

# Corpus callosum section for seizure control: rationale and review of experimental and clinical data<sup>1</sup>

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This contribution reviews several physiological and clinical prerequisites for consideration of corpus callosotomy for seizure control. Although there are experimental data suggesting that this procedure would fail to measurably improve an uncontrolled seizure disorder, initial clinical experience with the procedure appears to be generally favorable. More defined case selection and longer follow-up are needed to fully evaluate its effectiveness. An outline of selection criteria and postoperative evaluation concludes the contribution.

**Index terms:** Corpus callosum • Epilepsy • Epilepsy, surgery • Seizures

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Conceptual grounds for considering corpus callosum sectioning as a useful treatment for uncontrolled epileptic seizures, particularly primary or secondary generalized seizures, rest on several prerequisites:

1. Bilateral synchrony or near synchrony of cortical epileptiform discharges augments the seizure tendency, particularly for generalized attacks,
2. The corpus callosum serves as a major pathway for propagation of epileptiform discharges and must not play a significant role in inhibition of such discharges,
3. Sectioning of the corpus callosum must decrease or abolish the synchrony of epileptiform events and should inhibit the generation of generalized seizures,
4. Sectioning must not augment the quantity or propagation of cortically originating epileptiform discharges,

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5. Previous, well-documented clinical experience gives promise for success of the procedure and,

6. Any neuropsychological dysfunction consequent to corpus callosum sectioning must be imperceptible in the activities of daily life for the individual patient.

These principles would apply to division of other commissures, but most of the attention of this paper will be toward the corpus callosum.

Following an introductory anatomical and physiological survey, this paper will consider each of the prerequisites in turn.

### **Fundamental anatomical and physiological data**

The role that the corpus callosum and other commissures play in the propagation and synchrony of epileptiform discharges is based on anatomical and early physiological data.

*Anatomy:* The corpus callosum develops in proportion to the neocortex and therefore reaches its greatest size in man in whom it contains about 180 million axons.<sup>1</sup> It is the main commissural connection between the two cortices of man. Although the majority of fibers connect homotopic regions of the two hemispheres, heterotopic connections also exist.<sup>2</sup> There are considerable regional variations of distribution of callosal afferents: in the monkey they appear most abundant in the midposterior frontal region and in the association areas of the parietal lobe. However, they are absent in the areas of representation of the distal parts of the limbs in the primary motor and in the somatosensory areas as well as in the primary visual area.

As would be expected, callosal afferents connecting the frontal lobes occupy the rostral half of the corpus callosum. Connections between other lobes pass in the caudal half in the following rostral-caudal order: parietal, temporal, and occipital.

Callosal afferents appear to reach all layers of the cerebral cortex. Most axons probably end in layers III and IV, but there are differences between areas and species.<sup>2</sup> These factors, and differences in technique, may account for disagreement among authors concerning results. For example, Heimer,<sup>3</sup> using a modified Nauta technique in rats and opossums, found that most callosal afferents terminated in layers I and II.

Most callosal fibers are axons that originate in layer III, with some arising from layer V.

The anterior commissure interconnects the amygdala, olfactory bulbs, the piriform cortex, the entorhinal area, and portions of the temporal neocortex. The hippocampal commissure connects the several structures of the hippocampal formation.

*Physiology:* Stimulation of a cortical point evokes a potential at the corresponding point of the contralateral cortex.<sup>4</sup> This transcallosal response results from activation of orthodromic<sup>4-7</sup> and antidromic<sup>5,6</sup> pathways. The response lasts about 50 msec, during which time the surface becomes first positive, then negative with respect to a reference point. The response may be abolished by section of the corpus callosum. Grafstein<sup>8</sup> obtained a surface negative transcallosal response with a latency of 15–20 msec using the weakest effective stimulus to the surface of the cortex. A slightly stronger stimulus elicited a surface positive potential at a 10-msec latency preceding the negative wave. As will be shown below, this likely results from deeper penetration of the stimulating current. A still stronger stimulus evoked a spreading burst of activity after the positive-negative sequence. By changing the depth of the stimulating electrodes in the cortex, it was possible to change the configuration of the transcallosal response in such a way as to suggest that three different groups of callosal fibers may be involved. The negative phase, spreading burst activity, and positive phase, in that order, appear to be produced by excitation of neurons lying in successively deeper layers of cortex. Altering the excitability of different layers of the cortex at the stimulated point supported these observations. Recording the transcallosal response at different depths and applying a local anesthetic at the site of recording led Curtis<sup>7</sup> to conclude that the negative and positive phases represented depolarization of the superficial and deep layers, respectively.

Correlating these findings with her data led Grafstein<sup>8</sup> to conclude that callosal axons terminate in the homotopic contralateral cortex at approximately the same depth from which they arise.

These basic anatomical and physiological data set the stage for consideration that the corpus callosum plays a significant role in the propagation of epileptiform potentials and in mediating bilateral synchrony.

## Experimental and clinical studies

1. *Bilateral synchrony or near synchrony of cortical epileptiform discharges augments the seizure tendency, particularly for generalized attacks.*

Supporting, but inconclusive evidence for this would derive from an interictal or ictal association between generalized seizures and bilaterally synchronous epileptiform paroxysms in man. A corollary requisite is that the cortex plays an essential role in the elaboration of generalized seizures.

