Article abstract—A second consecutive series of 12 patients underwent microsurgical "central" commissurotomy idivision of the entire corpus callosum and hippocampal commissure) for the relief of previously intractable generalized seizures. This modified operation was found to be safer than the multiple commissurotomies performed in the first series of eight patients and was equally effective. Central commissurotomy was modified further by being performed in two stages, which reduced the length and severity of the "acute disconnection syndrome," a common cause of morbidity in the early postoperative phase.

Best results were obtained in patients who were not severely retarded, had signs of unilateral cerebral damage, and included akinetic spells as a prominent form of their generalized seizures. EEG showed that bilateral symmetric discharges became either unilateral or asymmetric after surgery, which emphasized the important role played by

the corpus callosum in conducting seizure discharges from one hemisphere to the other.

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"Central" commissurotomy for intractable generalized epilepsy: Series two

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Central commissurotomy is defined as the micosurgical extraventricular division of the entire orpus callosum and underlying, adherent hipocampal commissure. The operation seeks to reuce or relieve intractable generalized seizures but are unresponsive to anticonvulsants and not menable to standard methods of focal excision.

A growing body of evidence, clinical¹⁻⁵ and exerimental,⁶⁻⁹ suggests that the forebrain combissures, especially the corpus callosum, play a ajor role in the propagation of seizure discharges om one hemisphere to the other. If so, division these commissures should reduce the spread of lese discharges and help confine them to the abormal hemisphere. Thus, a generalized seizure exomes a partial one, or if the seizure threshold raised decisively, a seizure-free state ensues; her means of escape through subcortical pathways ight be blocked by moderate doses of anticonsistants. These are the theoretical bases for comissurotomy, and they have been tested in several hall series of patients.¹⁻⁵

In the early operations, many forebrain comissures were divided, requiring deliberate insion of the lateral and third ventricles, a hazdous undertaking: ventriculitis and irreparable mage to the sensitive structures surrounding eventricles were common complications. 10 If they did not occur, convalescence was often prolonged by the "acute disconnection syndrome"—apraxia of the left limbs, mutism, apathy, confusion, infantile behavior, and alternating partial motor seizures. Recovery was eventually attended by fewer seizures, but the ratio of risk to benefit was too high.

Two factors were responsible for making commissurotomy safer: the advent of microsurgical technique and the discovery that division of the corpus callosum alone (with the hippocampal commissure) was as effective as section of multiple commissures. Microsurgical technique reduced operative trauma to a minimum. Restriction of surgery to the corpus callosum allowed the surgeon to stay outside the ventricle by preserving the ependymal roof, and the incidence of infection dropped decisively. 10

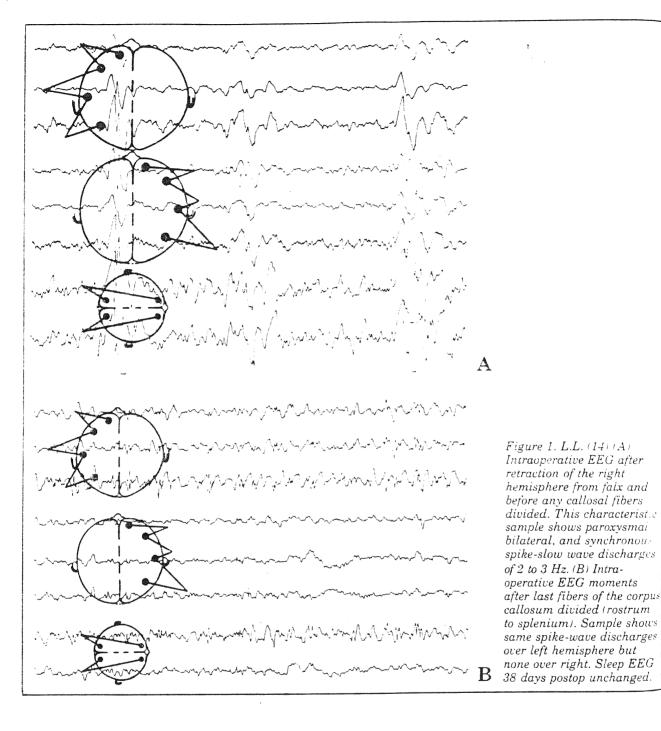
We have already reported the results of an initial series of eight patients who underwent multiple commissurotomies. 10 We now describe our experience with 12 more patients for whom surgery was restricted to total division of the corpus callosum and hippocampal commissure, or so-called "central" commissurotomy.

