe surgery are losses of memory function, including the rare but disabling syndrome of global amnesia, as well as the more common material-specific memory losses affecting short-term verbal memory in the language-dominant hemisphere and visual-spatial memory in non-dominant-hemisphere, temporal lobe operations. The Wada test, which was originally developed to determine hemispheric lateralization of language function,<sup>14</sup> was subsequently adapted by Milner and colleagues<sup>15</sup> to provide a measure of the risk for loss of memory function postoperatively. The Wada test has been used for many years to identify patients at risk for global memory loss,<sup>16</sup> and in fact, such losses are uncommon since the Wada test was universally adopted. However, reports of favorable memory outcomes in patients who failed the Wada test preoperatively (“false positives”) have called into question the reliability of this procedure in some patients.<sup>17</sup> The Wada test has also been useful in identifying lateralized temporal lobe dysfunction, which may correlate with the side of seizure onset,<sup>18,19</sup> the likelihood of a favorable seizure outcome, and more recently, prediction of the

**TABLE 70-1 Worldwide Surgical Procedures for Temporal Lobe Epilepsy**

PROCEDURE	BEFORE 1986*	1986-1990†
ATLX	2336	4862
SAH	—	568
Neocortical resection	825	1073
Lesionectomy	—	440

ATLX, anterior temporal lobectomy; SAH, selective amygdalohippocampectomy.  
 \*Total of 139 centers.  
 †Total of 2107 centers.  
 From Engel J. Surgery for seizures. *N Engl J Med.* 1996;334:647-652.

**TABLE 70-2 Surgical Approaches for Epilepsy**

- Resective surgery
  - Temporal lobe resections: “standard,” selective amygdalohippocampectomy (SAH)
  - Extratemporal resections
  - Lesional resections
  - Anatomic or functional hemispherectomy
- Radiosurgery
- Disconnection surgery
  - Corpus callosotomy
  - Keyhole hemispherotomies
  - Multiple subpial transection (MST)
- Neuroaugmentive surgery
  - Vagal nerve stimulation (VNS)
  - Deep brain stimulation (DBS)

**TABLE 70-3 Surgically Remediable Syndromes**

Temporal lobe epilepsy (TLE)	Idiopathic Mesial temporal sclerosis/mesial temporal lobe epilepsy
Extratemporal epilepsy	Lesional (tumor, vascular malformation, developmental, ischemic, traumatic)
Catastrophic epilepsy	Idiopathic Lesional (tumor, vascular malformation, developmental, ischemic, traumatic)
Secondarily generalized epilepsies	Lesional Hemimegalencephaly Diffuse cortical dysplasias Sturge-Weber syndrome Rasmussen’s encephalitis Porencephalic cysts Lennox-Gastaut syndrome

**TABLE 70-4 Engel’s Outcome Classification**

- I. Free of disabling seizures
  - Auras
  - ≥2 years seizure free
  - Generalized tonic-clonic seizures with drug withdrawal
- II. Rare disabling seizures (≤2 per year) cures ≥2 years
  - Nocturnal seizures only
- III. Worthwhile improvement
  - ≥2 years
- IV. No worthwhile improvement (≤90%)

From Engel J. Surgery for seizures. *N Engl J Med.* 1996;334:647-652.

**TABLE 70-5 Neuropsychological Assessment of Epileptic Patients**

FUNCTIONS	TESTS
Sensory functions	Halstead-Reitan examination
Motor functions: dexterity, coordination, speed, flexibility	Purdue Pegboard, Grooved Pegboard, Thurstone’s Uni- and Bimanual Coordination Test
Perceptual-motor functions	Beery Visuo-Motor Integration Test, Block Design, Rey-Osterrieth Complex Figure
Psychomotor development and intelligence	Griffith or Bayley Developmental Scales, Wechsler Intelligence Scales for Adults or Children (WISC, WAIS), Stanford-Binet
Attention	Concentration Endurance Test, Auditory Continuous Performance Test
Memory and Learning	
General	Wechsler Memory Scales for Children and Adults
Verbal: word lists, story recall	California Verbal Learning Test (CVLT)
Visual: faces, patterns	Rey-Osterrieth Complex Figure
Expressive: sentence construction	Boston Naming Test, Token Test
Receptive: comprehension	Peabody Picture Vocabulary Test (PPVT)
Written: reading, spelling	Wide Range Individual Achievement Test (WIAT)
Numerical operations	WIAT, Woodcock-Johnson Achievement Battery
Executive functions	Tower of London, Wisconsin Card Sorting Test, Fluency Tests
Personality	Rorschach, Thematic Apperception Test for Children or Adults, SCL-90R
Affective state	Beck Depression Inventory, Hamilton Anxiety Scale
Social adjustment	Vineland Adaptive Behavior Scales, Achenbach Child Behavior Check List (CBCL)
Quality of life	Quality of Life in Epilepsy questionnaires (e.g., QOLIE-31, QOLIE-AD-48)

## TLE AS A CHRONIC ILLNESS

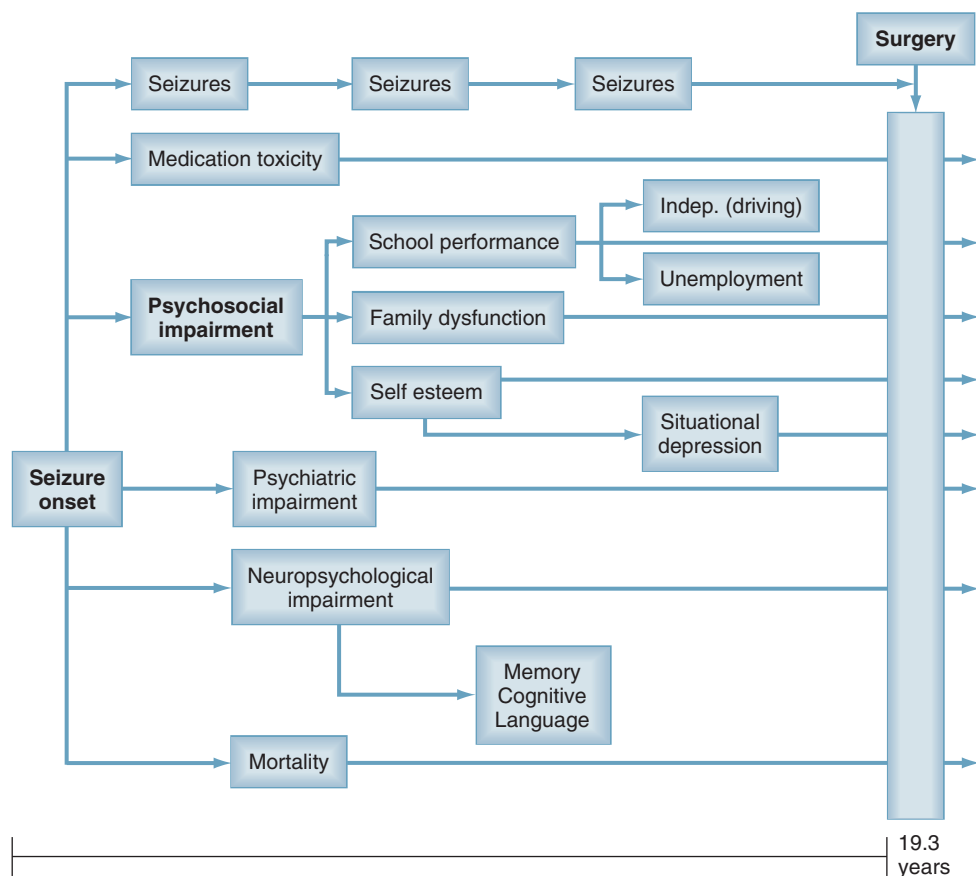


FIGURE 70-1 Temporal lobe epilepsy as a chronic illness.

risk for material-specific memory loss (particularly verbal memory loss) after surgery.<sup>20,21</sup> Nonetheless, the Wada test is invasive and requires a degree of patient cooperation, which may be suboptimal in young children and mentally retarded patients. Wada test results may be difficult to interpret in patients with bilateral language representation, excessive agitation, insufficient hemispheric inactivation by amobarbital (Amytal), or other procedural factors.<sup>13,22</sup> Functional neuroimaging modalities (i.e., functional magnetic resonance imaging [fMRI], [<sup>18</sup>F]fluorodeoxyglucose positron emission tomography [FDG-PET], and [<sup>99m</sup>Tc]-hexamethylpropyleneamine oxime single-photon emission computed tomography [HMPAO-SPECT]) are increasingly being used as noninvasive tools for localization of epileptogenic cortex and assessment of focal functional deficits in patients with intractable epilepsy.<sup>23-26</sup> [<sup>18</sup>F]FDG-PET, by imaging the rate of cerebral glucose metabolism, reflects neuronal losses and focal functional deficits in epileptic patients and serves as a predictor of postoperative seizure outcomes. In 70% to 90% of patients with temporal lobe epilepsy (TLE), interictal [<sup>18</sup>F]FDG-PET detects unilateral temporal hypometabolism or asymmetric bitemporal hypometabolism. This reflects neuronal loss in the damaged temporal lobe, correlates with clinical and neurophysiologic findings,<sup>24-26</sup> and has been associated with favorable postsurgical seizure control in several studies.<sup>25,27,28</sup> Patients with left mesial temporal lobe epilepsy (MTLE) and regional left hemispheric hypometabolism tend to have impairments in verbal memory and word fluency.<sup>29</sup> Although the laterality of hypometabolism as determined by [<sup>18</sup>F]FDG-PET is related to memory deficits

measured by the Wada test,<sup>30-33</sup> the location or spatial pattern of the metabolic changes that can predict impairment in Wada memory performance has not been characterized. If future studies can demonstrate a strong correlation between Wada memory scores and metabolism on [<sup>18</sup>F]FDG-PET, presurgical [<sup>18</sup>F]FDG-PET could play a role in predicting memory laterality during the presurgical evaluation.

fMRI represents neuronal activity indirectly via hemodynamic changes in the brain. The size of the cortical area activated and the number of involved neurons directly influence the magnitude of the changes in regional cerebral blood flow.<sup>34</sup> Studies comparing fMRI and Wada test results in the same patient have shown a high correlation (from 80% to 100%) between the two procedures when the studies were aimed at either investigating language lateralization<sup>35-38</sup> or assessing memory asymmetries.<sup>39-41</sup>

Even though it is likely that functional neuroimaging will ultimately supplant the Wada test, more studies are required to confirm the reliability of data obtained in the context of presurgical evaluation of epilepsy.