Jasper and Kershman<sup>9</sup> were among the first to correlate clinical seizure manifestations with the type of interictal EEG abnormality. Eighty-four percent of their patients with petit mal (now termed "absence") had bilaterally synchronous paroxysms, mostly 3-Hz spike-and-wave, while 48.5% of their grand mal patients had bilaterally synchronous discharges interictally. Kiloh et al<sup>10</sup> give similar figures. All of Aicardi and Chevrie's<sup>11</sup> 90 children with myoclonic epilepsy had bilaterally synchronous epileptiform paroxysms seen in association with the clinical jerks. Conversely, 80% of patients with bilaterally synchronous paroxysms had generalized seizures in Jasper and Kershman's series.<sup>9</sup> Similarly, 66% of Silverman's patients<sup>12</sup> with bilaterally synchronous spike waves, interictally, had grand mal and 26% had petit mal.

Ninety-eight percent of children with bilaterally synchronous sharp and slow wave complexes had generalized seizures, usually tonic.<sup>13,14</sup> This association forms the basis of the Lennox-Gastaut syndrome, characterized by generalized seizures, mostly tonic and absence; bisynchronous sharp and slow wave complexes; and mental subnormality.<sup>15,16</sup>

However, as suggested above, the association between generalized motor seizures and interictal bisynchronous EEG abnormalities remains incomplete. Noriega-Sanchez and Markand<sup>17</sup> found grand mal seizures in 92% of 108 patients with multiple independent (asynchronous) spike foci; only 15% of their 108 patients had interictal bilaterally synchronous spike-wave discharges. Similarly, Blume<sup>18</sup> found generalized motor seizures in 76% of children with multiple independent interictal spikes, and the coexistence of generalized epileptiform paroxysms (e.g., spike-and-wave) did not alter this incidence.

Most of the foregoing describes interictal EEG data. Gastaut and Broughton<sup>19</sup> have documented

EEG changes with generalized seizures. A grand mal seizure may be immediately preceded by generalized polyspike and wave complexes. The attack begins with diffuse desynchronization or generalized 20-Hz rhythmic waves slowing to 10 Hz. This later is gradually replaced by slow waves leading to spike-wave discharges. Diffuse desynchronization, 20-Hz and 10-Hz rhythmic waves, or polyspikes also characterize tonic seizures.<sup>13,19</sup> However, this correlation does not imply that clinical manifestations are simply the result of corticofugal volleys from cortical events represented by EEG potentials. Thus, although myoclonic attacks are accompanied by generalized polyspikes and waves, Gastaut and Broughton<sup>19</sup> found a variable relationship between the cortical discharges and the EMG-recorded myoclonic potentials. The myoclonus could precede, follow, or occur simultaneously with the bisynchronous cortical spikes. The association between 3-Hz spike-wave discharges and absence attacks is the closest of these EEG-clinical relationships.

The foregoing clinical data establish a relationship between bisynchronous cortical discharges and manifestations of generalized seizures. However, unanswered is the mechanism of this relationship and whether cortical bisynchrony or even cortical participation is prerequisite for generalized seizures to occur.

### *Cortical origin of generalized seizures*

A full clinical/experimental review of generalized seizures falls beyond the scope of this discussion. However, the cortical origin or requisite participation in generalized clinical and experimental seizures should be established before considering corpus callosotomy. There are several clinical and experimental data supporting this view, a portion of which is presented here.

### *Clinical data*

Lesions such as tumors or stroke, which are confined to the cortex, may give grand mal seizures. In fact, seizures occur more commonly if the tumor or stroke involves the cortical gray matter than if it is located elsewhere.<sup>20,21</sup> Of course, the existence of a lesion only suggests that an associated seizure arose from its vicinity. However, a tumor and other epileptogenic lesions in the mesial frontal region producing bisynchronous spike-wave discharges gave rise to the concept of secondary bilateral synchrony.<sup>22,23</sup>

Bancaud et al<sup>24</sup> and Goldring,<sup>25</sup> recording

from implanted electrodes, found that generalized motor seizures originated in the cortex, particularly frontal, and that subcortical structures became involved secondarily.

#### *Experimental data*

The feline generalized penicillin preparation is likely an appropriate model for human generalized epilepsy. Its findings suggest an essential role of the cortex in this condition. Fisher and Prince<sup>26</sup> obtained epileptiform activity first over the cortex and only subsequently in subcortical structures following parenteral penicillin injection. Moreover, application of penicillin bilaterally to the cortex produced synchronous spike-wave bursts, whereas subcortical application did not. Gloor et al<sup>27</sup> also obtained generalized spike-wave discharges by bilateral topical applications of penicillin to the cortices. Gloor's group (Quesney et al<sup>28</sup>), studying the relationship of spike-waves to spindles in this model, suggested that spike waves represent the response of hyperexcitable cortex to thalamocortical volleys which normally produce spindles. Moreover, Avoli and Gloor<sup>29</sup> showed that cortical ablation prevented conversion of thalamic spindles to thalamic spike-waves by penicillin, while Pellegrini et al<sup>30</sup> found that severing thalamic input altered and slowed, but failed to abolish, synchronous penicillin-induced epileptiform discharges of the cortex. This suggests that the cortex is more essential than the thalamus in generating synchronous spike-wave complexes.

Other models produce 3 per sec spike-waves by perhaps different mechanisms. Jasper and Droogleever-Fortuyn<sup>31</sup> obtained cortical discharges resembling 3 per sec spike-and-wave by stimulation of the intralaminar nuclei of the thalamus in the anesthetized cat. Hunter and Jasper<sup>32</sup> obtained behavioral arrest with bilateral twitching of the eyes and face with similar stimulation in the unanesthetized cat. Guerrero-Figueroa et al<sup>33</sup> obtained generalized seizures by placing an alumina focus in the midbrain reticular formation. The very considerable body of data concerning the cortical thalamic relationships will not be further presented here.