Materials and methods. All patients had been incapacitated by seizures for at least 4 years in

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spite of vigorous, carefully supervised regimens of anticonvulsant medications. "Incapacitated" meant an average of one seizure daily and inability to lead a reasonably normal life in a sheltered environment. Occupation, e.g., house painter, and severity of attacks, e.g., akinetic spells, were additional determinants.

At first, patients were required to have enough intelligence to understand the serious nature of the disorder, the innovative nature of the surgery, the necessity for frequent psychological tests, and the capacity to lead a reasonably productive life if seizures were relieved. These standards were relaxed to include a few retarded adolescents or adults as the safety and effectiveness of central commissurotomy became apparent.

Each candidate was admitted for physical examination, including blood levels of anticonvulsants, plain skull films, serial EEGs, and CT (Cerebral angiography and pneumoencephalography were excluded after the advent of CT.) Each patient underwent a battery of standard neuropsychologic tests: Reitan's modification of the Harstead battery¹¹ and special "split-brain" tests.¹²

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After operation, each patient was followed at egular intervals by a team composed of a neurologist, neurosurgeon, clinical psychologist, psyhiatrist, and research psychologist. Results of surgery were measured by the reduction in inapacity, as Taylor and Falconer recommended, using ictal, mental, emotional, and social status s the determinants of success or failure.

We modified Crandall's 14 criteria to evaluate the change in seizures effected by commissurotomy after 1 year: Group A, reduction of seizures by 80% or more. excellent; Group B, reduction of seigures by 50%, good: Group C, reduction in number equality of seizures, but less than 50%, fair; Group D, no change or seizures worse, poor.

The classification of seizures was that of the International League Against Epilepsy.

Method. A detailed description of the technique for central commissurotomy has been published. 4.5 We emphasize the need for microsurgical technique and for staying outside the lateral ventricle by

preserving the ependymal roof. The operation is now performed in two stages with a minimal interval of 2 months. This has made convalescence smoother by markedly diminishing or abolishing the transient but "acute disconnection syndrome." We have chosen arbitrarily to first divide the splenium (the underlying adherent hippocampal commissure) and the posterior half of the body of the corpus callosum. For this we now use the sitting position, and the craniotomy is performed more posteriorly (behind a line joining the parietal eminences). A silver clip marks the anterior extent of removal, retrieved at the second stage to be certain that no bridge of intact callosum remains.

Continuous EEG recordings are made during surgery (figures 1 through 3). Scalp electrodes are usually sufficient to record seizure discharges and their modification by commissurotomy. Anapsine, Fentanyl, and nitrous oxide constitute the anesthetics; nitrous oxide is turned off for 5 minutes at regular intervals to enhance the seizure dis-

Analysis of cases (table). For ease of comparison, the format of this table is the same as that used for series one.10 Patients 9 through 12 have already been reported in detail; their tabulation here shows the results of extended follow-up. A list of the preoperative anticonvulsants would be too long for inclusion in a table; all the standard drugs and many experimental ones had been given to each patient in different strengths and combinations for several years. After surgery, the preoperative drug regimen was continued, followed by a concentrated effort to reduce anticonvulsant dosages to less toxic levels.

