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## Effects of Lesions in Ventral Anterior Thalamus on Experimental Focal Epilepsy

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The effect of stereotaxic lesions of the ventral anterior thalamus, or the adjacent inferior thalamic peduncle, on experimental models of focal cortical epilepsy was studied. Acute epileptic foci in cat sensorimotor cortex were made by injection of tungstic acid gel. Following ipsilateral lesions of ventral anterior thalamus or the adjacent inferior thalamic peduncle in these animals there was a highly significant reduction in electrographic seizure frequency and duration compared to prelesion control periods. Interictal activity at the focus was not altered. The frequency and duration of spontaneous clinical seizures in five rhesus monkeys with chronic alumina cream foci in motor strip was continuously monitored in activity chairs. Both seizure frequency and duration decreased in all animals in the 4-week period after ipsilateral ventral anterior thalamic lesions as compared to the 4-week control period. Sham lesions did not have these effects. The thalamic lesions did not discernably alter behavior or neurologic function in these primates. Thus ventral anterior thalamic lesions decrease seizure frequency and duration in both acute and chronic experimental models of focal cortical epilepsy. These findings indicate that pathways originating in or passing through the ventral anterior thalamus play a role in the generalization of focal cortical seizures. These lesions in ventral anterior thalamus may be useful in the treatment of medically intractable seizures secondary to foci inaccessible to direct excision.

### Introduction

Seizure disorders of various types have been treated by focal diencephalic lesions in patients (2, 6, 8, 11, 14, 29, 35, 38). In some instances a significant improvement or cure has followed one of these procedures; in others no benefits have followed lesions in apparently similar locations. This variability is in part related to the difficulties inherent in accurate anatomical localization of stereotaxic lesions in patients where histologic confirmation is not available. The variety of seizure disorders included in published reports also contributes to this inconsistency of results.

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From these studies, however, has come the suggestion that two diencephalic sites might be particularly favorable ones, the Fields of Forel (8) and the ventral anterior thalamic nuclei (14).

We have chosen to examine the effects of lesions in ventral anterior thalamus and some of its connections on acute and chronic animal models of focal cortical seizures. In this study, the epileptic foci were restricted to sensory motor cortex and the location of the thalamic lesion confirmed histologically. Thus two of the major variables in the human reports on diencephalic lesions in seizure disorders could be controlled; that is, the site of origin of the seizures was constant and the consequences of sub-cortical lesions could be correlated with anatomic location.

### Materials and Methods

This study is based upon experiments conducted acutely in 15 adult cats and chronically in seven rhesus monkeys. (*Macaca mulatta*). Cats were anesthetized with open drop ether. After tracheotomy the cats were mounted in a stereotaxic headholder, the ether was withdrawn and gallamine triethiodide was given to immobilize the animals. A pump respirator was used to ventilate the animals and expired air was checked periodically for CO<sub>2</sub> levels. The scalp and pressure points were infiltrated with 1% lidocaine HCL at regular intervals to prevent pain. A wide craniectomy was performed exposing the pericruciate gyri as well as the ectosylvian and suprasylvian gyri. Cisternal drainage and bilateral pneumothorax were instituted to reduce movements of the brain. Tungstic acid gel, 0.01 ml, was injected subpially into the forepaw region of the sensorimotor cortex (1). Recordings were accomplished using glass micropipettes filled with 3 M KCL (3-5 megohms). Two recording electrodes, each mounted on a separate hydraulic micromanipulator and connected to a Field Effect Transistor probe, were used simultaneously, one positioned 1-2 mm from the cortical focus and the other placed in the midportion of the ipsilateral suprasylvian gyrus. The electrodes were inserted to a depth of 1.2-1.4 mm. The output of each was coupled to an a-c preamplifier and displayed on a cathode ray oscilloscope. Data was recorded using an FM tape machine with a frequency response of 5 khz. Lesions were made electrolytically in the thalamus with the aid of a stereotaxic atlas (7). Stainless steel electrodes were used with an RF generator to make the lesions.

Seizures were first recorded in the region of the focus, and 1 to 2 hr later they were recorded from the ipsilateral suprasylvian gyrus. After seizures were well established in the suprasylvian gyrus, the duration of interictal and ictal periods were tabulated for 1 hr. After this hour-long control period, lesions were placed and at least 30 min allowed to elapse before recording was begun again. Again the length of the interictal and

ictal periods recorded from the suprasylvian gyrus were tabulated, in all instances for at least 2 hr. In two cats, no lesions were made and in these animals seizures were followed for 12 hr.