The foregoing has shown that: (1) clinically there is a common but not invariable association between bilaterally synchronous epileptiform discharges and generalized seizures, (2) in man, at least some generalized seizures originate in the cortex, and (3) the cortex plays an essential role

in developing bisynchronous epileptiform potentials in some experimental models.

2. *The corpus callosum serves as a major pathway for propagation of epileptiform discharges and must not play a significant role in inhibition of such discharges.*

#### *Evidence for transcallosal propagation of epileptiform discharges*

Following the early work by Curtis<sup>4,7</sup> and Grafstein<sup>8</sup> on callosally transmitted signals, Ajmone Marsan<sup>34</sup> studied neurons in the homotopic area contralateral to an epileptiform focus in cats lightly anesthetized with barbiturate. The behavior of two-thirds of such extracellularly recorded units remained unaffected by paroxysmal depolarization shifts with burst firing at the focus. The most common form of secondary involvement was one or two action potentials, whereas high frequency repetitive bursts occurred in less than 15%. This behavior contrasted with that at the original focus where 99% of neurons participated in the paroxysmal discharge with burst firing. Moreover, burst firing at the epileptogenic focus interrupted any spontaneously occurring action potentials at the homotopic region.

Crowell<sup>35</sup> also studied the effects of epileptiform activity of one cortical area upon activity of homologous contralateral cortical neurons, most of which were recorded extracellularly. Barbiturate-anesthetized cats were used. Activation and arrest of action potentials occurred equally often in response to the interictal paroxysmal events at the focus. A common result was action potential activation followed by arrest of firing. However, when an afterdischarge occurred at the original focus, contralateral arrest of firing occurred more commonly than did activation, i.e., afterdischarges tended to reduce the spontaneous activity of contralateral neurons. Like Ajmone Marsan, Crowell found that marked activation of contralateral neurons was unusual, and many remained unaffected by epileptogenic activity at the focus.

However, when Crowell and Ajmone Marsan<sup>36</sup> performed the same experiment using local anesthesia, an excitatory response to afterdischarges occurred in about one-half of contralateral neurons (as compared to one-third with barbiturate anesthesia); while a decrease in action potential quantity occurred in about one-fifth (as compared to about one-half with barbiturate anes-

thetia). That is, during local anesthesia activation was the most common response of neurons contralateral to the site of origin of afterdischarges, while suppression of activity was the most common response during barbiturate anesthesia. Therefore, barbiturates appear to diminish excitatory drives and to enhance inhibitory actions on contralateral neurons by afterdischarge. Which situation applies best to a patient with modest or moderate anticonvulsant treatment is unknown.

Presumably, the effects described above were mediated by the corpus callosum as electrographic evidence of afterdischarge was present over contralateral cortex in intact preparations; corpus callosotomy abolished projected discharge.

Schwartzkroin et al,<sup>37</sup> by extracellular and intracellular recording, also studied unit activity contralateral to an epileptogenic focus in barbiturate-anesthetized cats. Early excitation (increase in action potential rate) with a latency of 5–25 msec occurred in 105 neurons; early excitation followed by inhibition (decrease in action potential rate) appeared in 42; inhibition alone occurred in 106 neurons; and late excitation, at 30–80 msec latencies, appeared in 25 cells. Almost all neurons from which good quality intracellular recordings were obtained generated an EPSP-IPSP sequence during the projected epileptiform event. EPSPs were either subthreshold for action potential generation or evoked one or more discharges (except for late excitation, see below). Arrest of firing correlated with hyperpolarization, which was probably an IPSP, but such was almost always preceded by an EPSP. It appears, therefore, that whether action potentials are activated or inhibited by transcallosal effects of an epileptogenic focus depends on the relative prominence of evoked EPSPs and IPSPs. Therefore, units which appear on extracellular recordings to be only excited or only inhibited probably receive both types of input.

Comparing these results with their experience with thalamocortical relay cells (see below) led Schwartzkroin et al<sup>37</sup> to conclude that the callosal fiber system is a less potent mechanism for spread of orthodromic activity than the cortical-thalamic system. In their callosal experiments, a relatively large number of cells remained unaffected by contralateral discharge and only weak recruitment of cells into excitatory firing patterns occurred, findings similar to those of above-described studies.

The late excitation which Schwartzkroin et al<sup>37</sup> recorded usually appeared in bursts whose characteristics suggested that they were antidromically activated: they bore no relationship to synaptic potentials, had regular interspike intervals, showed no decrement in amplitude, and contained abundant isolated initial segment action potentials. They thus resembled bursts seen in antidromically activated thalamocortical relay cells.<sup>38,39</sup> Such antidromic burst firing (“backfiring”), demonstrated in thalamocortical pathways and here in a transcallosal pathway, may exert a powerful synchronizing effect upon an epileptogenic focus if subsequent bursts propagate orthodromically back to this original focus terminates in a rich arborization contacting many cortical cells. Once again, such antidromic activation, transcallosally, occurred in only a small proportion of cells.

In summary, these experiments all suggest that, in cats, the corpus callosum does not serve as a powerful propagating agent for cortically originating epileptiform discharges. Lesion experiments, described in a subsequent section, may indicate otherwise.