The following observations integrate and complement the compressed information in the table:

1. Selection of candidates. The age of onset, frequency, and duration of seizures were not related to the outcome of surgery, but the severity of mental retardation, one type of seizure, and the presence of unilateral cerebral damage did predict the result of surgery. Two severely retarded patients (patients 14 and 18) with IQs below 70 were not measurably improved by commissurotomy. Five patients (patients 9, 10, 11, 16, and 19) with signs of unilateral brain damage (hemiparesis, dilated ventricle, or porencephalic cyst) had good or excellent results. Most akinetic spells (patients 9, 10, 13, 14, 17, and 20) were relieved immediately after surgery. even when other forms of seizures continued. However, follow-up has been short in the last two patients.

2. EEG. Bilateral, synchronous, spike, or spikewave discharges of different frequencies became asynchronous (figure 3) after complete division of the corpus callosum (patients 10, 12, 13, 14, 17, 18, and 20). In some cases (patients 14 and 19), bilateral seizure discharges became unilateral (figures 1 and 2), but such striking lateralization did not necessarily coincide with relief or reduction of clinical seizure.

3. Complications. No patients died, and there were no permanent or serious complications, in contrast to series one. Central commissurotomy made no seizures worse, nor did it impair any mental or physical functions as far as our tests

could determine.

4. Seizures. Generalized tonic-clonic seizures still occurred in some patients after central commissurotomy. In most, however, generalized seizures of any type were measurably improved by surgery; i.e., intractable seizures became tractable. This improvement became apparent in the early convalescent period in most patients. However, if the frequency of seizures was not reduced immediately by 50%, further improvement might still occur in the next year. 13.15

Reduction of both seizure frequency and anticonvulsant dosage coincided with overall improvement in cognitive, emotional, and social life.

Discussion. The operation. Cerebral commissurotomy has undergone considerable modification since it was introduced by Van Wagenen¹ in 1940. His pioneering operations consisted of division of many forebrain commissures—corpus callosum, hippocampal commissure, one fornix, and anterior commissure—in a variable manner. He published only one paper, in which he analyzed the results of 10 cases, but the longest follow-up was only 5 months. Bogen¹⁵⁻¹⁷ revived the operation in 1960 and varied it according to the areas from which seizure discharges arose. He performed an "anterior" commissurotomy—anterior commissure, rostrum, genu, and part of the body of the corpus callosum—for patients with discharges that were

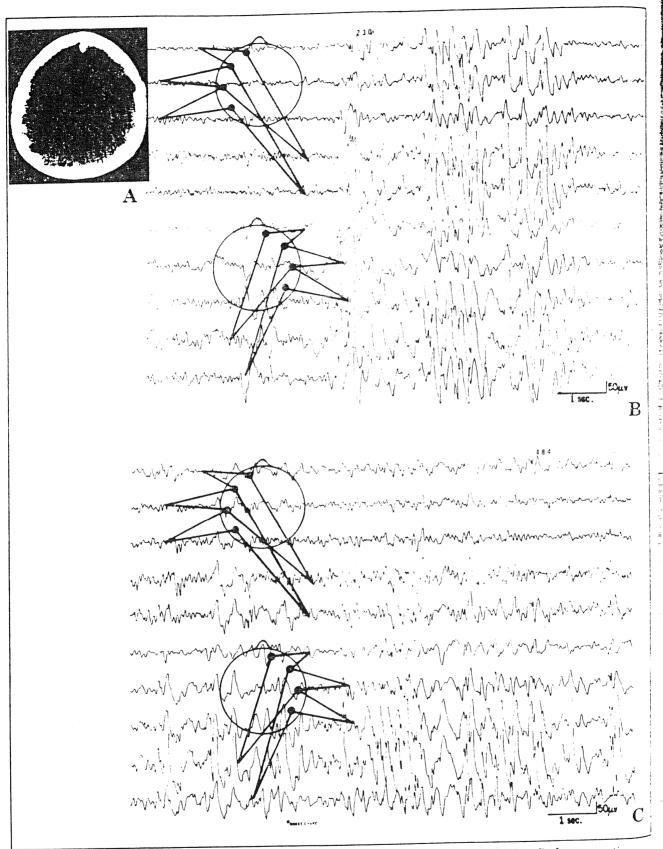


Figure 2. S.Y. (19) (A) Preoperative CT scan shows porencephalic cyst in right frontal lobe. (B) Intraoperative EEG before craniotomy. Bilateral, synchronous, spike-slow wave discharges of 2 to 3 Hz with some unilateral paroxysmal slow wave activity arising from right hemisphere. (C) Intraoperative EEG moments after last fibers of corpus callosum divided. Spike-wave discharges almost entirely confined to right hemisphere.