The animals were killed with an overdose of pentobarbital and the brains fixed in 10% formalin and then sectioned and stained with Nissl stain for a histologic verification of the lesion site.

Rhesus monkeys weighing 3–4 kg were anesthetized with pentobarbital and under sterile conditions a 1-cm trephine opening was made in the skull over the central sulcus. Aluminum hydroxide gel was injected subpially into the precentral and postcentral gyri in the hand region, in a manner previously described (10). Postoperatively the monkeys were followed for 60–90 days until well defined epileptic foci appeared on the scalp EEG tracings and clinical seizures became evident. The monkeys were placed in activity chairs with polygraph recording so that a continuous 24 hr day record could be kept of seizures over a period of weeks (12). Following a 4-week control period to document baseline seizure frequency, electrolytic lesions were placed in the ventral anterior thalamus stereotactically (18, 28). Following this procedure the animals were returned to the activity chairs and followed for another 4–8 weeks. Electroencephalograms were obtained before the thalamic lesions were performed and prior to acute experiments which were carried out at the end of the 4–8 week period.

Sham operations were performed on three animals. In two animals, under pentobarbital anesthesia, an electrode was placed in the ventral anterior thalamus without an RF lesion being made. In one animal, under the same anesthetic, an electrode was placed in the subcortical white matter. Electroencephalograms were also performed prior to the sham procedures. Following the sham procedures, these animals were also monitored for 4 weeks.

After the acute experiments, the monkeys were perfused with formalin and the brains sectioned and stained with Nissl stain for a histologic check of the lesion site.

## Results

*Acute Experiments with Cats.* For the first 30–40 min following injection 0.01 ml of tungstic acid gel into the forepaw region of the motor cortex there was no discernable change in the pattern of unit activity recorded from the cortex 1–2 mm from the focus. This was also true of unit activity recorded from the cortex of the midportion of the ipsilateral suprasylvian gyrus. An increase in the rate of firing of unit activity then occurred over 2–3 hr at the focus which progressed to a rapid burst pattern of firing. This burst pattern was followed, usually within 30 min, by periodic seizures. In the next 1–2 hr, the seizures spread to involve the

ipsilateral suprasylvian gyrus. At both the focus and the suprasylvian gyrus, each ictal episode was usually characterized by the abrupt appearance of a large field-potential which initiated a prolonged, high frequency burst of unit firing followed by a period of relative electrical silence (Fig. 1A). These episodes recurred at increasingly longer intervals until the seizure terminated with cessation of unit firing lasting for a minute or longer. This cycle was then repeated with initial burst firing at the focus again progressing to a seizure with ultimate spread to the suprasylvian gyrus. In animals without lesions, this pattern persisted unaltered for at least 12 hr.

The effects of the electrolytic lesions were similar whether the lesions involved the region of the nucleus ventralis anterior or whether they involved regions rostral to the thalamus which include the inferior thalamic peduncle (Fig. 2). Following a lesion, the extracellular units recorded in the suprasylvian gyrus during the interictal periods appeared much the same as the spontaneous activity recorded early in the course of the experiment. At the focus there continued to be rapid interictal burst firing, with ictal events characterized by the same sort of wave forms that were seen prior to the thalamic lesions (Fig. 1B).

In all but 2 of the 15 animals, lesions decreased the frequency of seizures recorded from the ipsilateral suprasylvian gyrus. Prior to lesions the mean interictal period for the 15 animals was 3 min, 35 sec,  $\pm$  1 min, 58 sec. The mean ictal period was 1 min, 18 sec,  $\pm$  34 sec. Following the lesions the mean interictal period was 10 min, 27 sec,  $\pm$  4 min, 8 sec and