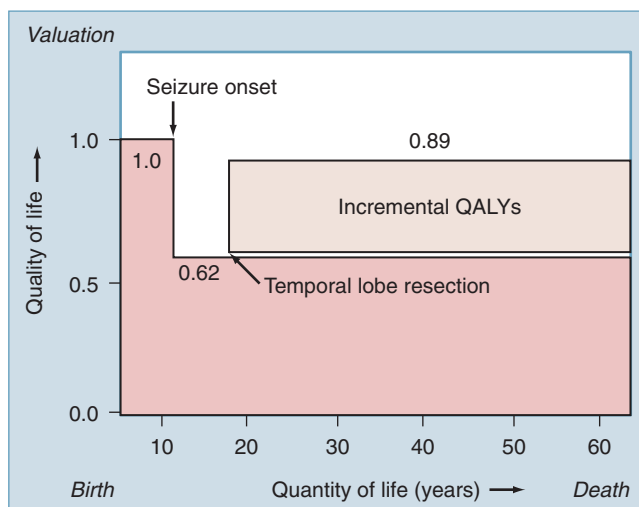
### Health-Related Quality of Life

Over the past decade, epilepsy-specific HRQOL instruments have been developed to assess the impact of epilepsy surgery on the “health” and “quality of life” of patients afflicted with intractable epilepsy. These instruments incorporate “generic” measures of health status previously validated in studies of health outcomes in other disease states, as well as “epilepsy-specific” measures of

health status, which are more sensitive to the cognitive, memory, and role limitation issues implicit in the disease of intractable epilepsy.<sup>8,42,43</sup> Contemporary outcome studies incorporate “health outcomes” measures in which the individual patient’s perspective becomes an integral aspect of the health care outcomes assessment.<sup>44</sup> To facilitate HRQOL studies in epilepsy surgery patients, assessment tools such as the Epilepsy Surgery Inventory (ESI-55) have been developed and validated for use in this population.<sup>42</sup> This instrument incorporates a “generic core” adapted from the RAND 36-Item Health Survey, along with 12 epilepsy-specific items addressing the domains of cognitive function, role limitations because of memory problems, and health perceptions.<sup>45</sup> Other instruments developed to assess HRQOL have included the Quality of Life in Epilepsy—89 (QOLIE-89)<sup>46</sup> and a shorter version, the QOLIE-10.<sup>44</sup>

### Cost-Effectiveness

The reduction in the morbidity associated with chronic epilepsy achieved with epilepsy monitoring and surgery appears to be accompanied by parallel reductions in long-term health care costs and unemployment. Recent advances in epidemiologic and “health outcomes” investigations have facilitated *cost-effectiveness studies* of epilepsy surgery. Cost-effectiveness studies incorporate established patient preferences for being in certain states of health, along with cost estimates of each health state, to assess the cost-effectiveness of surgical intervention. “Health states” are typically quantified on a scale of 0 to 1. For example, preference-based values for epilepsy-related health states include a healthy, disease-free patient (1.0), a patient with intractable complex partial seizures (0.62), and a postoperative, seizure-free patient (0.89).<sup>47</sup> This approach permits calculation of “*quality-adjusted life years*” (QALYs) by multiplying the expected postoperative survival in years by the appropriate quality adjustment factor (from 0 to 1), which reflects the outcome state.<sup>47,48</sup> The number of QALYs added to a patient’s life by successful epilepsy surgery can be estimated (Fig. 70-2) and, when combined with the cost of therapy, can be expressed as the cost, in dollars, of providing an incremental QALY to the life of a patient with intractable epilepsy. The “cost-effectiveness” of surgical intervention can then be expressed in various ways to provide a measure of the cost-effectiveness of epilepsy surgery that can be compared with other unrelated health care interventions.



**FIGURE 70-2** Estimated number of quality-adjusted life years (QALYs) added to a patient’s life after successful epilepsy surgery.

## COMPLICATIONS OF DIAGNOSTIC/SURGICAL PROCEDURES

Epilepsy surgery is safe and effective. Nevertheless, invasive diagnostic procedures and definitive surgical interventions do carry some risk, which must be considered when recommending surgical intervention to patients with intractable seizures.<sup>8</sup>

### Intracarotid Amytal Procedure (Wada Test)

Complications of the Wada test encompass the complications of transfemoral carotid angiography, including thromboembolism and stroke (0.5% to 1.0%), allergic reactions to contrast agents (1 in 40,000), and local complications of femoral artery puncture.<sup>49</sup> Rare mortality has been reported.<sup>16</sup>

### Depth Electrodes

For many years, depth electrodes were used routinely as part of the surgical evaluation of patients with intractable epilepsy.<sup>50</sup> In contemporary practice, noninvasive assessments, including structural MRI scans and improved surface electroencephalographic (EEG) monitoring techniques, have reduced the requirement for invasive recordings. An advantage of depth electrodes is that low-voltage, localized discharges emanating from medial structures, including the amygdala and hippocampus, may be detected as evidence of the site of seizure onset. Depth electrodes are invasive and associated with risk for infection (1% to 4%) and intracerebral hemorrhage, which has been noted to occur in 3% of parasagittal placements and 1% of lateral placements.<sup>49</sup> Rare mortality from depth electrodes has been reported to be caused by lacerations of large parasagittal draining and bridging veins or the posterior cerebral artery, as noted in one older series of 163 patients.<sup>51</sup> The use of modern stereotactic techniques has reduced the morbidity associated with depth electrodes, and recent studies report few complications with no permanent neurological deficits in most cases.<sup>52,53</sup> One study has suggested that a postoperative decline in verbal memory may occur with the implantation of hippocampal depth electrodes bilaterally.<sup>54</sup>

### Subdural Strip Electrodes

Subdural strip electrodes have provided a safe alternative to brain penetration by depth electrodes.<sup>55</sup> Strip electrodes are usually placed symmetrically over suspected sites of seizure onset and yield excellent recordings from neocortical structures. Although recordings from intracerebral sites are not provided with this modality, these electrodes do not require cortical penetration with its associated risks. The principal risk with subdural electrodes is infection, which may be manifested as superficial infection, meningitis, or brain abscess, as reviewed in an extensive series of 350 patients.<sup>55</sup> Other reported adverse events have included fever with temperatures higher than 102°F, migraine, and temporalis muscle fibrosis, as indicated in a prospective study of 55 patients. In another recent multicenter study, only five minor complications occurred in 131 patients, three of which were reported to be small hematomas not requiring evacuation.<sup>56</sup>

### Subdural Grid Electrodes

Subdural grid electrodes provide electrographic tracings from a large expanse of cortex and permit extraoperative brain mapping to localize eloquent functions in relation to the epileptogenic zone. Grid electrode placement requires a large craniotomy and the egress of numerous electrode cables through the scalp for the duration of the monitoring period (usually 1 to 2 weeks). The grid is removed at a second craniotomy, during which the



definitive cortical resection is performed. It is not surprising that bone flap infection and meningitis are prominent concerns as complications of this procedure. Infection rates of 22% were identified in an early Cleveland Clinic series but declined to 7% when cables were tunneled to exit percutaneously.<sup>57</sup> A contemporary series of 49 patients undergoing grid implantation reported a 4% infection rate, subdural hematoma formation requiring emergency evacuation in 8%, and brain swelling in 2%.<sup>58</sup> Other series have reported subdural hematoma formation in 8% and increased intracranial pressure and brain shift requiring premature removal of the grid.<sup>49</sup> Meticulous surgical technique with avoidance of injury to or compression of large cortical or bridging veins, tunneling of electrode cables, administration of perioperative antibiotics, and full utilization of mannitol and dexamethasone (Decadron) are likely to improve outcomes and prevent complications.<sup>49</sup>

## RESECTIVE SURGERY

### Temporal Lobe Epilepsy

Intractable epilepsy of temporal lobe origin is the most common syndrome for surgical consideration. It is thus no surprise that the majority of outcome data in the literature have focused on temporal lobe surgery. The syndrome of *mesial temporal lobe epilepsy* typically incorporates a history of an early insult in infancy or childhood,<sup>59,60</sup> hippocampal sclerosis and atrophy on MRI,<sup>61</sup> an abnormal creatine-*N*-acetylaspartate (NAA) ratio on magnetic resonance spectroscopy (MRS),<sup>62</sup> temporal hypometabolism on interictal PET,<sup>63,64</sup> and a characteristic pattern of hyperperfusion and hypoperfusion on ictal SPECT.<sup>59</sup> EEG studies reveal an anteromedial epileptogenic zone, and Wada testing reveals appropriate memory deficits.<sup>8,65</sup> Histopathologic analysis of resected hippocampi reveals loss of principal hippocampal neurons, synaptic reorganization, sprouting of mossy fibers, and enhanced expression of glutamate receptors.<sup>8,66,67</sup>

A smaller population of patients with “*cryptogenic*” TLE have normal MRI findings preoperatively.<sup>60</sup> Patients with “*lesional*” TLE have temporal lobe neoplasms, vascular malformations, disorders of cortical development, or traumatic/ischemic insults within the temporal lobe. These lesions may variably involve mesial temporal lobe structures or may be associated with hippocampal sclerosis (“*dual pathology*”)<sup>68</sup> and thus lead to distinct surgical approaches and outcomes.

### Mesial Temporal Lobe Epilepsy

#### Pathologic Substrate

The pathologic features of mesial temporal sclerosis (MTS) include (1) loss of principal neurons (atrophy), (2) glial proliferation (gliosis), and (3) sprouting of dentate granule cells.<sup>69,70</sup> When the loss of hippocampal principal neurons exceeds 50%, hippocampal atrophy is visible on MRI<sup>69</sup> and gliosis will be manifested as high signal on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images. Not uncommonly, some degree of hippocampal sclerosis is present contralateral to the side of resection and may not be detected by standard MRI assessment. Bilateral MTS is visible on MRI scans less commonly (5% to 10%).<sup>71</sup>

#### Seizure Outcomes

#### IMAGING, NEUROPSYCHOLOGICAL, ELECTROGRAPHIC, AND CLINICAL FEATURES

A variety of preoperative factors have been recognized over the years as identifiers of more favorable postsurgical outcomes with

regard to seizure control. Although seizures were well controlled in 91% of patients with MRI-defined unilateral MTS, the favorable outcome response to surgical intervention declined sharply to 62% in patients found to have bilateral MTS and was notably worse (only 50%) in patients without MTS.<sup>72</sup> However, depth electrode recordings in patients with radiographic bilateral MTS have suggested that some may have only a unilateral onset, and in this subset of patients excellent seizure outcomes may still be achieved, as evidenced in a small study of 5 such patients, 4 of whom were completely seizure free after 2 years of follow-up.<sup>71</sup> It has also been found in several studies that hippocampal hypometabolism noted on PET studies is strongly correlated with MRI findings of MTS and histologically confirmed neuronal atrophy and gliosis in this region,<sup>73,74</sup> thus outlining the prospective utility of PET in preoperative evaluation. In a similar vein, another study evaluating postsurgical patients seen at 1-year follow-up reported an 83% seizure-free rate in those with preoperative unilateral hippocampal hypometabolism,<sup>64</sup> in sharp contrast to just a 38% seizure-free rate in patients with either normal PET studies or evidence of multilobar hypometabolism. In a 5-year outcome assessment of 135 operated patients with imaging evidence of lesions, MTS, and normal hippocampi, 80% of patients with lesions, 62% of patients with MTS, and 36% of patients with normal hippocampi were found to be seizure free 2 years postoperatively.<sup>75</sup> Multivariate analysis may improve the prediction of outcome.<sup>76</sup> MTS, a “*known cause*” of epilepsy, and the absence of generalized seizures portend a satisfactory outcome. Satisfactory outcomes were achieved in 78% to 83% when both of these features were present, in 53% to 61% when one was present, and in 29% of patients when neither was present.<sup>77</sup> Preoperative evaluation with the intracarotid Amytal test (Wada test) has suggested that lateralizing memory deficits are independently predictive of a seizure-free outcome.<sup>20,65</sup>

Lateralization of seizure onset can be identified with either interictal<sup>78,79</sup> or ictal<sup>76,80,81</sup> EEG monitoring. In patients with nonlesional TLE, favorable seizure control was noted most often in those with concordance between their interictal EEG and MRI findings.<sup>82</sup> A 5-year follow-up study of 28 patients demonstrated that in 26 of them, a 75% reduction in seizures was noted in those who had a unilateral anterior to middle temporal epileptiform focus without discordant findings in other studies, the majority of whom (61%) were reported to be seizure free.<sup>79</sup>

In a recent review of 126 articles on temporal lobe resection published between 1991 and 2001, the median seizure-free rate was 70%, and of 63 factors analyzed, favorable outcomes were associated with (1) preoperative MTS, (2) anterior temporal localization of interictal epileptiform activity, (3) absence of preoperative generalized seizures, and (4) absence of seizures in the first postoperative week.<sup>83</sup> Age at seizure onset, preoperative seizure frequency, and extent of lateral resection had no association with outcome.