*Evidence for subcortical propagation of cortically originating discharges*

Corpus callosotomy will not help control partial or generalized attacks if cortically originating seizures initially propagate to subcortical structures and if the major synchronization of motor system effects occurs at thalamic or reticular system levels. This section presents some of the data bearing on this question.

Wada and Cornelius<sup>40</sup> applied aluminum hydroxide and ethyl chloride to the sensorimotor cortex of cats and obtained a chronic epileptogenic focus in that region. Paroxysmal events and electrographic seizures appeared in thalamus, basal ganglia, and limbic structures which persisted after surgical removal of the cortical epileptogenic lesion.

Wilder and Schmidt<sup>41</sup> created a chronic epileptogenic lesion by aluminum hydroxide gel on the sensorimotor cortex of monkeys. They found that propagation to the homotopic cortical region never occurred without involvement of subcortical structures, but subcortical propagation was not always associated with contralateral cortical involvement. Subcortical involvement enhanced activity of the original cortical focus. Contralateral motor manifestations only began when prop-

agation to subcortical nuclei occurred. In many of their recorded seizures, there seemed to be a preferential pathway for propagation to the mid-brain reticular formation which, in turn, was followed by dissemination to other subcortical structures and to the contralateral cortex (their Fig. 5). Tonic or clonic movements were preceded by spread of the seizure discharge to the mesencephalic reticular formation and to the subthalamic nucleus.

Following chronic epileptiform foci in the motor and premotor cortex of monkeys, Wilder et al<sup>42</sup> found that independent secondary foci appeared first in ipsilateral subcortical nuclei, then contralateral homotopic cortex, and then in contralateral subcortical nuclei. Such secondary foci were more active in subcortical structures than in contralateral homologous cortex.

Morillo et al<sup>43</sup> charted the sequential involvement of structures following establishment of a chronic (aluminum hydroxide) focus in the sensory motor cortex of cats and documented early and prominent subcortical epileptiform activity which appeared to enhance activity at the primary focus. Homotopic contralateral cortical activation appeared after subcortical involvement.

As mentioned above, Gutnick and Prince<sup>38,44</sup> recorded spike bursts antidromically in thalamocortical relay cells whose axons projected to a penicillin-induced cortical epileptogenic focus. Such antidromic activation provides, orthodromically, a powerful synchronizing influence upon the original cortical region.

Mutani et al<sup>45</sup> created bilateral asymmetric acute epileptogenic foci in the cortex of cats. Isolating such foci from subcortical structures markedly reduced the activity of such foci, whereas corpus callosum sectioning gave an opposite effect.

Kusske and Rush,<sup>46</sup> with tungstic acid gel epileptogenic foci in the motor cortex of cats, found that corpus callosum sectioning reduced the amplitude of afterdischarges in the contralateral cortex, but accelerated their spread to the contralateral thalamus.

Collins et al<sup>47</sup> charted the spread of penicillin-induced seizures from the right frontal cortex of rats by detecting regional metabolic increases via the 2-deoxyglucose technique. This work suggests that bilateral seizures develop from a unilateral focus primarily through increasing activation of intrathalamic pathways. Their seizures remained unilateral until sufficient medial thalamic units were activated bilaterally to engage,

transynaptically, areas in medial frontal or orbital frontal cortex bilaterally, from which pyramidal and extrapyramidal motor systems would become involved.

Mechanisms and pathways through which unilateral or bilateral cortical foci become associated with bilateral motor seizures remain to be fully determined. The motor, autonomic, and electrographic features of the tonic phase of a tonic-clonic (grand mal) seizure suggested to Gastaut and Broughton<sup>19</sup> that they represented massive discharge of the thalamic and brain stem reticular system, exerting its effects cranially on the EEG and caudally on the motor system. Collins' work (see above) would support this concept. Velasco et al<sup>48</sup> induced pentylentetrazole seizures in *encéphale isolé* cats and found increases in activity in the mesencephalic and pontine reticular formation prior to EEG manifestations of tonic-clonic seizures and prior to pyramidal tract involvement. This suggests that seizure activity propagates to spinal cord motor nuclei via reticulospinal and extrapyramidal pathways. Indeed, Mettler and Mettler<sup>49</sup> found that convulsive seizures could not result from cortical discharges if pyramidal tracts only were preserved; but could be induced when they alone were destroyed. This further emphasizes the role of the extrapyramidal system in generation of the motor manifestation of generalized seizures.

Finally, Wada and Sato,<sup>50</sup> kindling cats by amygdala stimulation, found that development of active and independent afterdischarges in the midbrain reticular formation was prerequisite for the occurrence of diffuse synchronized discharges and generalized seizures (stage 6).

The foregoing suggests that, at least in experimental animals, cortically originating seizures initially and preferentially spread to subcortical structures and that motor manifestations, contingent upon such spread, reflect involvement of the reticular system, its reticulospinal tract, and other extrapyramidal motor pathways. How corpus callosotomy would alter this sequence remains unclear.

*3. Sectioning of the corpus callosum must decrease or abolish the synchrony of epileptiform events and should inhibit the generation of generalized seizures.*

*Effect of corpus callosotomy on spread of focal seizures*

In 1926, Spiegel and Falkiewicz<sup>51</sup> obtained generalized convulsions in the dog following unilateral cortical stimulation even after section of

the corpus callosum, diencephalon, and mesencephalon. However, after midsagittal section of the pons, the convulsions remained confined to the contralateral limbs. Gozzano,<sup>52</sup> in 1936, found that local application of strychnine to one hemisphere produced spikes from both hemispheres, a phenomenon abolished by corpus callosotomy.