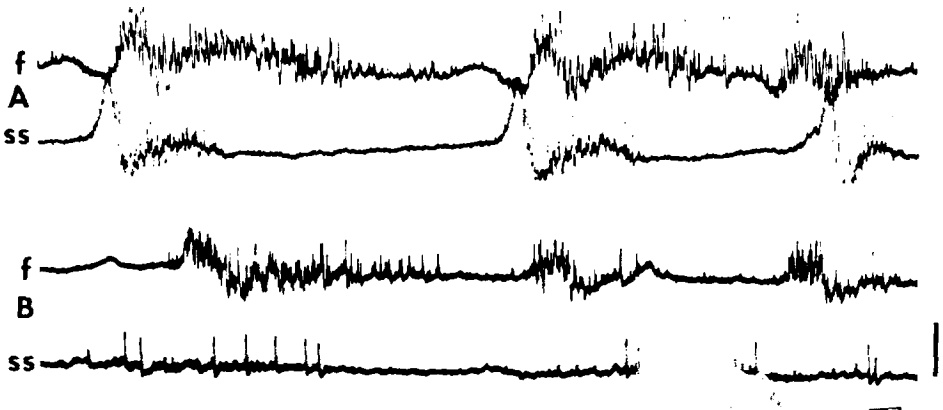


FIG. 1. A. Simultaneous record of an extracellular unit recorded from the sensorimotor cortex of a cat 2 mm from a tungstic acid epileptogenic focus (f) and an extracellular unit recorded from the ipsilateral suprasylvian gyrus (ss) during a seizure. B. Simultaneous record of an extracellular unit, in the same animal, following a lesion in the ventral anterior thalamus. There is an ictal event occurring near the focus (f) but only spontaneous cortical activity is seen in the suprasylvian gyrus (ss). Calibrations: 40 msec; 200  $\mu$ v.

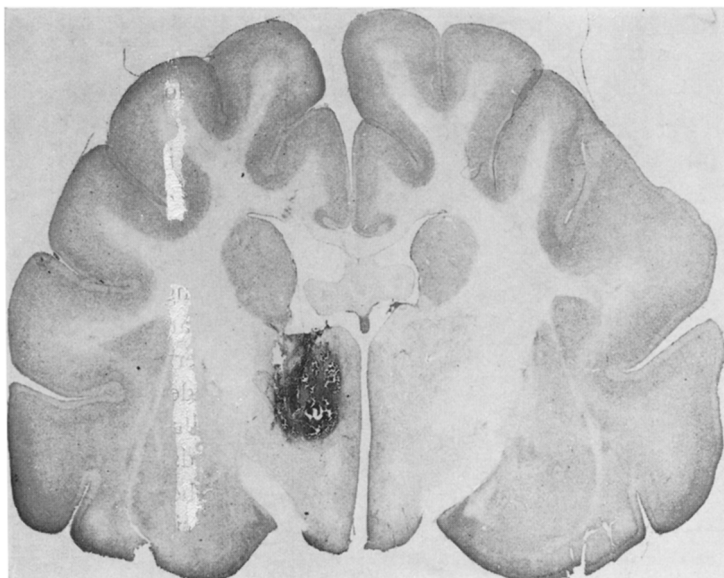


FIG. 2. A coronal section demonstrating an electrolytic lesion placed in the region of the inferior thalamic peduncle of a cat. This lesion led to a reduction in the frequency and duration of seizure activity induced by tungstic acid gel recorded from the ipsilateral suprasylvian gyrus.

the mean seizure duration was 47 sec,  $\pm$  39 sec. The data demonstrate a lengthening of the average interictal period, and a decrease in the average ictal period, comparing the control period for 1 hr prior to the lesions to the 2-hr period of recording following them. Using the Wilcoxin (36) signed rank test, this data is significant at a  $p < 0.004$  for both parameters.

*Chronic Experiments with Monkeys.* Spontaneous, recurring, clinically detectable seizures occurred in 60–90 days following injection of aluminum hydroxide gel into the arm area of sensorimotor cortex of rhesus monkeys. Electroencephalograms usually revealed epileptic activity in 45–90 days. Examination of the animals did not reveal any evidence of neurological deficits associated with the onset of seizures. The seizures were of focal onset in the appropriate somatic area, and occasionally became generalized. During the control period, seizure frequency varied considerably between animals, but was rather constant from week to week for a given animal (Fig. 3).

Sham operations did not reduce the frequency of recorded seizures (Fig. 3). In two animals, the seizure frequency increased following the sham lesion.