Age at the time of surgery (i.e., >45 years old) may be related to seizure outcome, with some studies suggesting less favorable outcomes<sup>84</sup> and others suggesting that older age does not predispose to a less favorable outcome.<sup>85,86</sup>

#### SURGICAL VERSUS BEST MEDICAL MANAGEMENT

A 5-year follow-up study compared the seizure outcomes of 148 operated and 94 nonoperated patients with TLE.<sup>87</sup> Freedom from seizures during the final year of follow-up was achieved in 62% of operated and 7.5% of nonoperated patients. Complete seizure freedom over the entire study period was achieved in 44.6% of operated and 4.3% of nonoperated patients. None of the nonoperated and 8.8% of the operated patients were free of the need for antiepileptic drugs (AEDs) at follow-up. Other adult studies have documented AED freedom in 21% and 35% of patients at 1- and 2-year follow-up, respectively.<sup>88,89</sup> Pediatric

studies have documented 30% to 44% AED-free rates at 2 years<sup>78,89</sup> and 30%, 35%, and 60% AED-free rates at 2, 5, and 10 years postoperatively, respectively.<sup>90</sup> The only prospective, randomized, controlled study of surgical versus best medical management for TLE compared the outcomes in 40 medically managed and 40 surgically managed patients.<sup>2</sup> At 1-year follow-up, 58% of the surgically treated and only 8% of the medically treated patients were free of seizures impairing consciousness.

In general, systematic reviews suggest that 66% to 70% of patients are seizure free at short-term (<5 years) follow-up.<sup>83,91-94</sup> Long-term (>5 years) follow-up studies show that 41% to 79% of patients remain seizure free after temporal lobe resection<sup>87,91,93,95-99</sup> and that 15% to 20% of patients have relapses after initial seizure freedom at 5 to 10 years after surgery.<sup>92,93,96,100</sup>

### SURGICAL APPROACHES TO MESIAL TEMPORAL LOBE EPILEPSY

The traditional “*en bloc temporal lobectomy*” incorporated a 5- to 6-cm lateral resection along with a portion of the amygdala and anterior hippocampus.<sup>8,101,102</sup> More centers now use a focused anteromedial resection in which restricted resection of the middle and inferior temporal gyrus is combined with thorough hippocampal removal.<sup>8,103-105</sup> Transylvian SAH permits exclusive resection of medial structures.<sup>8,106,107</sup> Awake surgery with intraoperative electrocorticography (ECoG) and functional brain mapping permits tailored resection of both lateral and medial structures.<sup>8,108,109</sup>

### EXTENT OF CORTICAL AND HIPPOCAMPAL RESECTION

In the early era of epilepsy surgery, lateral resection alone often yielded disappointing results with regard to freedom from seizures.<sup>110</sup> More recent studies in which lateral and mesial structures were resected have suggested that the extent of lateral resection does not correlate with seizure outcome.<sup>111,112</sup> One study reported that 53 of 100 patients were seizure free after a standard lateral resection was combined with complete amygdalotomy and minimal hippocampal resection.<sup>113</sup> The favorable outcomes after SAH,<sup>11,114</sup> the effectiveness of removal of any residual posterior hippocampus in reoperative surgery,<sup>115-117</sup> and the identification of posterior hippocampal onsets in depth electrode studies<sup>103</sup> all suggest that thorough hippocampal resection may be essential to optimize seizure outcomes.<sup>8</sup> Although earlier reports suggested that the extent of mesial resection had no association with seizure outcome, two more recent studies addressed this issue effectively and came to different conclusions.<sup>83</sup> In the first study, postoperative MRI was used to confirm the extent of mesial resection in 94 TLE patients and revealed a correlation of the extent of mesiobasal resection with seizure outcome, regardless of the extent of lateral resection.<sup>117</sup> In a separate, prospective randomized controlled trial, 70 patients with unilateral ictal onsets confirmed on intracranial recordings underwent temporal lobe resection and were randomized to partial or total hippocampectomy.<sup>105</sup> At 1- and 2-year follow-up, the group that underwent complete hippocampectomy experienced superior seizure outcomes (69% versus 38% seizure free at 1 year) without increased neuropsychological or neurological morbidity.

### IMPACT OF SURGICAL APPROACH

Although a small percentage of TLE patients may harbor epileptogenic zones exclusively in the lateral temporal neocortex,<sup>118</sup> the

majority of candidates for nonlesional temporal lobe resection have the syndrome of MTLE, for which resection of mesial structures is emphasized.<sup>8,59</sup> A long-term follow-up study of 50 patients managed with lateral resection alone revealed 44% to be seizure free at follow-up.<sup>119</sup> In Engel's compilation of seizure outcomes from 107 centers worldwide, outcomes were similar between centers regardless of the surgical approach, provided that the mesial structures were adequately resected.<sup>1</sup> In single-center studies, SAH and standard resections produced similar results.<sup>72</sup> In Yasargil's SAH series, 22 of 30 (73%) patients with TLE and depth electrode-confirmed hippocampal onsets were seizure free postoperatively.<sup>114</sup> These results after SAH compare favorably with studies of patients with histologically confirmed MTS undergoing standard anteromesial resections.<sup>120</sup>

A single-center study reported on the seizure outcomes of 321 patients who underwent various temporal lobe resections between 1989 and 1997.<sup>121</sup> This series incorporated 96 standard anterior temporal resections, 84 restricted lateral and generous mesial resections, and 91 SAH procedures. The notable finding was the absence of significant differences in seizure outcome between the three operative cohorts in which different resection strategies were used.<sup>8</sup>

### IMPROVEMENT IN SEIZURE OUTCOMES OVER TIME

Early investigations of temporal lobe resections documented seizure-free outcomes in 27% to 44% of patients in long-term follow-up.<sup>122-125</sup> This was during an era in which lateral resection was emphasized. Engel compared worldwide outcomes of earlier (1949 to 1984) and more recent (1986 to 1990) eras and documented superior outcomes in contemporary series (Table 70-6).<sup>1,8,10</sup> This was thought to result from improved methods of patient selection and convergence of surgical resection approaches to emphasize medial resection. Ultimately, in many patients seizure control is not static and may fluctuate over time.

In a study of patients with refractory TLE by Sperling and colleagues, 89 patients who underwent anterior temporal lobe resections between 1986 and 1990 were monitored postoperatively for 5 years.<sup>12</sup> Approximately 70% of the patients reported being seizure free over the past year (Engel class I). Only 55% of the patients were seizure free over the entire 5-year period after surgery. In those in whom seizures did develop, 55% experienced them within the first 6 months postoperatively, and almost 93%, relapsed within the first 2 years after surgery (Fig. 70-3). This suggested that in patients who were seizure free for the first 2 years after surgery, recurrent seizures were unlikely to develop thereafter.

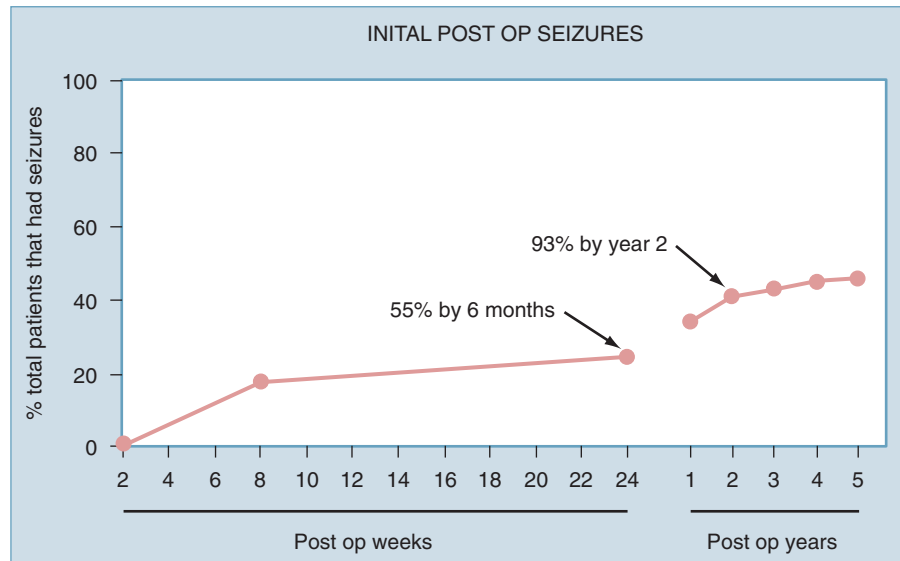
**TABLE 70-6 Worldwide Outcomes after Anterior Temporal Lobe Resection for Seizures**

PROCEDURE	N	SEIZURE FREE (2 yr)	REDUCTION	
			>90%	<90%
<b>PALM DESERT 1986: 39 CENTERS (1949-1084)</b>				
ATLX	2336	55.5%	27.7%	16.8%
<b>PALM DESERT 1992: 107 CENTERS (1986-1990)</b>				
ATLX	3579	67.9%	24.0%	8.1%
AHX	413	68.8%	22.3%	9.0%
Lx	293	66.6%	21.5%	11.9%

ATLX, anterior temporal lobectomy; AHX, amygdalohippocampectomy; Lx, lesionectomy.

From Engel J. Surgery for seizures. *N Engl J Med.* 1996;334:647-652.

**FIGURE 70-3** Total percentage of patients with postoperative seizures versus time of onset of the first postoperative seizure after anterior temporal lobe resection. (From Sperling M, O'Connor M, Saykin A, et al. *Temporal lobectomy for refractory epilepsy*. JAMA. 1996;276:470-475.)