Erickson<sup>53</sup> studied the afterdischarge pattern induced by electrical stimulation of the cerebral cortex of monkeys and the effect of corpus callosotomy on this pattern. In the intact animal, the epileptic discharge spread throughout the ipsilateral motor area before going to the opposite hemisphere. Clonic movements of extremities contralateral to the discharge reflected this spread, indicating involvement of a crossed motor pathway. Later, bilateral clonic movements occurred. Complete division of the corpus callosum totally prevented spread of discharges to the opposite hemisphere, and clonic movements remained contralateral to the cortical discharges. However, ipsilateral tonic and occasionally bilateral tonic movements accompanied the clonic movements. This likely reflected involvement of both uncrossed and crossed descending motor pathways from the unilateral cortical discharge. Thus, even confinement of the discharge to one hemisphere failed to prevent bilateral motor expression of the ictus.

Kopeloff et al<sup>54</sup> performed corpus callosotomy in four monkeys after unilateral aluminum oxide cream had produced bilateral cortical seizures. All subsequent seizures were clinically confined to the side opposite the original epileptogenic focus. Only minimal EEG abnormalities persisted in the opposite hemisphere.

As mentioned above, Crowell and Ajmone Marsan<sup>36</sup> found that complete corpus callosum sectioning prevented interhemispheric transmission of electrically produced afterdischarge. Partial sectioning only attenuated such transmission. Although corpus callosotomy prior to establishment of an aluminum epileptogenic lesion largely prevented interhemispheric spread of EEG spikes in Kopeloff and associates' study,<sup>54</sup> Nie et al<sup>55</sup> found independent contralateral discharges using a similar experimental design.

#### *Corpus callosotomy and cortical bisynchrony*

As discussed earlier, several types of experimental designs have established the essential role which the cortex plays in generalized epilepsy. Early preparations<sup>56-58</sup> consisted of creating bi-

lateral cortical epileptogenic foci in cats and monkeys by locally applying acute epileptogenic agents to homotopic cortical regions. This was carried out on two groups of animals. In the first, the cortical and subcortical structures remained intact. The second group consisted of a completely isolated cortical unit consisting of slabs of bilateral homologous cortex connected by the corpus callosum. Synchronous spikes and spike-waves followed bilateral application of the epileptogenic agent homotopically to both cortices in each preparation. Synchrony of the cortically isolated group equaled that of the intact animals. In the monkey, significant regional variations in the capacity for bilateral synchronization became apparent. Synchrony was most consistently developed with bilateral foci in frontal, precentral, or parietal areas, between which callosal projections are most abundant. Corpus callosotomy of the previously intact preparations disrupted synchrony in the cat, giving independent discharges in either hemisphere. Sectioning of the corpus callosum and the anterior and hippocampal commissures of the monkey converted the high degree of interhemispheric synchrony of the intact preparation (within 5-20 msec) to a coarse synchrony of 50-400 msec.

Similarly, Isaacson et al<sup>59</sup> established bisynchronous foci in rats by topical penicillin application to homologous cortices. Corpus callosum sectioning destroyed the synchrony. Seventy-five minutes later, interhemispheric correlation was again established with a time difference of 80-100 msec as compared to 20 msec prior to sectioning.

Mutani et al<sup>60</sup> modified the experimental design by using chronic foci and making them bilaterally asymmetrical. Bilaterally synchronous discharges resulted. Splitting the corpus callosum and hippocampal commissure destroyed the synchrony of the discharges; but synchrony remained when the cortices, joined by the corpus callosum, were isolated from all subcortical structures.

These findings indicated that the corpus callosum was in large part responsible for synchronization of bilateral spike wave discharges. However, the coarse synchrony remaining in some preparations after callosal sectioning suggested that alternate, less effective paths to bilateral synchrony of cortical epileptiform potentials exist.

Ottino et al<sup>61</sup> also obtained synchronous epileptiform discharges with bilateral acute foci in in-

tact cats. Splitting the corpus callosum and hippocampal commissure disrupted synchrony, but this was restored by intravenous Megimide or by additional local application of convulsant agents. Restoration of bilateral synchrony corresponded with increased amplitude of epileptiform potentials at both cortical and subcortical levels; in particular, marked epileptic involvement of medial thalamic nuclei and midbrain reticular formation corresponded with the synchrony. Following this, dividing the anterior commissure and diencephalon disrupted synchrony once again, which once again was restored by renewed application of convulsant agents locally or systemically. Again, large amplitude epileptiform potentials had to be present in the midbrain reticular formation for synchrony to become re-established. Dividing the posterior commissure, tectum, and tegmentum irreversibly destroyed synchrony.

In a similar preparation (bilateral strychnine foci to cat cortex), Mattson and Bickford<sup>62</sup> restored synchrony that corpus callosotomy had destroyed by deepening the barbiturate anesthesia.

Such findings again show that alternate pathways for cortical synchrony exist, including the corpus callosum, medial thalamus, and midbrain reticular formation. Are these the same alternatives for synchrony of motor systems or spread of unilateral foci? Are those besides the corpus callosum less or more efficient in mediating propagation and synchrony? Would they be more susceptible to anticonvulsant medication?

