# ROLE OF THE FOREBRAIN COMMISSURES IN AMYGDALOID KINDLING

*by*

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# ABSTRACT

The role of the forebrain commissures in the developing and developed kindled amygdaloid seizure in the rat was investigated. In the first two experiments, bisection of the corpus callosum, hippocampal commissure, and anterior commissure prior to kindling caused a significant facilitation in the rate of primary-site kindled seizure development. In the last experiment, bisection of the corpus callosum and hippocampal commissure after primary-site kindling facilitated the subsequent rate of secondary-site kindling. It is evident, that in the intact animal, the nonstimulated hemisphere is able to exert an inhibitory influence over the development of seizure activity in a stimulated hemisphere and that this effect is, in turn, mediated via the forebrain commissures.

The corpus callosum and hippocampal commissure were found to participate in the interference phenomenon since bisection of these structures either before or after primary-site kindling caused a facilitation in the rate of primary-site rekindling. In the first two experiments, an extracommissural, possibly brainstem, mechanism is suggested to mediate the transfer effect between the primary and secondary sites since bisection of the forebrain commissures prior to kindling had no effect on the rate of secondary-site kindling.

The development of primary generalized motor seizures is in part dependent on the integrity of the corpus callosum and hippocampal commissure. Bisection of these structures after primary-site kindling, however, abolished the subsequent development of primary generalized seizures in a significant number of rats. Therefore, it appears that if the commissures

are bisected prior to kindling, alternate pathways able to mediate the development of primary generalized seizures evolve.

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# INTRODUCTION

Over the last 100 years an extensive literature has evolved concerning the structure and function of the fibrous pathways connecting the cerebral hemispheres. Collectively these fiber tracts are referred to as commissures and are composed of myelinated fibers arising from various areas of the cortex and subcortex of the brain. These fibers are concentrated at the midline, where they form anatomically distinct bodies and cross to the opposite hemisphere. In this manner, they serve as important routes for the transmission of neural information between either homotopic or heterotopic areas of the hemispheres.

The corpus callosum represents most of the forebrain commissural fibers, whereas, the remainder are distributed between the anterior and hippocampal commissures. The corpus callosum can be viewed as a diffuse system of radiations projecting from the midline of the brain into the grey matter of the hemispheres. These radiations intersect with both projection and association fibers and thus form an extensive network of connections representing a large portion of the forebrain cortex. Due in part to the diversity in connections and the existence of marked species differences, a detailed description of callosal anatomy is beyond the scope of the present report. For similar reasons, a detailed discussion of either anterior commissure or hippocampal commissure anatomy is not possible.

## Brief Anatomical Outline

Early investigators assumed the corpus callosum functioned as a strict commissural system. That is, it served to connect homotopic points of the hemispheres. Eventually as knowledge of callosal anatomy grew, heterotopic

interhemispheric connections via the corpus callosum were subsequently described (Hamilton, 1886; Ransom, 1895; Van Valkenberg, 1911. Today it is generally accepted that the corpus callosum forms an important route for the transmission of neural information between a variety of forebrain areas. Furthermore, it is also recognized that not all areas of the mammalian forebrain are equally represented within the callosum. For example, relatively sparse callosal representation of the visual areas in the neocortex has been described in humans (Van Valkenberg, 1913), primates (McCulloch and Garol, 1941; Garol, 1942; Bailey, von Bonin, and McCulloch, 1950; Ebner and Myers, 1962; Myers, 1962), cats (Otsuka and Hassler, 1962; Ebner and Myers, 1965), and rats (Nauta and Bucher, 1954). Similarly, other areas of the neocortex have been found to vary in the extent to which they are represented within the corpus callosum. A large callosal representation of the motor, sensorimotor, and association areas of the cortex has been described in a number of species including primates (McCulloch and Garol, 1941; Ebner and Myers, 1962), cats (Ebner and Myers, 1965), and rats (Jacobson, 1965). Fibers ending in heterotopic areas of the contralateral cortex and subcortex have also been shown to pass via the corpus callosum. Fibers entering the internal and external capsule and the corpus striatum have been described by a number of authors (Hamilton, 1896; Van Valkenberg, 1911; McCulloch and Garol, 1941; Ebner and Myers, 1965; Jacobson, 1965).