A similar outcome study reviewed 148 patients who had an overall 44.6% seizure-free rate after 5 years, 62% of whom were seizure free in the previous year.<sup>87</sup> Another 5-year outcome study demonstrated similar results, with an overall 50% seizure-free rate at 5 years and a similar 62% seizure-free rate in the last 2 years of the study.<sup>75</sup>

#### ACUTE POSTOPERATIVE SEIZURES AND LATE IMPROVEMENT

Traditionally, immediate postoperative seizures were considered incidental to the trauma of surgery itself and not predictive of surgical outcome, analogous to early seizures after stroke or traumatic brain injury, which have not been shown to be reflective of long-term seizure outcomes.<sup>10</sup> This “running down” phenomenon was initially characterized by Rasmussen, whose early studies suggested that it occurred in as many as 15% to 20% of patients.<sup>126-128</sup> Recent investigations have not confirmed this belief, with only 5% of patients with TLE and immediate postoperative seizures experiencing improved seizure control over time. “Running down” may occur more commonly in patients with unilateral epileptiform discharges preoperatively.<sup>129</sup> Other studies, however, suggest that immediate postoperative seizure activity may predict poorer long-term seizure control in both adults<sup>130,131</sup> and children.<sup>132</sup>

#### INTRAOPERATIVE ELECTROCORTICOGRAPHY

For many years, temporal lobe resections “tailored” on the basis of intraoperative ECoG provided a standard surgical approach in many centers. Recent experience suggests that standardized anatomic resections may produce similar outcomes, and the appropriate role of intraoperative ECoG is not well defined in current practice. Early studies suggested that intraoperative ECoG may be useful to predict outcome, particularly if epileptiform discharges are present or absent in either preresection or postresection cortex.<sup>128,133,134</sup> Ojemann’s recent study used ECoG to define the extent of hippocampal resection in an attempt to both optimize seizure outcomes and minimize postoperative memory deficits though hippocampal sparing.<sup>109</sup> In contrast, two studies in which standardized anatomic resections were performed in the context of intraoperative ECoG before and after resection failed

to identify any predictive value with regard to ultimate seizure outcomes.<sup>135,136</sup> Other studies suggest a limited value of ECoG as a guide to the extent of resection for TLE.<sup>111,137,138</sup> Another study in patients with lesional temporal or extratemporal epilepsy in which resection was carried to normal tissue margins found that the extramarginal spike distribution was not associated with seizure outcome.<sup>139</sup> In contemporary practice, in which patient selection is guided by advanced imaging and video-EEG data, intraoperative ECoG is not used in some centers in the context of defined surgically remediable syndromes.<sup>83</sup>

#### Neuropsychological Outcomes

##### COGNITIVE OUTCOME

Intellectual function is generally preserved in adults<sup>12</sup> and children<sup>140</sup> after temporal lobe resection, and when seizure control is achieved, improvement in some measures has been reported. In the Graduate Hospital series of 89 consecutive patients undergoing dominant- and non-dominant-hemisphere resections, measures of verbal IQ were unchanged postoperatively and the study demonstrated improvements in performance and full-scale IQ.<sup>12</sup> In part, these improvements were believed to be attributable to practice effect. Subsequent studies have reported similar findings, including improvement in verbal IQ after non-dominant-hemisphere resections and performance IQ after dominant-hemisphere resections.<sup>141-144</sup>

##### GLOBAL MEMORY DEFICITS

Although uncommon in modern practice, global amnesia is a disabling complication of temporal lobe surgery. Two patients with global amnesia were described in an early Montreal Neurological Institute series of 90 dominant-hemisphere temporal resections.<sup>145</sup> These patients exhibited a syndrome of profound anterograde memory loss with preservation of cognitive performance, personality, early memory, and technical skills.<sup>146,147</sup> Earlier reports had described global amnesia after unilateral resection in either the dominant or nondominant hemispheres.<sup>143,147,148</sup> Evidence that hippocampal rather than lateral neocortical removal is critical to the production of global amnesia is provided by a report of a patient undergoing a staged resection



in whom global amnesia occurred only after the hippocampus was removed.<sup>145</sup> This is further supported by reports of global amnesia after SAH.<sup>149</sup> Contemporary series report rare postoperative global memory deficits at a frequency of less than 1%,<sup>49,143,150,151</sup> whereas a less profound postoperative “severe amnesia” may be more common.<sup>152</sup>

### **MATERIAL-SPECIFIC MEMORY DEFICITS**

Reported “material-specific” memory deficits include loss of short-term verbal and nonverbal memory postoperatively. In particular, short-term verbal memory loss is common after dominant temporal lobe resections, with significant decrements in verbal memory being reported in 25% to 50% of operated patients.<sup>153</sup> Verbal memory loss may accompany resections in the nondominant hemisphere, although at a much lower frequency.<sup>153</sup> Nonverbal memory deficits are less commonly identified, even after non-dominant-hemisphere resections,<sup>154</sup> although some authors report that these losses may be obscured by “practice effects.”<sup>153</sup> In the Graduate Hospital series, evidence of significant short-term verbal memory loss was identified in many patients after dominant-hemisphere temporal lobe resections, with a trend toward improvement after nondominant temporal lobe resections.<sup>12</sup> In a recent 10-year series of 321 TLE patients undergoing a variety of surgical approaches for the treatment of nonlesional and lesional TLE, verbal memory declined in 34%, improved in 19%, and remained stable in 46% of patients.<sup>121</sup> Weak preoperative performance on measures of verbal memory, young age at surgery, and operations on the nondominant side were associated with stability or improvement in verbal memory. Short-term nonverbal memory measures exhibited similar rates of improvement and deterioration. Weak preoperative performance on measures of nonverbal memory and dominant-side operations were associated with improvement, whereas advanced performance preoperatively and older age were associated with deterioration.<sup>121</sup>

The high frequency at which verbal memory impairment occurs after dominant-hemisphere temporal lobe surgery has stimulated interest in predicting which patients are at risk for postoperative deficits.<sup>8</sup> Recent studies have documented significantly greater risk for verbal memory loss in two categories of patients: (1) those with intact memory function and a normal hippocampus ipsilateral to the seizure focus (“functional adequacy” hypothesis) and (2) those with ipsilateral hippocampal atrophy but impaired memory function, presumably related to poor function within the hemisphere contralateral to the seizure focus to be resected (“functional reserve” hypothesis).<sup>8,155</sup> Patients with dominant-hemisphere TLE and a reversed Wada memory asymmetry score (i.e., better memory performance in the epileptogenic temporal lobe, with poor right temporal lobe performance) have been shown to have a greater risk for memory morbidity after left-sided resection, as well as poorer seizure outcome postoperatively.<sup>156</sup> Patients with dominant-hemisphere hippocampal atrophy who undergo contralateral, non-dominant-hemisphere resections are also at risk for verbal memory deficits.<sup>157</sup> Preoperative MRI studies of hippocampal volumes and left hippocampal MRS profiles (creatine/NAA ratio) also help predict the risk to verbal memory performance after surgery.<sup>62</sup>

In a recent study, a multivariate risk factor model for predicting postoperative decline in verbal memory was developed in which five risk factors were independently associated with outcome, including (1) dominant-hemisphere resection, (2) MRI findings other than exclusively ipsilateral MTS, (3) intact preoperative recall verbal memory, (4) relatively poorer preoperative immediate recall verbal memory, and (5) intact ipsilateral memory performance on the Wada test.<sup>8,158</sup> With this model, individual patients can be assessed with respect to their risk for deficits in verbal memory function after surgery.

### **STANDARD ANTERIOR TEMPORAL LOBECTOMY VERSUS SELECTIVE AMYGDALOHIPPOCAMPECTOMY: MEMORY OUTCOME**

In patients thought to be at risk for global or material-specific memory deficits postoperatively, various management strategies have been proposed to reduce these losses,<sup>8</sup> including memory mapping in the temporal neocortex with restriction of neocortical resection, SAH, or simple denial of surgery to these patients.<sup>159</sup> With reports of global amnesia occurring in patients undergoing SAH,<sup>149</sup> it was thought that it may be advantageous to perform selective mesial resection from the standpoint of preservation of material-specific memory, particularly short-term verbal memory function. Although some early outcome studies in small series of patients suggested a possible advantage of SAH over standard anterior temporal lobectomy from the standpoint of postoperative memory outcome,<sup>88,160</sup> this has not been supported by other studies, and there have been reports to the contrary.<sup>161</sup>

In a recent review of 140 patients undergoing either right or left SAH, a decline in verbal learning and memory occurred after 32% of the right-sided and 51% of the left-sided resections.<sup>54</sup> The left SAH patients were particularly at risk when preoperative testing revealed intact verbal memory function, late onset of epilepsy, and the absence of MTS on MRI. Collateral damage to adjacent temporolateral tissue during the transylvian dissection may exacerbate the deficits caused by hippocampal resection.<sup>54,162</sup> The role of deafferentation of the temporal circuitry during resection of the parahippocampal gyrus, amygdala, and hippocampus also needs to be considered. This is supported by PET evidence of worsening hypometabolism of the remaining temporal lobe neocortex after SAH.<sup>163</sup>

### **POSTOPERATIVE LANGUAGE DYSFUNCTION**

After dominant-hemisphere temporal lobe resection, a syndrome of transitory postoperative dysnomia or even aphasia is observed in as many as 30% of operated patients.<sup>164</sup> In most cases, the dysnomia or aphasia gradually disappears over a period of a few weeks. This occurs even when resections are guided by intraoperative or extraoperative language mapping.<sup>126,127</sup> The cause of this transitory phenomenon is unclear, but it is more common when resections are carried to within 1 to 2 cm of essential language sites as determined by mapping procedures.<sup>8,159,165</sup> Other explanations for this phenomenon include resection of inferior temporal lobe “inessential” language sites,<sup>166</sup> brain retraction and associated “neurometabolic edema,”<sup>167,168</sup> or deafferentation of white matter pathways. Some authors have suggested that such word-finding deficits represent an acute postoperative exacerbation of the preoperative deficits common in patients with TLE and that they last no longer than 1 year.<sup>169</sup>

Although some investigations of naming have not revealed enduring deficits at 6 and 18 months postoperatively,<sup>170-172</sup> others have suggested that significant, persistent word-finding difficulties do occur commonly after standard or anteromesial temporal lobe resection.<sup>164,173,174</sup> Such deficits have been reported to be associated with early risk factors for the development of seizures,<sup>173</sup> and with the pathologic state of the resected hippocampus.<sup>175</sup> In one study, 7% of patients undergoing standard dominant-hemisphere resections exhibited persistent postoperative dysnomia.<sup>174</sup> Ojemann described enduring language deficits after resections within 1 to 2 cm of identified language sites.<sup>176</sup>

The aforementioned findings stimulated interest in the value of intraoperative mapping and tailoring of the lateral neocortical resection. Ojemann and colleagues suggested that up to 17% of patients undergoing left temporal resections 4.0 to 4.5 cm from the temporal tip (a “standard” temporal lobe resection) without mapping would experience postoperative deficits.<sup>8,177</sup>



Some centers now restrict cortical resections to 3 cm of the middle and inferior gyrus without mapping and have reported minimal postoperative language deficits.<sup>103</sup> A general trend toward restricted lateral cortical resection in the temporal lobe has resulted in language mapping being less commonly used. It has not been studied whether such restricted resection may engender deficits not seen in patients undergoing mapping.