The corpus callosum also mediates synchrony in the systemic penicillin epilepsy model. With this, Pellegrini et al<sup>30</sup> found synchronous discharges with the bilateral cortical-callosal slab preparation. In intact cats, complete corpus callosum and anterior commissure sectioning permanently destroyed synchrony, not only of spike-wave bursts, but also of associated facial twitching.<sup>63</sup> Incomplete sectioning impaired synchrony, but did not abolish it. Musgrave and Gloor<sup>63</sup> also prepared a slab of cortex which was isolated from the remainder of ipsilateral cortex and from the thalamus but connected to intact contralateral cortex by the corpus callosum; the remainder of ipsilateral cortex remained connected to the thalamus but not to the corpus callosum. Most systemic penicillin-induced epileptic discharges within the slab occurred synchronously with those of the intact contralateral cortex, but lower in voltage. Epileptiform activity in the operated

cortex outside the slab occurred asynchronously with that of the intact hemisphere and the slab. Musgrave and Gloor postulated that discharges evoked in the cortex of the systemic penicillin model by thalamic volleys (which induce spindles in non-treated animals) are rapidly conducted to the opposite hemisphere by the corpus callosum to produce virtually synchronous epileptiform discharges.

That this mechanism may pertain to the intact human derives from field plot studies of spike-wave discharges by Lemieux and Blume.<sup>64</sup> Virtually all spike waves originated unilaterally. They usually spread to the contralateral side within 10–15 msec, appropriate for corpus callosum conduction time. However, in a minority of instances, interhemispheric conduction time exceeded 20 msec. This suggests that either extra-callosal routes may be used in some patients or that different callosal conduction times exist.

Finally, Catier et al<sup>65</sup> sectioned the corpus callosum of the *Papio papio* and converted the spontaneously occurring spike waves of this animal from synchronous to asynchronous.

*4. Sectioning of the corpus callosum must not augment the quantity or propagation of cortically originating epileptiform discharges.*

Using both acute epileptogenic foci in cats and chronic foci in monkeys, several authors have demonstrated increased activity of cortical epileptiform activity following corpus callosotomy.

Stavraky<sup>66</sup> found an increase in convulsive seizure susceptibility to acetylcholine and pentyl-enetetrazole eight to nine months after corpus callosum sectioning of cats as compared to before sectioning. The convulsive threshold was lowered, and the clonic phase was prolonged, occasionally to status epilepticus.

Seizures from chronic foci increased in frequency and severity when Kopeloff et al<sup>54</sup> divided the corpus callosum. Similarly, this procedure increased the activity of acute bilaterally asymmetrical foci.<sup>45,67</sup>

Wada and Sato<sup>68</sup> studied the effect of dividing the interhemispheric commissures on the kindling process from the amygdala in cats. No change in localized seizure susceptibility occurred as afterdischarge threshold, and generalized seizure triggering threshold remained the same. Dividing the corpus callosum and the hippocampal commissure accelerated progression to the final stage of generalized convulsive seizures. This phenomenon occurred regardless of



whether other structures such as the anterior commissure were divided or not. This likely reflects accelerated propagation from the seizure focus rather than a focal increase in seizure susceptibility.

Such results are in accordance with that of Kusske and Rush,<sup>46</sup> mentioned earlier, who found an accentuated spread of seizures to the contralateral thalamus after corpus callosum division in cats.

*Implications of clinical and experimental data pertaining to prerequisites 1-4*

The clinician will find it difficult to derive a unified direction from the foregoing. Although clinical studies found some correlation between bisynchronous epileptiform events and generalized seizures, both interictal and ictal correlations are imperfect.

Unit studies showed that the corpus callosum's transmission of epileptiform events was weakly excitatory and could decrease the quantity of contralateral discharge. Cortical epileptogenic foci readily spread to subcortical structures, and it remains possible that the corpus callosum sectioning would enhance such propagation. Greater thalamic activation by corpus callosotomy might explain the augmented quantity of focal epileptiform discharges which some workers recorded in their experiments.

On the other hand, the physiological work has been carried out in monkeys, cats, and rats. It is likely that the greater development of the corpus callosum in man means that it plays a proportionally greater role in propagation and synchronization of epileptiform foci. This would increase the significance of works from that of Erickson to those of Gloor's group which demonstrate the prevention of spread and disruption of synchrony by corpus callosotomy.

*5. Previous, well documented clinical experience gives promise for success of the procedure.*

Coincidental with Erickson's experimental work, Van Wagenen and Herren<sup>69</sup> reported on 10 patients in whom the corpus callosum was partially or completely divided. A beneficial effect on generalized motor seizures appears to have occurred.

Luessenhop et al<sup>70</sup> carried out the same procedure in 4 children aged four months to seven years. They found that the procedure effectively controlled the 3 children of this group with primary unilateral seizures, but not those of the

infant. However, their follow-up period was only 17-36 months at the time of reporting.

Bogen et al<sup>71</sup> reported on 10 patients in whom complete transection of the anterior commissure and corpus callosum was carried out in a single operation. They presumed that the hippocampal commissure was also divided with the corpus callosum. Nine of the 10 patients had improved: they reported that generalized convulsions had been almost completely controlled for two to seven years (median, 4 yrs). Focal seizures had also improved, but less dramatically.