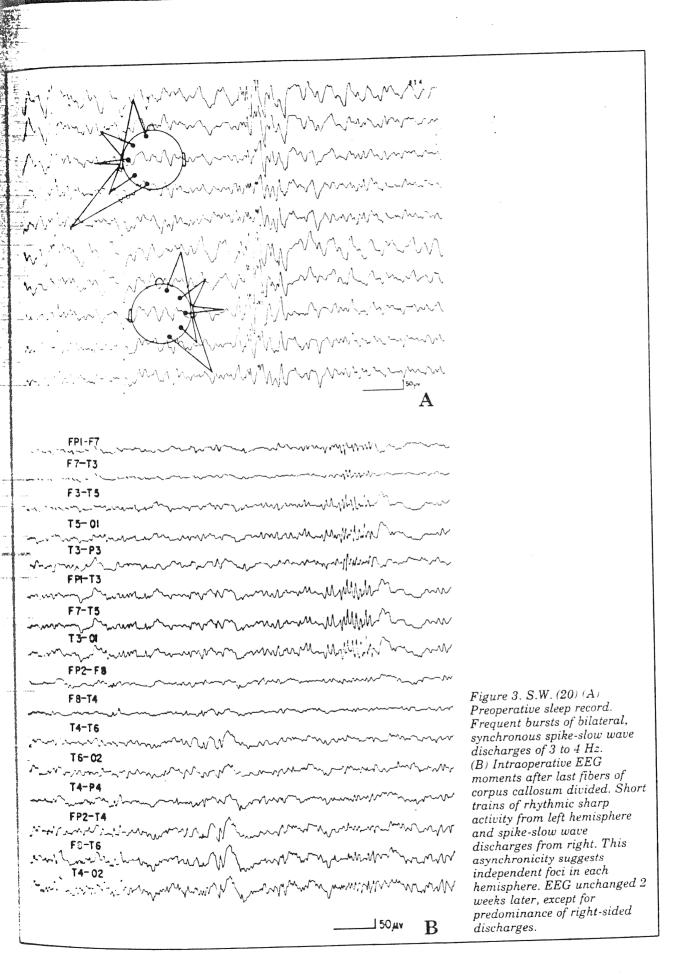


Table. Analysis of second series

Case	Age at onset of seizures	Seizure type and frequency	Preoperative EEG	Neurologic examination	
D.H.	10 yrs. Herpes sim- plex encephalitis RT subtemporal decompression	Generalized: Akinetic complex partial	RT temportal spike and slow waves, becoming generalized	LT hemiparesis aggressive, agitated, poor concentration Previously A student, now failing	
P.S. (10)	18 months: Febrile convulsions	Generalized: Tonic-clonic akinetic Partial: Motor complex	LT spike wave discharges, propagating to RT	Apraxia LT hand Hyperkinetic Aggressive	
D.S. 11)	12 years: Resection Astrocytoma LT frontal lobe (close to broca)	Generalized: Tonic-clonic absences Partial: Motor complex	LT frontal spikes. spreading to LT and RT hemisphere	Normal, bland	
S.P. (12)	7 years: Mumps Encephalitis	Generalized: Tonic-clonic absences Partial: Motor complex	Bilateral synchronous and asynchronous spike- wave discharges	Normal, husky, combative, dangerous	大学 一年
T.C. 13)	9 years: Undetermined cause	Generalized: Tonic-clonic (status) akinetic absence Partial: complex	Bilateral synchronous and asynchronous spike- wave discharges	Normal, pleasant, cooperative	
.L. 14)	15 months: Unde- termined cause	Generalized: Tonic-clonic (status) akinetic absence Partial: Complex	Bilateral synchronous and asynchronous spikes	Retarded, dysphasia	
(.W. 15)	13 years: Undetermined cause	Generalized: Tonic-clonic absence Partial: Motor	Bilateral spike- wave discharges. Focal spikes R, Temporal, L, Frontal-parietal	Normal Suicide attempt Divorced, depressed	
.A. 16)	10 yrs; Perinatal head injury	Generalized: Tonic-clonic absence. Partial: Motor	Diffuse spike-slow wave predominantly RT hemi- sphere with spread to left	LT hemiparesis since birth	
R. 17)	11 yrs: Undetermined cause	Generalized: Tonic-clonic akinetic absence Partial: Complex	Bilateral synchronous and asynchronous spike- wave discharges	Normal N-P tests: LT hemisphere dysfunction	
(.H. (S)	10 yrs: Measles Encephalitis	Generalized: Tonic-clonic Partial: Complex motor	Diffuse, multifocal spikes: Bi-temporal with shifting predominance	Retarded Paranoid	
Y. 91	8 yrs: Perinatal head injury	Generalized: Absence Partial: Motor complex	Bilateral, diffuse spike- wave discharges slow waves; RT frontal	Mild retardation LT hemiparesis since birth	CT CT cep froi