Persistent, severe dysphasia has been reported in 1% to 2% of patients undergoing dominant-hemisphere temporal resections, even with language mapping.<sup>116,143,178,179</sup> Such adverse postoperative outcomes occur as a result of resection of essential language cortex or manipulation or thrombosis of the middle cerebral or anterior choroidal artery.<sup>180</sup>

## Neurobehavioral and Psychosocial Outcomes

### PSYCHIATRIC OUTCOME

Psychiatric morbidity has been reported to occur in 15% to 50% of patients with epilepsy in the literature.<sup>181,182</sup> There is a high prevalence of psychopathology, including depression, in candidates for temporal lobe resection both preoperatively and postoperatively.<sup>183,184</sup> One study reported postoperative improvement or resolution of long-standing depressive symptoms in 47% of patients undergoing temporal lobe resections, thus suggesting that preoperative depression is not a contraindication to surgery.<sup>185</sup> In the same study, depression occurred *de novo* in 10% of operated patients. Improvement in depression postoperatively is more likely in patients who are rendered seizure free.<sup>186,187</sup> Preoperative assessment of the risk for chronic depressive symptoms postoperatively may be achieved by using measures of emotional adjustment, such as the Washington Psychosocial Seizure Inventory.<sup>187</sup> The early postoperative period is characterized by the dynamic expression of varying psychopathologic conditions. In one study, half of the patients with no psychopathology preoperatively exhibited symptoms of anxiety, depression, and emotional lability 6 weeks postoperatively.<sup>188</sup> Other reports have documented new psychiatric problems in 31% of patients and resolution of psychiatric diagnoses in 15% of patients in the 6 months after surgery.<sup>183</sup> One study reported that 10% of 121 patients with TLE who underwent epilepsy surgery required postoperative psychiatric hospitalization.<sup>189</sup> The *de novo* appearance of hypomania requiring psychiatric hospitalization,<sup>190</sup> psychogenic seizures (particularly in females undergoing nondominant temporal lobe surgery),<sup>183,191</sup> and neurotic or psychotic symptoms<sup>192</sup> postoperatively demonstrates the necessity for comprehensive psychosocial and psychiatric assessments both preoperatively and postoperatively. In the context of a thorough preoperative evaluation, a history of psychotic symptoms does not represent an absolute contraindication to surgical intervention, although an exacerbation of symptoms may occur postoperatively.<sup>8</sup>

### PSYCHOSOCIAL OUTCOME

It is increasingly being recognized that the syndrome of intractable TLE embraces comorbid conditions beyond the encumbrance of frequent, intractable seizures. Such comorbidity includes psychosocial, psychiatric, and neuropsychological impairment, medication toxicity, and excess mortality rates.<sup>8</sup> These impairments develop as a result of frequent, disabling seizures during critical stages of personal development and may not resolve immediately after surgery.

Patients are aware of epilepsy-associated disabilities and hope for their resolution after surgery. In a study of 69 preoperative patients, their aims for epilepsy surgery beyond freedom from seizures included desire for work, ability to drive, independence, socializing, and freedom from AEDs.<sup>9</sup> The psychosocial

outcomes of successful surgery were assessed in a 5-year follow-up study of the long-term changes in 61 surgical and 23 medically managed TLE patients.<sup>193</sup> In this study, 68% of the surgery group exhibited improved psychosocial status, as opposed to 5% of the medically managed group. Individuals who underwent surgery were found to be more likely to drive, live independently, work full-time, and be financially independent. Remaining seizure free was not a prerequisite for improvement in psychosocial measures in this study, although other investigations have documented diminished psychosocial adjustment in patients with recurrent seizures.<sup>194</sup>

## Health-Related Quality of Life

A clear relationship has been documented between psychosocial status and quality of seizure control in medically managed epileptics.<sup>195</sup> Similarly, in postoperative patients, seizure-free patients score more favorably than those with either auras or recurrent seizures on a variety of measures.<sup>45</sup> In the only randomized, controlled trial of epilepsy surgery versus best medical management to date, patients who underwent surgery were documented to have improvement in both seizure outcomes and HRQOL.<sup>2</sup> The surgical group consistently scored higher than the medical group as early as 3 months after surgery and continuing to 12 months on both the QOLIE-89 and measures of school or job performance. Another study showed better HRQOL in postoperative seizure-free patients than in those with persistent auras and persistent seizures.<sup>42</sup> In another study of patients 2 years postoperatively, both seizure-free patients and those with a 90% reduction in frequency experienced significant improvement in HRQOL.<sup>89</sup> When compared with the health status of patients with other chronic diseases, postoperative patients with persistent seizures scored worse than did those with heart disease, hypertension, or diabetes. When patients were seizure free postoperatively, they scored better than patients with these non-neurological illnesses.<sup>196</sup> In a study reviewing nonsurgical and surgical patients evaluated preoperatively and 1 and 2 years postoperatively, significant improvement was identified on 10 of the 17 scales of the QOLIE-89 in patients who were entirely seizure free.<sup>197</sup> Significantly more improvement was noted at 2-year follow-up than at 1-year follow-up. In addition, patients with persistent auras were not significantly improved when compared with patients with persistent seizures.<sup>197</sup>

In a large prospective surgical series of 396 patients in which the QOLIE-89 was administered before surgery and up to 5 years after surgery, the most substantial improvement in HRQOL occurred immediately after surgery in all patients, but additional improvements over time were seen in the seizure-free group.<sup>198</sup> The effect, in this study, seemed to stabilize at 2 years after surgery and was related to the duration of freedom from seizures. Another method of determining well-being is to assess patients' perceived effect of surgery or their satisfaction with the results. A recent study found that of 396 patients, 80% would make the same decision (to have surgery) if given the choice again, and 91% to 92% reported a strong or very strong positive impact of surgery (influenced by freedom from seizures and gainful employment).<sup>199</sup>

## Cost-Effectiveness of Surgical Treatment

Wiebe and coworkers used decision-analysis modeling and an intention-to-treat approach to compare medical and surgical treatment of intractable TLE in a Canadian population of 200 patients treated either surgically or medically over a 35-year period.<sup>48</sup> In their model, surgery required a larger initial expenditure; however, by 8 years after surgery, the cost savings engendered by the 57 seizure-free patients made surgical management less expensive than medical management across the entire cohort

of surgical patients. Thus, surgical therapy was more cost-effective than medical management in this population.

In a decision-analysis model of surgical versus best medical management of intractable TLE, Langfitt used Rochester, New York, cost data to address the relative cost-effectiveness of different treatments.<sup>8,47</sup> This investigation used public health clinical research methods that express the cost-effectiveness of treatment as a “marginal cost-effectiveness ratio” (MCER), which represents the dollar cost per QALY added to treated patients’ lives postoperatively. Each postoperative outcome state was assigned a quality adjustment on the basis of the ESI-55 scores achieved by 42 patients undergoing evaluation for surgery. With a state of total health adjusted to 1.0, patients with intractable seizures preoperatively were adjusted to 0.62; postoperative states were adjusted as follows: no seizures, 0.89; auras only, 0.80; and recurrent complex partial seizures, 0.72. In this model, a patient rendered seizure free after surgery would improve from 0.62 to 0.89 on the adjustment scale, and if this patient lived for 40 years in this state of health, the patient would accrue an additional 10 QALYs. The calculated MCER was \$15,581 per QALY, which compares quite favorably with the cost of other health care interventions. Another study reported a cost-effectiveness ratio of \$27,200 per QALY.<sup>200</sup> By comparison, the calculated MCER for lifetime tuberculosis screening for a 20-year-old African American was \$324,537 per QALY.<sup>47</sup> The MCER calculated for stenting versus balloon angioplasty for symptomatic, single-vessel coronary artery disease was \$29,893 per QALY.<sup>47</sup> In addition, the calculated MCER for asymptomatic intracranial aneurysm repair was \$28,441 per QALY.<sup>47</sup>

A recent study sought to determine whether health care costs change when seizures become controlled after surgery.<sup>201</sup> Total costs for seizure-free patients had declined 32% by 2 years after surgery because of less use of AEDs and inpatient care. Costs did not change in patients with persisting seizures, regardless of whether they underwent surgery. In the 18 to 24 months after evaluation, epilepsy-related costs were \$2068 to \$2094 in patients with persisting seizures versus \$582 in seizure-free patients. They concluded that costs remain stable for more than 2 years after evaluation in patients with TLE whose seizures persist but that patients who become seizure free after surgery use substantially less health care than before surgery. Further cost reductions in seizure-free patients can be expected as AEDs are successfully eliminated.

### Complications of Temporal Lobe Resection

In a review of the accumulated worldwide experience on temporal lobe resective surgery before 1993,<sup>49</sup> significant/impairing complications were uncommon and included *death*,<sup>51,124,143,202-204</sup> *infection*,<sup>49,143,167</sup> *hemiparesis* from manipulation or thrombosis of the middle cerebral artery or anterior choroidal vasculature or from direct brainstem injury or resection,<sup>203,205-209</sup> *visual field deficits* from resection of Meyer’s loop fibers in the roof of the temporal horn,<sup>209-211</sup> *hemianopia*,<sup>179,211,212</sup> as a result of excessive tissue resection or infarction, postoperative *hematoma* formation,<sup>124,143,202</sup> and rare *third cranial nerve*<sup>203,206</sup> and *seventh cranial nerve*<sup>213</sup> palsies. There was a trend toward reduced mortality and morbidity over time in a large, single-center series and in a worldwide survey of 2282 operations performed between 1928 and 1973.<sup>124</sup>

In a contemporary, single-center study of 329 temporal lobe neurosurgical interventions (in 321 consecutive patients), 28 complications were reported (8.5%), including no mortalities, meningitis (1.5%), subdural hematoma (0.6%), deep venous thrombosis (1.2%) and neurological complications (5.2%).<sup>121</sup> In another single-center study of 215 patients undergoing temporal lobe surgery between 1984 and 1999, complications included mild hemiparesis, hemianopia, transient cranial nerve palsies, and transient language difficulties.<sup>214</sup>