Five animals had electrolytic thalamic lesions placed. Animals E1, E2, 019 and 537 showed decreases of 82.7, 85.8, 77.3 and 52.1%, respectively, in the frequency of their seizures following thalamic lesion. These lesions

were all centered in the ventral anterior thalamus as indicated in Fig. 3. The location of the lesion in animal E2 in coronal section is shown in Fig. 4. One animal, 528, had a reduction of only 6.2% following the thalamic

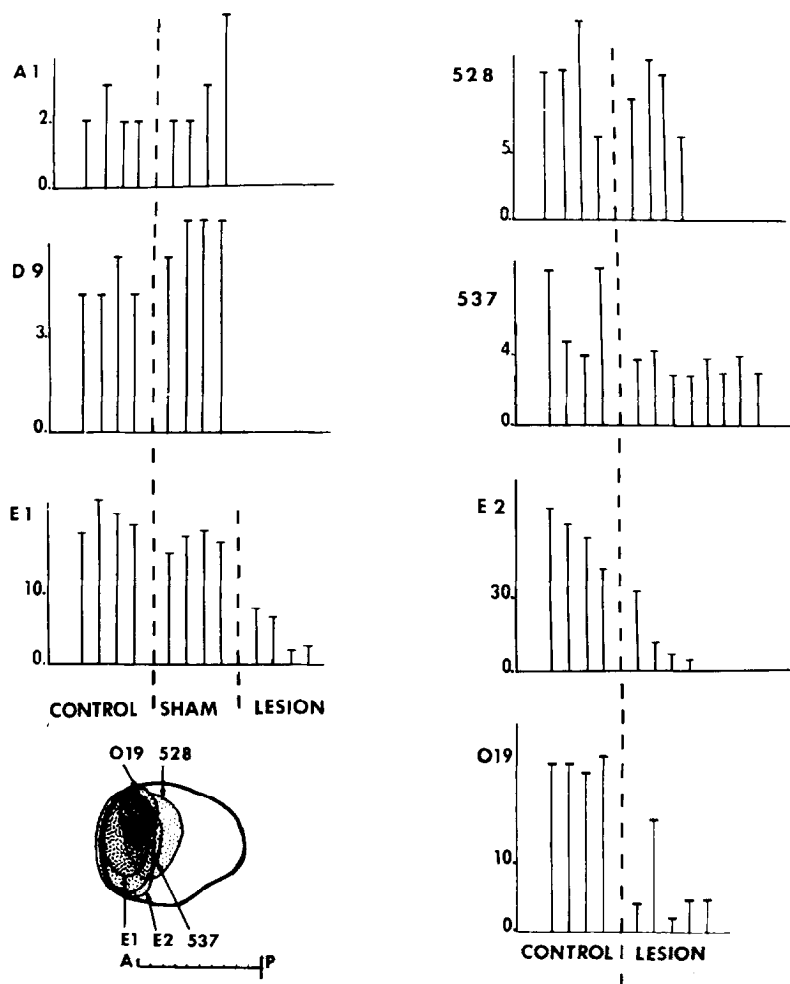


FIG. 3. Each bar represents the weekly seizure totals recorded from each of seven monkeys with alumina gel foci while in activity chairs. Seizures are recorded for each week in the control period, following a sham lesion or following an electrolytic lesion. Three animals, (A-1, D-9 and E-1) had sham lesions placed. These did not significantly alter seizure frequency. Five animals had electrolytic thalamic lesions placed. In the lower left is a composite drawing in which lesions are reconstructed in a schematic fashion in the parasagittal plane, 3 mm from the midline (as adapted from Olszewski's atlas (18)). Animals E-1, E-2, 019 and 537 had lesions centered in ventral anterior thalamus. These animals had a marked reduction in seizure frequency after these lesions. Animal 528 has a lesion placed more posteriorly in ventrolateral thalamus, with little drop in the number of seizures following the lesion.