W . 9)	6 yrs: Febrile seizures at 6 months	Generalized: Tonic-clonic akinetic absence	Bilateral, symmetrical and asymmetrical spike- wave discharges, frontal predominance	Normal 	IQ:

Other pertinent	Age at	Type of	G	Hospital	
data	operation	operation	Complications	stay	Followed
10 82 Atrophy RT hemisphere Dilated RT lat- eral ventricle	15 years	Central commissurotomy one stage July 18, 1975	Acute disconnection syndrome	16 days	5 years
IQ : 89 Normal	15 years	Central commissurotomy one stage Jan. 23, 1976	Acute disconnection syndrome Meningitis	46 days	4½ years
10-83 Dilated LT frontal horn "Scar" LT frontal	23 years	Central commissurotomy 1. Anterior stage Apr. 23, 1976 2. Posterior stage Feb. 4, 1977	1. None 2. None	1, 27 days 2, 17 days	3½ years
Q: 80 Normal	16 years	Central commissurotomy one stage Dec. 30, 1976	Acute disconnection syndrome	22 days	3½ years
IQ :76	19 years	Central commissurotomy one stage June 24, 1977	Acute disconnection syndrome	30 days	3 years
IQ: 60 Proriasis	21 years	Central commissurotomy one stage Sept. 22, 1978	Acute disconnection syndrome; wound infection from scratching scalp; bone disks removed	44 days	2 years
IQ : 91 -	25 years	Central commissurotomy 1. Posterior: Sept. 14, 1979 2. Anterior: Oct. 16, 1979	1. None 2. None	1. 19 days 2. 18 days	1 year
IQ: 80 RT tem- pural lobectomy age 17	20 years	Central commissurotomy 1. Posterior: Sept. 14, 1979 2. Anterior: Dec. 4, 1979	1. None 2. None	1. 10 days 2. 12 days	l year
№ 84	25 years	Central commissurotomy 1. Posterior: May 27, 1980 2. Anterior: June 17, 1980	None Acute disconnection syndrome	1. 17 days 2. 18 days	8 months
PQ < 70	20 years	Central commissurotomy 1. Posterior: May 6, 1980	1. Anger + disconnection syndrome	1. 32 days	l year
IQ: 71 CT Scan: Poren- cophalic cyst RT frontal	16 years	2. Anterior: July 25, 1980 Central commissurotomy 1. Posterior: June 20, 1980 2. Anterior: Oct. 7, 1980	2. Confusion, dysphasia 1. None 2. Infected bone disk Posterior plate removed	 18 days 17 days 18 days 	6 months
IQ.63	20 years	Central commissurotomy 1. Posterior: Nov. 21, 1980	1. Severe RT-LT	1. 25 days	4 months
		2. Anterior: May 1, 1981	dissociation 2. None	2. 36 days	continued