In a multicenter study at six different centers in Sweden, the complications in 449 operated patients were reviewed.<sup>56</sup> In 247 temporal lobe resections, one mortality occurred in a 62-year-old woman who experienced a postoperative hematoma. Hemiparesis occurred in 5 patients, in 1 patient after neocortical resection and in 4 patients after resections involving the hippocampus. These complications were thought to be due to anterior choroidal artery infarction and manipulation of “perforating vessels.” Other complications included hemianopia (0.4%) and cranial nerve injury (0.9%). A clear correlation between age and severity of complications was noted. Few complications occurred in those younger than 35 years. “Manipulation hemiplegia” was originally described by Penfield and colleagues<sup>208</sup> and may be caused by manipulation/injury to the anterior choroidal artery or the middle cerebral artery in the sylvian fissure. The resultant hemiparesis was thought to be more likely in older patients with atherosclerosis and hypertension and was one of the main complications of temporal lobe surgery in those older than 35 years. In a Norwegian epilepsy surgery series,<sup>215,216</sup> “large” complications occurred in 1 of 64 patients younger than 19 years and in 7 of 61 adult patients, thus confirming an increased risk for postoperative complications in older patients. Additional support is provided by another study of 215 operations performed between 1983 and 1999 in which permanent complications occurred in only 3 of 215 patients, and these patients were older than 30 years.<sup>214</sup>

Recent reports of unusual complications after temporal lobe resection include four cases of cerebellar hemorrhage believed to be related to postoperative epidural suction drains<sup>217</sup> and diplopia associated with transient trochlear nerve palsy in three patients.<sup>218</sup>

### MORTALITY AFTER TEMPORAL LOBE RESECTION

The annual death rate attributable to epilepsy, which reflects accidents, suicide, and sudden unexpected death due to epilepsy (SUDEP), is higher in patients with chronic epilepsy than in the general population.<sup>8</sup> Studies of the impact of postoperative freedom from seizures have revealed that successful temporal lobe surgery lowers but does not normalize the overall mortality associated with chronic epilepsy.<sup>219</sup> In the Graduate Hospital series, all late mortalities (four) occurred in patients with recurrent seizures, including three with SUDEP and one suicide.<sup>12</sup> In another study, late mortality was studied and occurred in 2% of seizure-free patients and in 11.9% of patients with recurrent seizures.<sup>214</sup>

### Lesional Temporal Lobe Epilepsy

Lesions of various types are identified in 15% to 30% of patients with intractable TLE.<sup>8,220,221</sup> These lesions may be neoplastic (astrocytoma, ganglioglioma, pleomorphic xanthoastrocytoma, dysembryoplastic neuroepithelial tumor), vascular (cavernous hemangioma, arteriovenous malformation [AVM], angioma), dysgenetic (microdysgenesis, focal or diffuse dysplasia, Sturge-Weber syndrome, tuberous sclerosis), or traumatic/ischemic. In a review of 167 patients with temporal or extra-temporal lesions, 15% had hippocampal sclerosis or “dual pathology.”<sup>268</sup> In further investigations of dual pathology, significant hippocampal neuron loss was identified in patients with lesions located adjacent to the hippocampus and in those with a history of “early injury.”<sup>222,223</sup>

In patients with mesial temporal lobe lesions and intractable epilepsy, studies of lesional resection alone, without resection of mesial structures (“lesionectomy”), have produced disappointing results, with 22%,<sup>224</sup> 19%,<sup>225</sup> and 43%<sup>226</sup> of patients rendered seizure free in small series.<sup>8</sup> In those with laterally located lesions, seizure outcome is improved when complete lesion resection is achieved.<sup>117</sup> When lesional removal is performed along with

standard mesial resection, seizure outcomes were improved, with 85%,<sup>226</sup> 91%,<sup>227</sup> and 92%<sup>228</sup> of patients being rendered seizure free in various series. Other authors have recommended gross total resection of the lesion along with an additional 5 to 10 mm of adjacent epileptogenic tissue (“lesionectomy plus”) and sparing of mesial structures in the case of lateral lesions without dual pathology (i.e., normal hippocampus) and have reported favorable seizure outcomes with this approach.<sup>8,121,229</sup> In patients with temporal lobe lesions and dual pathology, resection of mesial structures along with the lesion has been recommended.<sup>230</sup>

The value of ECoG in guiding decisions regarding the extent of extralesional tissue resection is controversial<sup>231</sup> and has been addressed in reports of patients with TLE and various tumors<sup>57,111,225,228</sup> and AVMs<sup>227</sup>; these reports suggest an advantage conferred by resection of epileptogenic tissue, including mesial structures, along with lesional resection. Despite a possible advantage from the standpoint of seizure control, hippocampal resection in lesional cases may cause significant neuropsychological morbidity when hippocampal sclerosis is absent on MRI, particularly in dominant-hemisphere resections. In cases in which the hippocampus is not invaded by tumor, the approach of “lesionectomy plus” may confer less morbidity in dominant-hemisphere resections while maintaining favorable seizure outcomes.<sup>229</sup> Excision of a presumed epileptogenic region without lesional resection tends to result in poor outcomes.<sup>231</sup>

### Extratemporal Epilepsy

The protean clinical manifestations of the extratemporal epilepsies result from the varied pathogenetic features of these disorders and the eloquent brain regions that are affected by seizures arising in the broad expanse of the frontal, parietal, and occipital lobes.<sup>8</sup> Extratemporal epilepsy patients undergo surgery less commonly than do patients with TLE.<sup>1</sup> The epileptogenic regions are often large and ill defined, thus mandating larger resections, and surgical approaches include lobar and multilobar, central and tailored resections, topectomy, and MST. Extratemporal resections are often combined with callosotomy or MST to improve efficacy. In a series of 2177 patients older than 51 years at the Montreal Neurological Institute, operations included temporal (56%), frontal (18%), central/rolandic (7%), parietal (6%), occipital (1%) and multilobar resections, as well as hemispherectomy (11%).<sup>49,232</sup>

### Seizure Outcomes

The outcomes of extratemporal resections have historically been less favorable than those achieved with temporal lobe surgery, with approximately 45% being seizure free after surgery.<sup>1</sup> Improved imaging, patient selection, mapping, and surgical methods have resulted in improved outcomes in contemporary reports. In a study of 60 patients with extratemporal epilepsy, structural abnormalities were present in 83% of the patients.<sup>233</sup> Surgical resection of the frontal, parietal, and occipital lobes was performed. Preoperative mapping with grids and strips was performed in 50%, and the remainder underwent intraoperative mapping with ECoG. At 4 years’ follow-up, 61% of the patients with focal lesions were seizure free versus 20% of the patients without histopathologic abnormalities. In a review of patients undergoing frontal lobe resections with adjunctive MST and callosotomy when appropriate, 72% were Engel class I or II postoperatively.<sup>234</sup> In another study of patients undergoing frontal lobe surgery, 24 underwent intracranial monitoring and 80% were Engel class I or II postoperatively (64% seizure free).<sup>235</sup> In this series, patients without lesions had better outcomes than those with lesions. In a review of frontal lobe epilepsies, 72% of lesional and 40% of nonlesional patients had an excellent outcome (Engel class I, II) after frontal lobe resection, with seizure-free

rates of 44% and 24%, respectively.<sup>236</sup> In a report of seizure outcomes in 37 patients with intractable frontal tumoral epilepsy, 67% of patients were Engel class I or II with 35% being seizure free.<sup>237</sup>

### Complications of Extratemporal Resection

Complications of extratemporal resections include those related to invasive monitoring with grids, surgical complications of resection or MST, and neurological sequelae of intentional resection of or inadvertent injury to regions of eloquent cortex.<sup>8</sup> The complications in one study included three wound infections and three neurological deficits that resolved slowly.<sup>233</sup> In frontal lobe resections in Broca’s area, within the posterior 2.5 cm of the opercula, the inferior frontal gyrus is usually spared,<sup>232</sup> and language sites identified by stimulation mapping techniques within the middle frontal gyrus may contribute, if resected, to transient or long-standing expressive aphasia.<sup>177</sup> Resection of the supplementary motor cortex may produce a transient syndrome consisting of postoperative mutism, contralateral neglect or hemiparesis, and diminished spontaneous movement, which usually resolves spontaneously over a period of weeks.<sup>238,239</sup> The cognitive effects of frontal resections are usually well tolerated.<sup>240</sup> Preservation of draining veins and arterial supply to the central area is a key consideration.<sup>49</sup> Partial resection of the non-dominant-hemisphere facial motor cortex is usually well tolerated; however, complete removal may produce long-standing perioral weakness.<sup>115,241,242</sup> The superior resection margin should be located no closer than 2 to 3 mm below the lowest elicited thumb response. Rasmussen described successful removal of the dominant-hemisphere facial motor cortex, provided that the vascular supply to the central area is meticulously preserved.<sup>8,241,242</sup> Large parietal resections behind the rolandic cortex can be accomplished with reported hemiparesis rates as low as 0.5%.<sup>242</sup> When resections are extended into the parietal operculum, visual field defects may occur if the resections are carried deep into the white matter.<sup>203,242</sup> A non-dominant-hemisphere parietal syndrome develops in some patients after large parietal resections, and in the dominant hemisphere, care must be taken to preserve Wernicke’s area. In the occipital lobe, complete resection produces the expected contralateral hemianopia, and excision in the dominant hemisphere to within 2 cm of Wernicke’s area may result in dyslexia.<sup>242</sup>

### Extratemporal Lesional Epilepsy

Lesional resection alone has provided favorable results in extratemporal sites, with 9 of 14 patients (64%) being seizure free in one study<sup>224</sup> and 17 of 18 patients (94%) being seizure free in another study.<sup>243</sup> A meta-analysis of lesional epilepsy in all sites showed that 44% of the patients were seizure free after simple excision and 67% were seizure free after “seizure surgery.”<sup>244</sup> Lesionectomy with removal of hemosiderin-stained brain resulted in freedom from seizures in 73% of patients with occult vascular malformations.<sup>245</sup>

Cortical dysplasias are associated with a unique pattern of intrinsic epileptogenicity, and intraoperative ECoG is thought by some authors to provide useful information for guiding resection and ensuring optimal seizure outcomes.<sup>246,247</sup> In a large series of patients undergoing surgery for focal epilepsy secondary to cortical dysplasia, 49% were seizure free.<sup>248</sup> Fifty-eight percent of those undergoing complete resection and 27% of those with incomplete resection were seizure free. Other reports suggest universal freedom from seizures in 100% of patients with Taylor’s balloon cell-type cortical dysplasia after complete lesionectomy without ECoG mapping.<sup>249</sup> Other neuronal migration abnormalities, such as “double cortex,” do not benefit from resective surgery.<sup>250</sup>



## Hypothalamic Hamartomas

“Intrahypothalamic” hypothalamic hamartomas (HH) may be associated with intractable partial, gelastic, and generalized seizures,<sup>251</sup> as well as retardation and behavioral disorders, whereas precocious puberty predominates in the “parahypothalamic” subset.<sup>252</sup> Although several reports have documented successful surgical removal of these lesions and relief of seizures with transcallosal or modified subfrontal approaches,<sup>253</sup> such intrahypothalamic surgery raises concern regarding complications of the approach, as opposed to direct intrahypothalamic resection of these lesions. A recent study reported the results of transcallosal surgical resection of HH in 26 patients with refractory epilepsy in a prospective outcome study.<sup>254</sup> Fourteen (54%) patients were completely seizure free, and 9 (35%) had at least a 90% improvement in total seizure frequency. They also reported postoperative improvement in behavior and cognition. The likelihood of a seizure-free outcome seemed to correlate with younger age, shorter lifetime duration of epilepsy, smaller preoperative HH volume, and 100% HH resection. Another recent study looked at 37 patients with HH and symptomatic epilepsy who underwent transcortical transventricular endoscopic resection.<sup>255</sup> Eighteen patients (48.6%) were seizure free. Seizures were reduced more than 90% in 26 patients (70.3%) and by 50% to 90% in 8 patients (21.6%). Additionally, the mean postoperative hospital stay may be shorter in endoscopic patients than in patients who undergo transcallosal resection.