The largest recent series consists of 20 patients reported by Wilson et al<sup>72,73</sup> ranging from nine to 40 years (median, 20.5 yrs). The seizure disorder had to be medically refractory for at least four years. Initially, only patients were considered if they would be capable of a "reasonably productive life" with few or no seizures. Later, some mentally subnormal patients were sectioned, but they were not improved. Seventeen of these 20 patients had more than one type of seizure. Sixteen had grand mal, 15 absence, 15 complex partial, 8 akinetic, and 3 simple partial. In the first group of 8 patients, the entire corpus callosum, hippocampal commissure, one fornix, and the anterior commissure were divided in 3 patients; and only the anterior half of the corpus callosum, one fornix, and the anterior commissure in 5 patients. Because of complications, the operation was limited in the subsequent 12 patients to the corpus callosum and hippocampal commissure. The authors could not perceive any difference in effectiveness between these two procedures.

On preoperative EEGs, generalized epileptiform paroxysms appeared in 17 patients and focal, multifocal, or regional spikes in 14 patients.

Follow-up of these two series at the time of reporting was short: 29-48 months (median, 31 mo) for the first group and four months to five years (median, 18 mo) for the second. With respect to seizure control, they reported a reduction by 80% or more in 5 patients, 50%-80% reduction in 11 patients, less than 50% reduction in 1 patient, and no change or worse in 2 patients. However, only 2 of 19 patients are no longer taking anticonvulsants while 8 are taking two types of anticonvulsants and 7 are taking three types. One patient in the first group died of surgical complications. According to their tables, the procedure is about equally effective for grand mal, absence, akinetic, complex partial, and simple partial attacks. Patients with unilateral brain

**Table.** Anterior callosotomy (London, Canada, series)

Eight patients were followed for 15–60 mo (median, 43 mo)	
Generalized motor seizures	7 patients
Atypical absence	7 patients
Generalized epileptiform paroxysms	8 patients
Age at operation	12–32 yrs (median, 25 yrs)
Improved	3 patients
Equivocal	2 patients
Not improved	3 patients
Two postoperative anticonvulsants	8 patients

damage were claimed to have fared particularly well, and this is in accord with Van Wagenen and Herren's original experience. Although some EEGs appear to have improved with a decrease in bilateral synchronization of discharges, the considerable interpatient variability prevents clear conclusions.

Gates et al<sup>74</sup> reported on the effect of complete division of the corpus callosum in 6 patients. Three of the 6 became seizure-free, 2 had occasional partial seizures, and 1 remained with frequent attacks. Their follow-up ranged from four to 24 months. All still took anticonvulsants, but in lesser amounts. They reported that all postoperative EEGs had a marked decrease or abolition of generalized discharges.

Dr. John Girvin and I have investigated and operated on 8 patients, dividing the anterior half of the corpus callosum (*Table*). Seven of the 8 patients had generalized motor seizures including grand mal, tonic, myoclonic, and atonic attacks. Seven had atypical absence attacks. The median age of seizure onset was 5.5 years. The age of operation ranged from 12 to 32 years, with a median of 25.5 years. All patients had generalized epileptiform paroxysms on their preoperative EEGs. In each instance, the field distribution of these bisynchronous discharges was maximum in the frontal regions. Three of these patients had independent bifrontal spikes. An additional 4 patients had multiple spike foci which appeared principally in one or both of the frontal regions.

Our follow-up ranges from 15 months to 60 months (median, 43.5 months). In 3 patients, there are less attacks, the patients have less of a tendency to fall, and consciousness is more preserved. One of these has about the same number of attacks, but they are shorter and consciousness

is not as impaired. In 2 patients, the effect is equivocal, and 3 patients have clearly not improved. The preoperative intelligence quotients of the improved patients were: 90, 79, 64. Those of the unimproved patients were: 66, 62, and 45. This relationship between preoperative intelligence and effectiveness of the operation concurs with the experience of Wilson's group. None of our patients has suffered any obvious neuropsychological or motor impairment following the procedure aside from transient mutism and left hand apraxia in some patients. All of our patients still take two or more anticonvulsants.

#### *Comments about clinical studies*

The place that corpus callosum sectioning will ultimately occupy in epilepsy therapy remains far from determined. Although Wilson et al<sup>73</sup> acknowledged that other pathways for epileptic propagation exist, he and other authors of clinical series emphasize those physiological works favoring corpus callosotomy. As reviewed in this paper, abundant physiological data exist which suggest that, theoretically, the procedure could aggravate an epileptic condition.

Despite its long history, the procedure remains innovative, an aspect which may have impeded objective evaluation. The follow-up period for these series is too short for firm conclusions. Preoperative electrophysiological evaluations have been incomplete in that ictal EEG data rarely appear in reports in the literature. Although most patients appear to have partial and secondary generalized seizures, the group remains excessively heterogenous for complete study of a single type of epileptic condition. Evaluation of effectiveness remains a problem: although Wilson's group claims good (greater than 50% reduction) or excellent (greater than 80% reduction) results in 16 of 19 followed cases, 15 of these 19 patients remain on two or more anticonvulsants.

Unfortunately, an innovative procedure can receive an unfair trial initially as it attracts only those patients whose epilepsy is severe enough to resist more conventional therapy.

Attention has not been focused in this review upon the utility of commissurotomy for complex partial seizures of temporal lobe origin as this type of attack has not provided the major impetus for introducing this procedure. However, tables in Wilson and associates' communications<sup>72,73</sup> claim good or excellent effectiveness in 10 of 12 such cases. The tables of Wilson's group indicate

at least as good success with complex partial seizures when the division was restricted to the entire corpus callosum and hippocampal commissure (1982) as when the anterior commissure and one fornix were included (1977). The lack of EEG or stereo-EEG recorded seizures constitutes a major drawback of their work and weakens any pathophysiological interpretation of their results with respect to complex partial seizures.