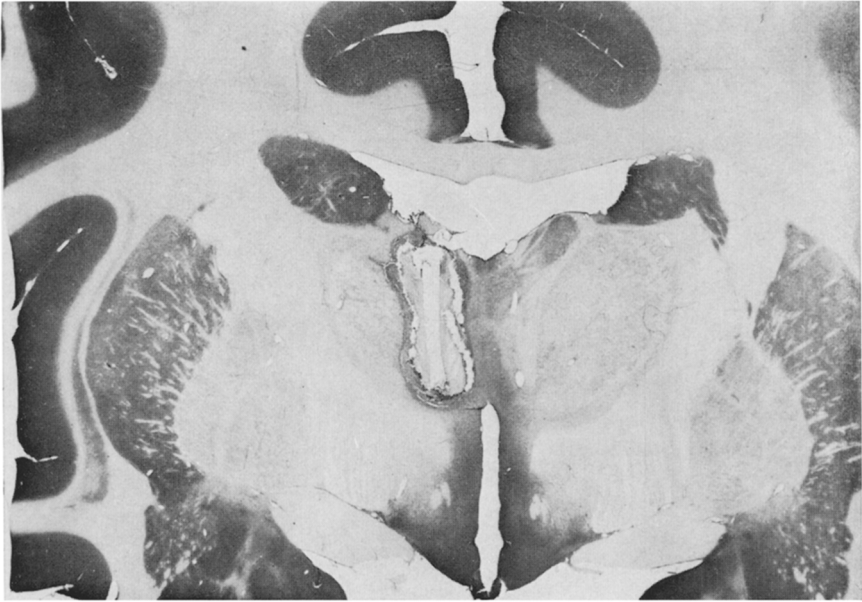


FIG. 4. Coronal section demonstrating an electrolytic lesion in the ventral anterior thalamus in animal E-2. Following the placement of this lesion there was a significant reduction in the number of seizures observed in this animal.

lesion (Fig. 3). The lesion in this animal was found to be centered in the ventral lateral thalamic nucleus (Fig. 3). In addition to the reduction in frequency of seizures following the ventral anterior thalamic lesions, evaluation of the polygraph records of the animals' seizure activity following these lesions suggested that a decrease in seizure duration also occurred.

Electroencephalograms obtained 4-8 weeks following a lesion in each animal showed that the focus was still intact.

Postoperative behavioral evaluation of the animals revealed that two of them had a mild contralateral hemiparesis which was not detectable in either animal 2 weeks later. Each animal's alertness, desire for food, and motor activity in the chair was not changed in any observable way from the preoperative state following recovery from surgery. The monkeys continued to eat normally, moved about actively and were alert following the procedure. One animal, 019, developed a mild left sided resting tremor about 10 days following the placement of the lesion. This disappeared about 2 weeks after its onset.

*Acute Experiments in Monkeys.* In animal E2, typical interictal burst activity described previously from alumina cream foci in monkeys (26) was seen at the focus with normal activity recorded from other areas of the ipsilateral hemisphere. No seizures were recorded from this animal during the course of the acute experiment. An animal with a sham lesion



in the thalamus demonstrated interictal bursts, with ictal activity recorded both from the region of the focus and from the ipsilateral cortex and also the contralateral area homologous to the site of the epileptogenic lesion.

### Discussion

Focal lesions in the ventral anterior thalamus (VA), or in the inferior thalamic peduncle (ITP), acutely decreased the frequency of seizures recorded from the ipsilateral midsuprasylvian gyrus in cats with focal epileptogenic lesions in the sensorimotor cortex. The epileptogenic foci remained active, with ictal phenomena occurring there. However, afterdischarge did not propagate to the suprasylvian gyrus as frequently and when propagated did not persist for as long a period of time as prior to the lesion.

In those monkeys with alumina cream epileptogenic cortical foci with lesions centered in VA, clinically detectable seizures decreased considerably in the 4–8 week period of follow-up. In the one animal with a similar focus, but a lesion centered in ventral lateral thalamus (VL), posterior and slightly lateral to the lesions in the other animals, the seizure frequency decreased only slightly. In all these animals there was no persisting neurological or behavioral deficit.

Thus the lesions which were associated with marked decreases in seizure frequency and duration consistently involved either VA or ITP. Some other adjacent structures including other thalamic nuclei, the medial fore-brain bundle and the anterior commissure were involved in some of the lesions but none consistently. The effect clearly has anatomic specificity, since comparably sized lesions in VA or VL had differential effects.

With the decrease in clinically detectable seizures, the scalp EEG foci remained active and microelectrode recording revealed interictal burst firing pattern at the focus. Thus it appears that lesions in VA or ITP impede the propagation of afterdischarges from the focus to other regions of the brain. Consideration of the structure of VA and ITP and their physiologic roles as presently defined suggests several possible mechanisms for this effect.

The VA receives afferent fibers from multiple centers, with the largest projection arising from the medial segment of globus pallidus and passing to VA via the ansa lenticularis or directly across the internal capsule (23). Another major projection to VA are axons of the nonspecific radiation that arise from the rostral pole of the intralaminar and midline thalamic nuclei and pass through VA (24). This nonspecific thalamic radiation forms a common neuropil with the pallidothalamic fibers in the medial one-third of VA (23). An additional relationship between globus pallidus and VA is provided through direct connections from globus pallidus to

nonspecific thalamic nuclei, especially centrum medianum (16). Other afferents enter VA as collaterals from the internal capsule. These arise on the one hand from the ascending brain stem reticular system, and on the other from the cortex, and are thought to represent components of the corticobulbospinal tract (23).