## Cerebellar Seizures

The classic teaching that epileptic seizures do not arise from the cerebellar cortex has been challenged by several reports of focal motor seizures with secondary generalization in which the seizure focus appeared to be within the cerebellum.<sup>8,256</sup> Five of eight patients achieved freedom from seizures after resection of their cerebellar lesions.

## Catastrophic Epilepsy

“Catastrophic epilepsies” are those in which panhemispheric syndromes are associated with intractable seizures. Such syndromes include Rasmussen’s encephalitis, developmental syndromes (i.e., hemimegalencephaly, tuberous sclerosis, hamartomas, Sturge-Weber syndrome), and congenital hemiplegia/porencephaly.<sup>257</sup>

## Hemispherectomy

Although the original surgical approach of anatomic, complete, en bloc hemispherectomy with sparing of the basal ganglia, hypothalamus, and diencephalon<sup>114,242,258</sup> was successful from the standpoint of seizure control, the immediate and delayed complications were daunting.<sup>49</sup> In particular, these procedures created a large area of denuded, unsupported subcortical tissue and significant volumes of intracranial dead space that led to repeated microhemorrhage and subdural membrane formation, referred to as “superficial cerebral hemosiderosis.”<sup>98</sup> Late complications in the postoperative course occur in as many as 38% of patients<sup>259</sup> and include hydrocephalus,<sup>260</sup> increased intracranial pressure, neurological demise, or even death.<sup>261</sup> An alternative approach to hemispheric decortication (i.e., removal lobe by lobe) was reviewed in a large pediatric series.<sup>257</sup> The study reported that 26 of 48 patients were seizure free with a reduced rate of delayed complications.<sup>257</sup> Nevertheless, perioperative mortality occurred in 3 patients, and intraoperative blood loss and coagulopathy complicated the clinical course, particularly in children without brain atrophy or with hemimegalencephaly. In another version of “cerebral hemicortectomy,” the entire cortical surface is “degloved” to the level of the white matter. In one study this

resulted in 8 of 11 patients being seizure free, 1 patient with hydrocephalus, and no mortalities or delayed complications.<sup>262</sup>

With the introduction by Rasmussen of the technique of modified or “functional hemispherectomy,” in which a generous central and temporal resection is juxtaposed with deafferentation of the frontal and occipital lobes, postoperative complications were significantly reduced.<sup>115,242</sup> With deafferentation rather than removal of the frontal and occipital lobes, the volume of intracranial dead space is reduced.<sup>8</sup> In a 7-year follow-up study of 14 patients, no hemosiderosis or hydrocephalus occurred, and 10 of the 14 patients were seizure free.

Over the last 15 years, the approach of hemispheric deafferentation as a preferred alternative to resection has been advanced by several authors, all of whom perform increasingly limited resections in concert with hemispheric deafferentation. During this period, “peri-insular hemispherotomy” was introduced, in which a smaller craniotomy and a much reduced peri-insular (opercular frontal, parietal, temporal) resection are combined with deafferentation of the frontal, parietal, occipital, and temporal lobes.<sup>263</sup> This study reported favorable seizure outcomes (9 of 11 patients seizure free and 1 of 11 improved 95%). In addition, the study documented reduced operative time, as well as a decrease in perioperative and delayed complications. Hemispherectomy in children has been found in recent studies to result in freedom from seizures in 43% to 79% of patients.<sup>264-273</sup>

The “transylvian keyhole functional hemispherectomy” advanced by Schramm and colleagues<sup>274,275</sup> represents a true “minimalist” approach to hemispheric deafferentation.<sup>8</sup> A linear scalp incision and a 4- by 4-cm craniotomy provide the limited exposure required for a transylvian approach to the circular sulcus, through which access to the entire ventricular system is gained.<sup>8</sup> Transventricular hemispheric deafferentation and amygdalohippocampotomy resulted in significantly decreased blood loss and a reduced mean operating time when compared with a Rasmussen-type functional hemispherectomy. Of the 20 patients reviewed, 88% were seizure free, and 6% had improvement in their seizures. This approach is facilitated in patients with hemispheric atrophy and not recommended in those with hemimegalencephaly.<sup>8</sup> In a modification of this technique, another study evaluated 34 patients undergoing “transopercular hemispherotomy,” after which 67% of patients were seizure free.<sup>276</sup>

## DISCONNECTION SURGERY

### Multiple Subpial Transection

MST was developed by Morrell and colleagues to permit the treatment of partial epilepsies in which the seizure focus resides exclusively or partially within eloquent cortical regions.<sup>277</sup> In a review of the Rush Presbyterian experience with 100 patients, seizure outcomes were stratified according to MST performed alone (32 patients) or in conjunction with cortical resection (68 patients).<sup>277</sup> Class I and II outcomes were achieved, respectively, in 38% and 25% of patients with partial seizures undergoing MST alone, in 58% and 13% of patients with Landau-Kleffner syndrome treated by MST alone, and in 49% and 10% of patients when MST was performed in conjunction with resection procedures. In another review of 20 MST procedures performed without resection, less favorable outcomes were reported.<sup>278</sup> Yet another study of 12 patients undergoing MST with or without resection revealed less favorable outcomes, including Engel class II (1), III (2), and IV (9).<sup>279</sup> A study of long-term outcome reported a late increase in seizure frequency in 19% of patients treated by MST with or without resection.<sup>280</sup> A meta-analysis of an aggregate international experience consisting of 211 patients at six centers revealed that 53 underwent MST alone and 158 underwent MST plus resection.<sup>281</sup> An “excellent outcome,” defined as



greater than a 95% reduction in seizures, was achieved with MST plus resection in 87% of patients with generalized seizures and in 68% with complex partial seizures; with MST alone, 71% of patients with generalized seizures and 62% of patients with complex partial seizures had excellent outcomes.

As an increasing number of patients have undergone MST, we have been able to evaluate the neurological deficits resulting from this procedure. MST has been associated with a reduction in verbal fluency but preservation of spoken and written language abilities.<sup>277</sup> In this same study, 41 of 45 patients undergoing MST in Wernicke's area had preserved receptive function, including comprehension of spoken and written words. One patient suffered a deep hemorrhage causing a speech deficit. In 44 transections in the hand motor cortex, strength was preserved, and activities of daily living could be performed with the affected hand.<sup>277</sup> Of 7 transections in the leg area, which were described as technically difficult, 2 patients suffered footdrop because of subcortical venous hemorrhage. Overall, neurological complications were observed in 17% and permanent deficits were identified in 7%. No mortalities occurred. Two cases of "remarkable" intraoperative brain swelling and edema have been described, with a large intracerebral hematoma discovered in 1 patient.<sup>278</sup>

### Corpus Callosotomy

The procedure of subtotal or staged total corpus callosotomy has been recommended less frequently since widespread introduction of the vagal nerve stimulator.<sup>8</sup> Nevertheless, an abundant literature attests to the utility of callosotomy as palliative treatment in patients with multiple or poorly lateralized (and unresectable) epileptogenic foci, secondarily generalized tonic-clonic seizures, and injurious drop attacks because of tonic or atonic seizures with resultant falls and injury.<sup>282-286</sup> Early studies revealed increased focal seizures in 25% of patients undergoing callosotomy.<sup>285</sup> It has been reported that 70% of patients will achieve elimination of seizures or at least a greater than 80% reduction in their frequency.<sup>284,285,287</sup>

In a recent series of 23 patients with intractable generalized seizures, patients underwent partial division (17) or total division (6) of the corpus callosum.<sup>288</sup> Forty-one percent of the patients were completely seizure free or nearly free of the seizure types targeted for treatment. Forty-five percent of the patients experienced a greater than 50% reduction in seizure frequency. Simple partial motor seizures developed in 4 patients postoperatively. In addition, mentally retarded patients tended to have poorer outcomes. Fifty-seven percent of patients experienced a transient disconnection syndrome that resolved. One patient suffered a clinically silent right frontal infarction related to venous thrombosis. The average hospital stay was 7.7 days.

Callosotomy is particularly effective for drop attacks. In a study of 52 patients with drop attacks (tonic or atonic seizures), 42 (81%) exhibited complete cessation of drop attacks, with greater success occurring in those undergoing total callosal section.<sup>289</sup> Two adult patients suffered a marked disconnection syndrome that gradually remitted, and 14 patients experienced transient akinetic states that resolved in several weeks. In another study of 20 patients monitored for 3 years, 10 exhibited a marked improvement in QOL, and 10 had greater than a 50% reduction in their seizures.<sup>290</sup> In another cohort of 17 patients, 9 had greater than an 80% reduction in targeted seizures, and overall, 88% of the patients reported satisfaction with the surgical outcome because of improved alertness and responsiveness.<sup>291</sup>

The surgical and functional complications attributable to corpus callosotomy are well described in the literature, with a larger number of complications noted in earlier series.<sup>49,228</sup> The main complications reported are acute disconnection syndromes, more common with total callosotomy, and the rare "split brain" syndrome. Subtotal (70% to 80%) callosotomy has been recom-

mended as an initial procedure to minimize this complication. Surgical complications such as hemorrhage and infarction are related more to obtaining access to the interhemispheric fissure. With modern advances in microsurgical approaches and careful patient selection, corpus callosotomy is a safe procedure and a technique that is currently underused.

## NEUROMODULATORY SURGERY

### Vagus Nerve Stimulation

Since Food and Drug Administration approval in 1997 of VNS as palliative treatment of patients older than 12 years with intractable partial seizures, tens of thousands of patients have undergone implantation of a left vagus nerve stimulator.<sup>292,293</sup> In prospective clinical trials, a median partial seizure reduction of 34% after 3 months and 45% at 12 months was achieved in patient groups both younger and older than 50 years. Twenty percent of patients at 12 months had 75% or greater reductions in seizures, thus demonstrating improved seizure control over time.<sup>292,293</sup> At 3 months, generalized seizures were reduced by 46%. Improvements in mood have also been reported.<sup>294</sup> Although it has been observed that figural memory worsens when VNS is active during memory tasks,<sup>295</sup> no change in cognitive functions has been noted.<sup>296</sup> In patients with greater than 50% improvement in seizure frequency, QOL measures were improved.<sup>296,297</sup> In a long-term study looking at the effectiveness of VNS in epilepsy patients, seizure frequency was reduced by 26% 1 year after implantation, by 30% 5 years after surgery, and by 52% 12 years after implantation.<sup>298</sup> A more recent study suggested that VNS could be a safe and effective alternative therapy in children with drug-resistant epilepsy who are not candidates for epilepsy surgery.<sup>299</sup> In this study, after a mean follow-up of 31 months, 38% of the patients had a reduction in seizure frequency of greater than 90%.

