

Editorials

INTERNET-ONLY PUBLICATION

THIS week the *Journal's* table of contents lists one title that is on our Web site but does not appear in the print version. The *Journal's* first Web-only Image in Clinical Medicine, "A Hair-on-End Skull,"¹ can be found at <http://www.nejm.org>. We plan to release about one Image in Clinical Medicine per month as a featured, Web-only publication. This Web-only feature is free and available to all visitors to the site. The Internet offers journals an opportunity to publish additional articles and other features without having to expand the size of their printed editions. For example, some of our articles already include supplementary material available only on the Web. Such supplementary material is carefully selected on the basis of its importance to the printed article and its relevance to readers. In recent years we have received many Images in Clinical Medicine that are acceptable for publication, but the space for them in the printed *Journal* is limited. We have decided to publish some of these Images only on the Web.

The review and editorial process for Internet-only material will be the same as for all other manuscripts, and the same standards of quality will apply. Internet-only publications will be listed in the print version of the *Journal* and in our index. They will be indexed in Medline, can be cited in the literature, and will continue to be available indefinitely on our Web site. Internet-only publications are assigned electronic "page numbers" (e.g., e1) that will make them easy to find and cite. Increasingly, scientific journals are using the Internet to publish more than what appears in their printed pages. We welcome comments on our new Web-only feature.

EDWARD W. CAMPION, M.D.
KENT R. ANDERSON
JEFFREY M. DRAZEN, M.D.

REFERENCES

1. Ramos-Remus C, Galvan-Villegas F. A hair-on-end skull. *N Engl J Med* 2001;345:e1.

Copyright © 2001 Massachusetts Medical Society.

FINALLY, A RANDOMIZED, CONTROLLED TRIAL OF EPILEPSY SURGERY

IN all of modern medicine, few generally accepted therapeutic interventions are as underutilized as surgical treatment for epileptic seizures. More than 2 mil-

lion people in the United States have epilepsy, and 400,000 to 600,000 of them have seizures that cannot be controlled by antiepileptic drugs.¹ As many as one quarter to one half of these people are potential candidates for surgical treatment, yet a 1990 survey revealed that only 1500 therapeutic surgical procedures for epilepsy were performed in the United States in that year and that the rate of use of surgery for epilepsy was equally low in other industrialized countries.² Surgical treatment for epilepsy was essentially nonexistent in the developing world 10 years ago,² although it is now offered in some developing countries.³ Even if the rate of surgical treatment had doubled in the past decade, however, it would have had only a small effect on the health care burden imposed by epilepsy.⁴

It is difficult to understand why physicians, as well as patients, remain reluctant to choose surgical treatment for epilepsy, since this therapeutic intervention has offered the only chance of cure for this disorder for more than a century.⁵ Furthermore, thousands of published reports have documented its safety and efficacy. True, brain surgery is invasive, but neurosurgical techniques have improved greatly in recent years, whereas uncontrolled epileptic seizures still present a substantial risk of disability and death.^{6,7} Although pre-surgical evaluation can be expensive, modern neurodiagnostic techniques have markedly reduced the need for costly, invasive studies,⁸ and the cost of surgery for epilepsy remains a small fraction of the cost of a lifetime of disability. Certainly, an important obstacle to surgery's taking what many believe to be its rightful place in the therapeutic armamentarium for epilepsy has been our failure to apply the gold standard for the evaluation of therapeutic efficacy — the randomized, controlled trial.

Why has there never been a randomized, controlled trial of surgery for epilepsy? In this regard, surgery for epilepsy has been a victim of its own success. The construction of an ethical randomized, controlled trial requires equipoise — honest doubt about the outcome. Most epilepsy centers currently report rates of freedom from seizures of 70 to 90 percent among patients with surgically remediable epileptic syndromes.⁸ Given that uncontrolled epileptic seizures may increase the risk of death by a factor of almost five,⁶ how can a patient with drug-resistant epilepsy who is referred for surgical treatment ethically be randomly assigned to continued pharmacotherapy? Equipoise certainly does not exist in the minds of those who are asked to perform the surgical intervention.

Finally, however, in this issue of the *Journal*, Wiebe and his colleagues report the results of a randomized, controlled trial of surgical treatment for epilepsy that they were able to justify ethically because the waiting list for surgery at their institution already exceeded one year.⁹ Consequently, they could randomly assign 40 patients with temporal-lobe epilepsy to a medical-

treatment protocol during the one year of expected delay without introducing additional risk and assign another 40 to immediate surgery. This clever protocol design required the authors to make two concessions that might have compromised their ability to obtain significant results: the follow-up time had to be limited to one year, which is short for demonstrating the beneficial effects of successful surgery on the quality of life and social functioning; and randomization took place before presurgical evaluation, so that patients were not definitively identified as appropriate candidates for surgery at the time they were randomly assigned to the surgical group. Nevertheless, the study did yield statistically significant differences in outcome with respect to both seizures and quality of life, as well as a trend with respect to social functioning. More important, perhaps, this study has also demonstrated that a well-designed randomized, controlled trial of surgery for epilepsy can be completed successfully.