Case	. Postopera- tive EEG	Ictal	Postopera- tive anti-con- vulsants	Mental	Emotional	Social	Overall evaluation of surgery	Comment
D.H.	Spike-slow waves con- fined to RT hemisphere, i.e. improved	Generalized: None com- plex-partial, occasional; Group B	Phenytoin Primidone	To vocational institute	Normal, calm, cheerful	Normal, in- dependent, earns living as trades- man.	Good	Objective evidence of unilateral cerebral damage predicts a good result from commissurotomy. Case history given in previous report.
PS.	RT temporal spikes, occa- sional No propaga- tion to left side	Generalized: Tonic-clonic, occasional Group B	Phenytoin	Distract- ed eas- ily, but quick to under- stand	Hyperkinetic, friendly	Cooperative, capable of earning a living. Poor social background	Good	May go 8 months without seizure. Studied extensively by neuropsychologist (Gazzaniga) since discovered to have residual speech in RT hemisphere. Case history given in previous report
D.S.	May/76: Dra- matic im- provement, not sustained; Improved by second opera- tion	Generalized: Tonic-clonic rare Absences: Occasional Partial: Mo- tor. None Group B	Phenytoin Valproate	Duil	Cooperative, cheerful	Works for father as la- borer	Good	Evidence for intact bridge of corpus callosum, which still propagates seizures discharges. Case history given in previous report. Seizures well controlled.
S.P.	Less pro- nounced than preop and with RT sided emphasis	None for 3 years Group A	Phenytoin discontinued 1980	Alert, brighter	Cooperative, cheerful, no aggression	Graduated from special high school June, 1980. Capable of earning liv- ing	Excellent	Combination of reduced anticonvulsants and surgery gave dramatic control antisocial beht wior. Excellent seizure control.
T.C.	Unchanged, but less pro- nounced	None for two years. Group A	Phenytoin Phenobarbital Carbamaze- pine	IQ to 89 Severe dyspha- sia Post-op still present, but mild	Cheerful, dependent	Cooperative. Attends reg- ular school (vocational)	Excellent	Although EEG did not lateralize postop, and was very unstable, pa- tient improved to point where all seizures stopped by Oct. 1978. Se- vere dysphasia for one year, and still present (mild). Probably meant bilateral dam ge enhanced by jm- missurotomy
L.L.	Striking lateralization of spikes to L hemisphere	Generalized: Tonic- clonic ab- sence, no akinetic Partial: Mo- tor. Group C	Phenytoin Valproate	Retarded -	Friendly	Dependent	Poor	In spite of lateralization of seizures on EEG, clinical seizures not much reduced. Retardation (IQ below 70 may indicate bilateral, severe brain damage with multiple seizure foci. Such retardation a possible contradiction to commissurotomy.