Reported side effects include voice alteration, hoarseness, throat or neck pain, headache, cough, and dyspnea.<sup>300</sup> Adverse events in adults include infection requiring antibiotics or removal of the device (or both) and transient paralysis of the left vocal cord with hoarseness and aspiration.<sup>301</sup> There is an extraordinary report of self-inflicted vocal cord paralysis in 2 developmentally disabled patients by manipulation and rotation of the pulse generator within the subclavicular pocket.<sup>302</sup> Such a report mandates that patients be observed for manipulation of the device. In a review of adverse events in 24 children implanted with the vagal nerve stimulator, 15 events occurred in 11 patients, including lead fractures, wound erythema, requested removal of the device, abscess, malfunction, gastrostomy, recurrent psychosis, and diminished speech volume.<sup>300</sup> Removal of electrodes from the vagus nerve can be difficult. One paper reported resolution of a deep wound infection with antibiotics alone, thus suggesting that removal of the device might not always be necessary.<sup>303</sup> No increase in sudden unexpected, unexplained death with the vagal nerve stimulator was identified when implanted patients were compared with appropriate cohort populations.<sup>304</sup>

### Deep Brain Stimulation

In the past, brain stimulation in the cerebellum, the caudate nucleus, and the anterior, centromedian, and ventralis intermedius thalamic nuclei has been performed in an attempt to modulate cortical excitability.<sup>305,306</sup> Small controlled trials in 14 patients who underwent cerebellar stimulation showed that 2 were improved and 12 were unchanged.<sup>307</sup> In another study, 4- to 6-Hz stimulation of the ventral caudate nucleus led to a reduction in neocortical and mesial temporal epileptic discharges and electrical spread of seizures, but clinical seizure data were

not assessed. Caudate nucleus stimulation for epilepsy has not yet been tested in controlled studies. A small placebo-controlled study of stimulation of the centromedian nucleus showed no significant benefit.<sup>308</sup> An initial report of patients undergoing DBS in the subthalamic nucleus described a greater than 80% reduction in daytime seizures.<sup>305</sup> In another study, 5 patients with various seizure types underwent stimulation through bilateral electrodes in the anterior thalamus.<sup>309</sup> They reported a significant decrease in seizure frequency, with a mean 54% reduction (mean follow-up of 15 months). Two of the patients had a 75% or greater reduction in seizures. The observed benefits, however, did not differ between stimulation-on and stimulation-off periods, thus suggesting that either a placebo or carryover effect was present. Currently, a multicenter prospective randomized trial of scheduled chronic anterior thalamic stimulation in patients with medically intractable localization-related epilepsy is under way. Electrical stimulation of the hippocampus has also been reported in an attempt to block temporal lobe seizures.<sup>310</sup> In another small series, 3 patients with complex partial seizures had DBS electrodes implanted in the amygdala-hippocampal region.<sup>311</sup> Over a mean follow-up of 5 months, all patients had a greater than 50% reduction in seizure frequency. In 2 patients, AEDs could be reduced. Complications with DBS for epilepsy, such as hemorrhage and infection, have been reported in about 5% of patients,<sup>312</sup> although the hemorrhage is often not clinically significant.

There is growing interest in methods of neurostimulation that are modulated by input from sensing devices. A small pilot study reported that responsive stimulation controlled with an external computer system terminated some spontaneous seizures in eight patients, four with bilateral anterior thalamic stimulation and four with focal cortical stimulation.<sup>313</sup> In this study, analysis of electrographic seizure severity in stimulated versus nonstimulated events was used to rule out non-stimulation-associated effects and suggested both an immediate effect and a possible cumulative antiepileptic effect of high-frequency stimulation. A multi-institutional clinical study is also under way in patients with medically intractable partial onset seizures treated with a cranially implanted responsive neurostimulator (RNS). The RNS pulse generator continuously analyzes the patient's ECoG tracings and automatically triggers electrical stimulation when specific ECoG characteristics programmed by the clinician are detected. An initial single-center experience in a feasibility study of this device described a 45% decrease in seizures in seven of eight patients with a mean follow-up of 9 months.<sup>314</sup>

## STEREOTACTIC RADIOSURGERY

### Radiosurgery for Hypothalamic Hamartomas

HH may be associated with an epileptic encephalopathy marked by medically intractable gelastic and other seizures and behavioral and cognitive decline. Recent reports of successful treatment of HH with Gamma Knife surgery (GKS) have offered an attractive alternative to open surgery.<sup>315-318</sup> In a multicenter study of 10 patients undergoing GKS in seven centers, 4 patients were seizure free (Engel class I), 1 had rare nocturnal seizures, 1 had rare partial seizures, and 2 were improved.<sup>316</sup> A European, multicenter, prospective trial of GKS for HH has enrolled 60 patients, 27 of whom have exceeded 3 years of follow-up.<sup>319</sup> Ten of the 27 patients (37%) were seizure free (Engel class I). This study emphasized a temporal evolution of changes in seizure frequency during the postirradiation period: a slight improvement in seizure frequency within the first 2 months, followed by

transient worsening, with a subsequent reduction and ultimate remission in favorable cases. Behavioral improvements, in addition to EEG normalization, occurred in a more linear fashion. Minimal side effects were reported. Patients treated with doses exceeding 17 Gy to the margins of the HH seemed to have greater rates of seizure remission than did those receiving less than 13 Gy.

### Radiosurgery for Supratentorial Tumors

Given the diverse pathologic features and locations of central nervous system tumors associated with intractable epilepsy, the effects of GKS on tumor progression and seizure outcome are not well studied. One study divided 24 patients into two groups distinguished by the amount of radiation directed to surrounding tissue.<sup>320</sup> Outcome was assessed at a mean of approximately 2 years after GKS as "excellent" (Engel class I or II) or not. Patients in the high-dose group achieved a 66% improvement rate as compared with 42% in the low-dose group, with all patients exhibiting adequate tumor control. This report suggested that higher GKS doses to the epileptogenic region surrounding the tumor may improve seizure outcomes.

### Radiosurgery for Arteriovenous Malformations

The potential efficacy of GKS in the treatment of symptomatic localization-related epilepsies has best been demonstrated in the treatment of AVMs. One large series reported that seizures remitted after GKS in 69% of patients with AVM and epilepsy.<sup>321</sup> Subsequent studies of both proton beam treatment and GKS showed a combined rate of seizure remission of 73% to 80%.<sup>322-324</sup> A recent large case series emphasized that the incidence of seizure remission is better with smaller AVMs.<sup>324</sup> However, another study noted that seizures remitted independent of radiologic remission of the AVM, thus suggesting that the effects of irradiation near the lesion, rather than improvement of the AVM itself, may be important in control of seizures after GKS.<sup>321</sup>

### Radiosurgery for Cavernous Malformations

It is difficult to draw conclusions about seizure outcome after radiosurgery for cavernomas given the limited studies in the literature. In general, seizure remission appears to be lower than that encountered in patients after treatment of AVMs. The effect of dose to adjacent brain tissue around the margin of the cavernous malformation, thought to be important in the case of tumors and possibly AVMs, has not been systematically studied with regard to seizure control for patients with cavernomas. Excess morbidity in terms of postoperative hemorrhage and edema remains a concern. An early study suggested that GKS did not appreciably alter the natural course of cavernous malformations while exposing patients to radiation-induced complications that exceeded by seven times those expected with the same dose for AVMs.<sup>325</sup> A more recent retrospective comparison concluded that traditional open resection resulted in better seizure control and a lower risk for hemorrhage than GKS did.<sup>326</sup> A retrospective multicenter trial reported on 49 patients with cavernomas treated by GKS.<sup>327</sup> All patients had epilepsy that was medically intractable and were monitored for more than 12 months after treatment. The mean marginal dose was 19.2 Gy. Twenty-six patients (53%) became seizure free (Engel class I), 10 patients (20%) had a substantial decrease in the number of seizures (Engel class II), and 13 patients (26%) had little or no improvement. The average time to seizure remission was 4 months, and severe radiation-induced edema developed in 7 patients, but they recovered fully.

## Radiosurgery for Mesial Temporal Lobe Epilepsy

The rationale for treatment of MTLE with GKS is less compelling than in the disorders discussed previously because MTLE is amenable to open surgery.<sup>328</sup> All of the studies in the literature differ in their treatment protocols and results, with most failing to achieve complete remission from seizures.<sup>329-334</sup> An earlier study had demonstrated that 6 of 7 patients (86%) studied over a 2-year follow-up period were seizure free after radiosurgery.<sup>329</sup> A more recent trial reported that 13 of 21 patients (62%) were seizure free (Engel class I) after radiosurgery for MTLE.<sup>334</sup> The variability in outcome of GKS therapy for MTLE may reflect differing approaches to the dose and target volume more than the anatomic target of the mesial temporal lobe structures.<sup>328</sup> Taken together, these studies suggest that low-dose protocols are less successful than higher-dose protocols. No significant clinical or neuroimaging changes occur until approximately 9 to 12 months after treatment, and the most dramatic drop in the seizure rate occurs between 12 and 18 months, coincident with the development and resolution of maximal MRI changes. Reported morbidities include visual field deficits, headache, nausea, vomiting, and depression.

Beyond seizure control, studies have begun to evaluate secondary outcome measures such as cognition and QOL. Three reports of neuropsychological outcome after GKS for MTLE are available.<sup>332-334</sup> One prospective, multicenter trial reported no mean neurocognitive changes through a 2-year follow-up period.<sup>334</sup> Similarly, one small series reported no group mean changes at 6 months of follow-up, although some individuals showed a decline in at least one cognitive domain.<sup>332</sup> Another small series reported on three participants with a 27-month follow-up who underwent dominant-hemisphere low-dose GKS.<sup>333</sup> No long-term consistent changes in neurocognitive measures were found, although each patient showed a decline in a measure of verbal memory. They concluded that the neurocognitive changes after GKS appear to be similar to those after anterior temporal lobectomy.

Overall, although GKS for MTLE is promising, the optimal treatment protocol has not yet been determined and the relative benefits in terms of seizure resolution and avoidance of complications have yet to be clearly demarcated from those of open surgery. A National Institutes of Health–sponsored multicenter pilot study on the safety of GKS for MTLE has recently been completed.<sup>328</sup> In this study, patients who would normally qualify for anterior temporal lobectomy for unilateral MTLE were randomized to either a 20- or 24-Gy dose. A total of 30 subjects were enrolled and monitored for 3 years; the preliminary results are promising, with safety well within that expected after routine GKS and favorable efficacy and neuropsychological profiles.

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