Frost et al,<sup>75</sup> Poblete et al,<sup>76</sup> and Brazier<sup>77</sup> have demonstrated the importance of the anterior commissure for contralateral spread of amygdala discharges. The hippocampal commissure is the major interconnection between the hippocampal formations.<sup>2</sup> However, as with extratemporal foci, abundant alternate pathways exist for propagation to diencephalic, mesencephalic, and other structures.<sup>2,78</sup>

An unsettled question is the efficacy of complete vs. frontal corpus callosotomy. Luessenhop et al,<sup>70</sup> Wilson et al,<sup>73</sup> and Gates et al<sup>74</sup> divided the entire corpus callosum although Wilson et al<sup>72</sup> postulate that partial division may ultimately prove to be sufficient. Gordon et al<sup>79</sup> modified the extent of division according to the site of discharge. This approach appears to be the more reasonable. Bisynchronous epileptiform paroxysms such as spike-and-wave and sharp-and-slow-wave complexes are usually maximally expressed over the frontal lobes. Frontal foci appear to more readily lead to bisynchronous discharges than other regions<sup>22,80,81</sup> and to be the most common origin for grand mal attacks.<sup>24,25</sup> Because the majority of corpus callosum fibers connect homotopic regions and because those from the frontal lobe pass in its rostral half, it would seem reasonable to restrict the callosotomy to the anterior half for the high percentage of patients whose unilateral and bisynchronous discharges are primarily frontal. It appears that most of the neuropsychological changes observed after corpus callosotomy (see below) relate to transection of axons in its posterior third.<sup>2</sup>

6. *Any neuropsychological dysfunction consequent to corpus callosum sectioning must be imperceptible in the activities of daily life for the individual patient.*

Van Wagenen and Herren<sup>69</sup> were gratified to find that division of the corpus callosum gave minimal unwanted effects in activities of daily life. Sperry<sup>82</sup> stated that verbal intelligence, calculation, established motor coordination, personality, and temperament are all substantially preserved following commissurotomy.

However, further testing reveals that significant deficits do exist. The left and right hemispheres appear to function independently in most conscious mental activities. For example, patients following complete corpus callosum sectioning are unable to name a visual stimulus presented to the hemisphere non-dominant for language. Objects identified by touch with one hand cannot be found or recognized with the other. Fortunately, most of these deficits are compensated for or concealed under ordinary conditions by exploratory movements of the eyes, shifting of hands, and through auditory and other clues that enable sensory information to be projected to both halves of the brain. However, such patients would appear to be more vulnerable to some subsequent unrelated insult. For example, a stroke-related right homonymous hemianopsia could render a right-handed patient whose corpus callosum was completely sectioned unable to name what he sees. Gordon et al<sup>79</sup> found that patients in whom the posterior sector of the corpus callosum was preserved were able to transfer highly detailed information of different sensory modalities in contrast to those with a complete section.

Bilateral motor coordination in performing newly learned movements appears to be impaired for patients with both complete and partial commissurotomy, but much of this work has compared the patients to normal subjects.<sup>82</sup>

Dimond<sup>83</sup> found a gross depletion of attentional capacity with a complete corpus callosum section, but this was absent in the partial commissurotomy patients.

Although patients or families have not appeared to notice any impaired memory following this procedure, formal testing reveals a moderate memory impairment and this appears to apply to patients with both partial and complete commissurotomy.<sup>82</sup>

The foregoing appears to indicate that corpus callosum section should spare the posterior sectors so as to decrease the apparent neuropsychological complications. If such sectioning were insufficiently effective, the procedure could be completed on a second occasion.

## Conclusion

*A plan for corpus callosotomy: patient selection, operation, and postoperative evaluation:* Given our current clinical and basic knowledge, corpus callosotomy should be restricted to those patients who have medically uncontrolled generalized

motor seizures, including grand mal, tonic, or myoclonic attacks. Patients whose seizures rapidly generalize from an actively epileptogenic unilateral lesion would be included.

Because seizures can change significantly with brain development, only late adolescent or adult patients should be considered to assure that improvement after callosotomy would have not occurred spontaneously. When the value of the procedure has been determined more precisely, younger patients may be included. Although the effectiveness of corpus callosum sectioning likely varies with intelligence, mildly or moderately retarded patients should be included initially as uncontrolled generalized motor seizures constitute a major management problem in this group of patients.

Ictal or repeated interictal EEG data should demonstrate abundant bisynchronous epileptiform discharges, and the bisynchrony (primary or secondary) should be frontal or frontocentral. Until the value of the procedure has been more accurately assessed, the rare patient with posterior-mediated bisynchrony should be deferred.

The initial callosotomy should spare the splenium. If a second trial of major anticonvulsants at non-toxic levels fails, then completion of the procedure after a minimum of one year might be indicated. Whether other commissures should be sectioned for other types of seizure disorders (such as complex partial) is not considered here.

Neuropsychological evaluation should compare the preoperative functioning to the postoperative functioning of the same patient. Comparison with normal controls in assessing the complications of callosotomy is less helpful.

The value of corpus callosotomy may lie in its ability to assist anticonvulsant medication to control a seizure disorder. Because the selection process presently leans toward the more severely affected patients, an assessment of such effectiveness may well require retrial of several anticonvulsant regimens postoperatively. Therefore, a follow-up period of at least three years, and preferably five years, will be required.

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