-	Postopera- tive EEG	Ictal	Postopera- tive anti-con- vulsants	Mental	Emotional	Social	Overall evaluation of surgery	Comment
	Striking lateralization of spikes to L hemisphere after completion second stage	All seizures reduced by 50% plus, but not abolished No partial seizures Group B	Valproate Carbamaze- pine Diazepam	Normal	Friendly, doc- ile, not de- pressed Capable of in- dependence	Attending vocational school	Good	May go months without having a seizure. Example of slow but definite improvement. Second case like 10 (P.S.) with speech in RT hemisphere
	Spikes confined to RT hemisphere LT normal	Dramatic cessation to all seizures Group A	Phenytoin Valproate Carbamaze- pine	Normal IQ to 86	Cheerful, open active	Plays golf Capable of indepen- dence	Excellent	Another example of immediate, dramatic cessation of seizures where evidence for unilateral brain damage. Immediate, good results usually sustained, predicting bright future.
	Definite diminution of spikes in LT hemisphere (CT. N-P findings)	All seizures markedly reduced, but under one yr. Group B	Phenytoin Phenobarbital	Dull	Friendly	Listless Capable of training for job Cooperative Friendly	Good	Early gain of seizure control argues well for continued improvement. No loss of consciousness with seizures. Speech hesitant. Case suggests that 2 months wait between operation is minimum to diminish or prevent acute disconnection syndrome.
	Definite diminution spikes in LT hemisphere	Generalized: Tonic-clonic 1-2/wk, par- tial motor 1/ wk Group C	Phenytoin Carbamaze- pine Clonazepam	Retarded	Paranoia completely gone. now friendly and cooperative	Sheltered workshop	Fair	See case 14. Operation did improve seizures, but not to marked degree. Retardation, when severe, may be a relative contradiction to commissurotomy.
	Spike discharges confined to RT hemisphere after second operation	50% reduction of seizures after 1st operation Group B	Phenytoin Carbamaze- pine Primidone	Border- line nor- mal	Childish	Dependent	Good	Although no lateralization of EEG after first operation, definite clinical diminution of seizures, even though porencephalic cyst RT frontal, and first operation was transection of splenium and posterior body of corpus callosum.
	Marked assymmetry of spike discharges, but no lateralization	No akinetic seizures since second operation occasional focal seizures Group B (but less than 1 year		Dull Normal	Childish	Dependent Friendly Cooperative	Good	Dramatic relief of akinetic seizures for first time in life, but only four months follow-up. Alternating focal seizures (motor) occur every few days, and occa- sional "nodding" spells

predominantly in the frontal and temporal lobes. If the seizures were more diffuse, he did a "complete" commissurotomy: the whole corpus callosum, hippocampal commissure, massa intermedia of the thalamus, one fornix, and anterior commissure. Bogen's reports showed that commissurotomies were effective in relieving or reducing many forms of diffuse, generalized seizures and that the "acute disconnection syndrome" did not occur after his "anterior" operation. 17 Luessenhop et al 3 found that the operation was particularly effective in children with brain damage localized to one hemisphere.

The first Dartmouth series of eight cases began in 1972. Microsurgical technique was added to Bogen's recommended single-stage division of multiple commissures. The series ended with the discovery of an unacceptably high morbidity rate and one death. Ventriculitis, sterile and bacterial, occurred too often and was too disabling for surgery to be recommended, even though we found that the operation often relieved previously intractable seizures.

During an 18-month moratorium, we found that the operation might not lose effectiveness when division was restricted to the corpus callosum. If so, with magnified vision, the integrity of the ventricular system could be maintained by preserving the thin ependymal lining that forms the roof of the lateral ventricle. The original experiments of Erickson on monkeys strongly suggested that the corpus callosum was the major pathway for the spread of seizure discharges from one hemisphere to the other. His work was reaffirmed in experimental animals. The

With patient 9, a second series of operations began, and microsurgical "central" commissurotomy alone was performed. Analysis of these 12 cases, presented here, has shown a decided reduction in morbidity without loss of effectiveness.

In a further refinement of commissurotomy, we perform the surgery in two stages with a minimum 2-month interval between the operations. This has made convalescence smoother, with decisive reduction in the intensity of the "acute disconnection syndrome." The remarkable ability of the brain to recover function when lesions are staged was well demonstrated in Faugier-Grimaud's¹⁸ experiments on monkeys. He concluded that the rapid recovery of the placing response in primates after staged operations was probably due to the "reorganization of lesion-induced nervous activity rather than to the [retained] integrity of any one brain structure or aggregate of 'specialized' neurons."