Although the full extent of the projection of VA or of nonspecific thalamic nuclei upon the cortex have not been settled, projections from VA to cortex can be demonstrated in animals (13, 22, 23) and in man (3, 19). The axons from the anterior nonspecific nuclei which pass through the medial third of VA continue rostrally in ITP (24) to the orbitofrontal cortex. The orbitofrontal cortex then has widespread projections to other cortical regions and to subcortical structures including recurrent circuits to the globus pallidus (via striatum (9)), and nonspecific thalamic nuclei (15).

About half of the neurons in VA do not project rostrally (23). Of these caudally directed fibers, half cross the midline to project to the contralateral nonspecific radiation. Uncrossed components of the caudally directed axons appear to project back on the posteriorly located nonspecific nuclei (23).

Physiologically, VA participates in so-called nonspecific thalamic mechanisms. The medial third of VA (where nonspecific fibers pass) has been identified as a preferred site for eliciting cortical recruitment (4, 30, 31). Low intensity stimulation in that region results in widespread cortical responses of short latency both ipsilaterally, and to a lesser extent, contralaterally (4). Lesions in this locus are unusually effective in blocking cortical recruitment (25, 30). Lesions of ITP or orbitofrontal cortex also interfere with cortical recruitment (27).

As might be anticipated from the effects on cortical recruitment, the generalized 3/sec spike and wave pattern induced in the electrocorticogram by stimulation of the midline thalamus is markedly diminished by ITP lesions in the cat (34). This diminution is restricted to the ipsilateral cortical component of the generalized discharge if the ITP lesions are unilateral (34).

Studies of the generalization of afterdischarge from focal cortical seizures, utilizing various stimulus parameters applied to the motor cortex have demonstrated some preferential pathways for seizure spread. Hayashi (5) suggested a pathway from the motor cortex involving the homolateral globus pallidus with input to the substantia nigra and brain stem reticular system. He also suggested a second pathway from the cortex to a medial thalamic nucleus and then to the ipsilateral globus pallidus. Udvarhelyi and Walker (33) noted spread of afterdischarge from the face motor area to the basal ganglia and thalamus. Wilder and Schmidt (37) with alumina

foci in monkey motor cortex, showed that propagation occurred with greatest frequency to the ipsilateral caudate nucleus and globus pallidus along with marked involvement of centrum median nucleus. The globus pallidus is early and prominently involved in seizure afterdischarge in all these studies. It projects, of course, to VA through the fasciculus and ansa lenticularis and by way of centrum medianum nucleus (16, 23). Specific thalamic nuclei, especially VL, are also strongly involved in seizure afterdischarge. However, a VL lesion in one of our animals did not significantly reduce seizure frequency. It seems likely that seizure generalization by way of the specific thalamic nuclei may be mediated through the nonspecific thalamic system, since these two systems are intimately related anatomically (24) and physiologically (20, 21). Thus there is physiologic evidence that the nonspecific thalamic system and pallidal circuitry may have major roles in the spread of both generalized and focal seizure processes. Lesions in VA have a potential for altering both of these systems involved in the spread of seizures. The nonspecific thalamic radiations and the pallido thalamic connections and the interaction between them are interrupted by those lesions.

On the other hand, ITP lesions (which had an effect on seizure generalization similar to VA lesions in the acute cat preparations) interrupt projections from VA to orbital frontal regions concerned with the nonspecific thalamic system. Thus interruption of the nonspecific thalamic system may be the more essential factor in diminishing seizure generalization.

Unilateral VA lesions were well tolerated in our chronic experiments. This is in contrast to the behavioral effects of bilateral VA (or ITP) lesions, where severe disruption of behavior was noted in chronic cats (27, 34). The solitary report of bilateral VA lesions in man (32) did not describe such behavioral disruptions in a small series of patients with mental illness. Thus the role of bilateral VA lesions in the treatment of epilepsy must be further evaluated experimentally, especially in regard to behavioral effects.

Ventral anterior or inferior thalamic peduncle lesions have been little used in the treatment of human epilepsy. The data presented here suggests that a trial of unilateral lesions in the human epilepsy analogue of our animal models is certainly warranted. Indeed some of the beneficial effects that had been ascribed to ventral lateral thalamic lesions in human epileptics may, as was inferred by Mullan (14), be due to their encroachment on VA. Thus VA lesions appear to be indicated in selected cases of medically intractable epilepsy with foci in motor or speech cortex or widely distributed in one hemisphere, these being cases where direct surgical excision of the cortical focus carries a risk of significant functional impairment.

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