Even though four patients assigned to the surgical group did not undergo surgery, 58 percent of the patients in the group were free of disabling seizures at one year, as compared with only 8 percent of those assigned to receive medical treatment.⁹ Of the patients assigned to the surgical group who actually underwent surgery, 64 percent were free of disabling seizures. This figure is somewhat lower than those reported recently for carefully selected patients with mesial temporal-lobe epilepsy,^{10,11} but the surgical group in the study by Wiebe et al. included several patients with complicated epilepsy, as evidenced by the fact that six required invasive presurgical investigations. Overall, the seizure-related outcome was similar to previously published results for the surgical treatment of unselected patients with temporal-lobe epilepsy.¹² Furthermore, in all patients in the surgical group who continued to have seizures, the frequency of seizures decreased. In contrast, only 34 percent of those in the medical group had such a decrease.

The quality of life for patients with epilepsy is clearly related to the recurrence of seizures,¹³ but it takes some time for lifestyle to improve after seizures have been eliminated by surgery. That patients in the surgical group in the study by Wiebe et al. had significantly higher scores on a quantitative measure of the quality of life at the end of one year than patients in the medical group is impressive.⁹ The strong trend toward higher rates of employment and school attendance in the surgical group⁹ is also meaningful.

This randomized, controlled trial should help alleviate residual doubt about the efficacy of surgical treatment for temporal-lobe epilepsy, but it is not the end of the story. This definitive demonstration that randomized, controlled trials comparing surgery for epilepsy with medical therapy are feasible should stimulate many more studies involving patients with other forms of drug-resistant epilepsy that are surgically remediable.

For surgically remediable syndromes that begin early in life, before the acquisition of essential social and vocational skills, the question of when to consider surgical intervention is particularly important. Properly timed, successful surgery can avert irreversible psychosocial consequences of disabling seizures.¹⁴ Since the number of available antiepileptic drugs has doubled in recent years, it could literally take a lifetime to prove that a patient's seizures are unresponsive to all medications in every conceivable combination. However, recent evidence suggests that drug-resistant epilepsy may be predicted after only one or two appropriately chosen pharmaceutical agents have been proved ineffective.¹⁵ Thus, for many patients, it may be reasonable to consider surgical treatment within a year or two after the onset of disabling epileptic seizures, when eliminating seizures should offer the best chance for a return to a full and productive lifestyle.

Even if referrals for surgery for epilepsy increase, successful outcomes with respect to seizures may not have a maximal beneficial effect on patients' lives until referring physicians stop considering surgical intervention for seizures a last resort. True equipoise exists with regard to the timing of surgical intervention. Therefore, to establish surgery as the treatment of choice for epileptic syndromes such as mesial temporal-lobe epilepsy, randomized, controlled trials must now be conducted to evaluate the potential benefits of early surgical intervention for these conditions.

JEROME ENGEL, JR., M.D., PH.D.

UCLA School of Medicine
Los Angeles, CA 90095-1769

REFERENCES

1. Hauser WA, Hesdorffer DC. *Epilepsy: frequency, causes and consequences*. New York: Demos Press, 1990.
2. Engel J Jr, Shewmon DA. Overview: who should be considered a surgical candidate? In: Engel J Jr, ed. *Surgical treatment of the epilepsies*. 2nd ed. New York: Raven Press, 1993:23-34.
3. Wieser H-G, Silfvenius H. Overview: epilepsy surgery in developing countries. *Epilepsia* 2000;41:Suppl 4:S3-S9.
4. Murray CJL, Lopez AD, eds. *Global comparative assessment in the health sector: disease burden, expenditures, and intervention packages*. Geneva: World Health Organization, 1994.
5. Horsley V. Brain-surgery. *Br Med J* 1886;2:670-5.
6. Sperling MR, Feldman H, Kinman J, Liporace JD, O'Connor MJ. Seizure control and mortality in epilepsy. *Ann Neurol* 1999;46:45-50.
7. Pilcher WH, Roberts DW, Flanigin HE, et al. Complications of epilepsy surgery. In: Engel J Jr, ed. *Surgical treatment of the epilepsies*. 2nd ed. New York: Raven Press, 1993:565-81.
8. Engel J Jr. Surgery for seizures. *N Engl J Med* 1996;334:647-52.
9. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345:311-8.
10. Sperling MR, O'Connor MJ, Saykin AJ, Plummer C. Temporal lobectomy for refractory epilepsy. *JAMA* 1996;276:470-5.
11. Thadani VM, Williamson PD, Berger R, et al. Successful epilepsy surgery without intracranial EEG recording: criteria for patient selection. *Epilepsia* 1995;36:7-15.
12. Engel J Jr, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J Jr, ed. *Surgical treatment of the epilepsies*. 2nd ed. New York: Raven Press, 1993:609-21.
13. Vickrey BG, Hays RD, Rausch R, et al. Outcomes in 248 patients who had diagnostic evaluations for epilepsy surgery. *Lancet* 1995;346:1445-9.