Epilepsy. It is not appropriate in this paper to discuss the conflicting theories about the origin and propagation of generalized seizures, except to comment on two observations that should be incorporated into any theory: (1) The corpus callosum plays a major role in the propagation of seizure discharges from one hemisphere to the other. (2)

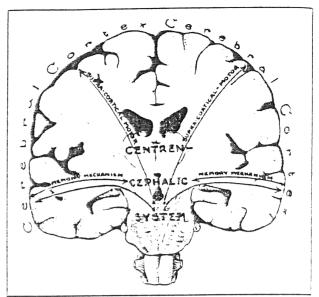


Figure 4. Penfield's drawing of the centrencephaton. 1954.

It has yet to be proved that any type of generalized seizure, including "petit mal" (with characteristic 3-Hz spike-wave discharge), originates in the human "centrencephalon." Penfield and Jasper! defined the "centrencephalon" as "that neuronal system centering on the higher brain stem . . . which has a symmetrical functional relationship with the cortex of the two cerebral hemispheres" (figure 4).

From Goldring's²⁰ direct stimulation of the thalamus during surgery for epilepsy and Gloor's injections of drugs into the carotid and vertebral arteries of patients who were candidates for surgery, to the results of central commissurotomy, the evidence is strong that in humans most, if not all, generalized seizures are of cortical origin and that the corpus callosum plays a key role in their propagation.

The corpus callosum has reached its highest development in humans. It is composed of 200 million fibers, of which at least 60% are myelinated (capable of fast conduction). They fan out through each hemisphere to end in discrete columns within homotopic cortices. For example, a cell of or gin begins in layer III of pyramidal neurons. Its according terminates in layers V and VI of the opposite equivalent cortex. The pattern is designed for instant transfer of cognitive activity from one hemisphere to the other, as Gazzaniga and Le Doux continue to demonstrate.

It is reasonable to believe that such a large system as the corpus callosum is easily captured by abnormal impulses that theoretically can travel as fast as any discharges released from the "centred cephalon" with its ancient, multisynaptic network of unmyelinated or poorly myelinated neurops

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bilateral, symmetric discharges.

Even if generalized seizures do originate as foci in the cortex and propagate horizontally across the callosum, they must also descend vertically to the final common path of the anterior horn cell. During descent they may branch into the "cenrencephalon," which could modify the intensity and quality of the discharge. Collins et al²³ demonstrated this horizontal and vertical spread of local seizures in the cat brain by desoxyglucose autoradiography; discharges that branch into the centrencephalon" remain ipsilateral.

Of course Penfield and Jasper 19 did not conceive the idea of a "centrencephalon" merely to explain an origin or means of propagation for "petit mal" seizures. The concept of such a central-integrating area may still be useful, as "basal ganglia" is useful to describe an anatomic (and to a lesser degree functional) area. If Penfield and Jasper 19 had knowledge of present clinical and laboratory investigations, they might have expanded this "functional" system to include another central structure lying just above the ventricular boundary, the corpus callosum.

After central commissurotomy, some patients still have generalized seizures and still produce bilateral symmetric discharges. Thus, midline structures other than the corpus callosum must conduct some seizure discharges. We are unsure whether these structures are of equal or secondary importance to the corpus callosum, but our own experience and that of Erickson6 in primates indicates that the callosum is a primary system for the propagation of seizure discharges.

We have also observed that akinetic seizures may be relieved immediately after central commissurotomy. It is not clear how or why such a sudden total loss of consciousness and muscular activity can be counteracted by the operation, but it is reasonable to suggest that some midline area, such as the "centrencephalon," participates in akinetic seizures—a further reason for including the corpus callosum within it. Akinetic seizures may be a valuable clue to the participation of the higher brainstem and "centrencephalon" in generalized epilepsy.

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The term "central" commissurotomy was coined by James Moore. Ph.D., department of philosophy, Dartmouth College His paper "Split brains and atomic persons" has been accepted for publication in Philosophy of Science.

We thank the publishers Little. Brown and Company for Permission to reproduce Penfield's drawing of the centrenrephalon.

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