14. Engel J Jr. The timing of surgical intervention for mesial temporal lobe epilepsy: a plan for a randomized clinical trial. *Arch Neurol* 1999;56:1338-41.
15. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314-9.

Copyright © 2001 Massachusetts Medical Society.

GENETIC CLUES TO THE CAUSE OF PRIMARY PULMONARY HYPERTENSION

PRIMARY pulmonary hypertension is a devastating disease that is invariably fatal without definitive therapy. The disorder is more appropriately called a syndrome, since it is characterized by a set of clinical and pathophysiological features common to a variety of underlying causes. The proposed causes of primary pulmonary hypertension range widely, from environmental (e.g., hypoxia) to autoimmune (e.g., systemic lupus erythematosus) to drug related (e.g., dexfenfluramine use). Although genetic determinants no doubt indirectly influence the propensity for primary pulmonary hypertension to develop in response to these factors, a heritable form of primary pulmonary hypertension, familial primary pulmonary hypertension, has also been recognized since 1948.¹ The incidence of familial primary pulmonary hypertension in the general population ranges from 1 to 2 cases per million, accounting for 6 percent of the 187 cases of primary pulmonary hypertension in the registry of the National Institutes of Health²; its pattern of inheritance appears to be autosomal dominant with incomplete penetrance, since the disease develops in no more than 20 percent of persons at risk. Familial primary pulmonary hypertension is an uncommon form of an uncommon disease, yet its heritability provides the opportunity for the use of contemporary genetic approaches to elucidate the molecular basis of the disease.

Two related articles in this issue of the *Journal*^{3,4} further our understanding of the genetic and molecular determinants of familial forms of primary pulmonary hypertension. Newman and colleagues³ report the results of a detailed genetic study of a large kindred with familial primary pulmonary hypertension. In the light of the findings in earlier studies of genetic linkage that the locus for familial primary pulmonary hypertension is found on chromosome 2q31-32, the investigators surveyed the known genes in this large chromosomal region for biologically plausible candidates. They identified a unique member of the transforming growth factor β (TGF- β) receptor family, known as bone morphogenetic protein receptor II, as a possible candidate because this receptor can modulate vascular-cell growth. Their logical hunch proved correct when they detected a missense mutation — a substitution of guanine for thymine at position 354 — in exon 3 of the gene for bone morphogenetic pro-

tein receptor II (*BMPR2*) in all affected family members. In earlier studies, over 25 other mutations in *BMPR2* had been identified, with each mutation transmitted within a given family.⁵

To understand how a mutation in *BMPR2* may lead to primary pulmonary hypertension, we must first review the vascular pathological features of the disease. Pulmonary arterial lesions in patients with primary pulmonary hypertension are characterized by medial hypertrophy, concentric laminar intimal fibrosis, and plexiform lesions with obstruction of the arterial lumen, aneurysmal dilatation, and proliferation of interconnected vascular channels (occlusive arteriopathy). The laminar changes and plexiform lesions are associated with proliferation of both vascular smooth-muscle cells and endothelial cells. In some cases of primary pulmonary hypertension, these proliferative changes may represent adaptive (or maladaptive) responses to an exogenous stimulus, such as hypoxia. In familial primary pulmonary hypertension, however, the genetic findings suggest that vascular-cell proliferation is the primary event in the development of lesions.

As a member of the TGF- β receptor family, bone morphogenetic protein receptor II is poised to regulate cell proliferation in response to ligand binding. The ligands for the TGF- β receptor family include TGF- β and its superfamily members, bone morphogenetic protein and activin. These growth factors have pleiotropic effects on endothelial and vascular smooth-muscle cells that depend on the environmental and developmental context of the signal, as well as the specific TGF- β receptor family members to which they bind. For example, endothelial-cell proliferation is potently inhibited by TGF- β ; however, proliferation can be stimulated in the presence of vascular endothelial-cell growth factor and fibroblast growth factor.⁶ Similarly, TGF- β and bone morphogenetic protein can inhibit migration and proliferation of vascular smooth-muscle cells; however, both can also promote growth of vascular smooth-muscle cells under certain conditions: TGF- β can induce mitogen synthesis and its release from quiescent vascular smooth-muscle cells that, in turn, support cell proliferation,⁷ and low concentrations of bone morphogenetic protein directly stimulate proliferation of vascular smooth-muscle cells. As a complement to its actions as an inhibitor of cell growth, TGF- β can also induce apoptosis of endothelial and vascular smooth-muscle cells. Even in this context pleiotropy is apparent, however, since TGF- β has been shown to protect vascular cells from apoptosis induced by other agents.⁸

These actions of the TGF- β superfamily on vascular cells are mediated by a family of cognate receptors. Broadly speaking, the TGF- β receptor family comprises three classes: types I, II, and III.⁸ The TGF- β superfamily exerts its principal effects by binding to heteromeric complexes of type I and type II receptors, which are transmembrane signaling molecules with