Many of the remaining forebrain interhemispheric connections are provided by either the anterior or hippocampal commissures. The anterior commissure is a relatively small bundle of fibers located on the midline of the basal forebrain. Fibers passing through the anterior commissure

generally arise from temporal lobe and olfactory structures. The relative commissural representation of these two areas has been linked to the position of the species on the phylogenic scale. For example, in mammals lower than primates anterior commissure fibers originate largely from structures associated with the olfactory system (Cajal, 1901; Fox and Schmidt, 1943; Brodal, 1948). The temporal areas of the cortex and related temporal lobe structures provide a relatively sparse contribution to the commissure. In primates and humans the majority of fibers in the anterior commissure have been found to originate from temporal lobe structures (Mettler, 1935; Rundles and Papez, 1938; Bucy and Kluver, 1940, 1955; Garol and McCulloch, 1941; Fox, Fisher, and Desalva, 1948; Whitlock and Nauta, 1956).

The hippocampal commissure functions as an important neural connection between the two hippocampi. It is a large bundle of fibers arising from the hippocampus, bifurcating ventral to the splenium of the corpus callosum, and descending towards the basal forebrain as the fornix. In addition to its function in connecting the hippocampi, it also provides an important outflow for the transmission of information to other structures of the brain. This is mediated by the fornix. The fornix has been shown to project to a variety of structures including the septum, olfactory tubercle, anterior thalamus, mammillary body, and hypothalamus (MacLean, 1949; Guillery, 1956; Valenstein and Nauta, 1959; Green, 1964; Livingston and Escobar, 1971).

## Role of the Forebrain Commissures in the Spread of Epileptiform Activity

### A. Pre-electroencephalographic Studies

The work of Jackson (1870) and Gowers (1901) showed that epileptic seizures could be divided into a number of classes. In one class, the

seizure appeared to simultaneously involve all parts of the body; in another class, the seizure appeared in one half of the body but subsequently spread to involve the whole body. Seizures such as these in which the whole body participated came to be referred to as generalized seizures.

Early anatomists were particularly concerned with determining which structures in the brain mediated the spread and generalization of seizures. Lewandowsky (1907) suggested that the corpus callosum was responsible for the spread of seizure activity between the motor cortices and the subsequent generalization of the seizure. Previous reports, however, had failed to find any significant effect on the generalization of seizures evoked by the electrical stimulation of the cortex in callosum-bisected dogs (Unverricht, 1883; Frank and Pitres, 1883). Karplus (1914) employed stricter anatomical controls in his studies but also failed to effect the generalization of seizures produced by electrical stimulation of the motor cortex in callosum-bisected monkeys and dogs. As an explanation of his results he suggested that perhaps the seizure impulses originating in the one motor cortex spread to the contralateral cortex by way of pathways situated in the brainstem. Alternate explanations were also offered. Some authors believed that the seizure impulses triggered an excitation of the vasomotor centers and these in turn caused increases in the intracranial pressure or changes in the blood flow which contributed to the generalization of the seizure (Krause, 1911; Marburg and Ranzi, 1920; Tillman, 1916). This explanation was later discarded when it was found that generalization of the seizure occurred before any significant change in the intracranial pressure was observed (Spiegel and Falkiewz, 1926).

Much of the early research was concerned primarily with determining the role played by the corpus callosum in the spread of seizures. Little

attention was paid to the possible involvement of the other forebrain commissures in this phenomenon. Spiegel and Falkiewz (1926), however, found that bisection of all fiber connections crossing the midline rostral to the rhombencephalon in the dog failed to disrupt motor seizures elicited by electrical stimulation of the cortex. Similarly, in later studies bisection of the fibrous pathways passing through the rhombencephalon was also ineffectual in disrupting the electrically induced motor seizure (Spiegel and Takagi, 1927). The results of these studies indicated that seizure generalization was able to occur over at least two distinct routes. The one route included pathways rostral to the rhombencephalon, whereas, the other included pathways in the rhombencephalon. Both groups of investigators considered the possibility that in the absence of a particular route for propagation and generalization of seizure impulses other, alternate, routes could be recruited into service. The only evidence available, however, relating to the spread and generalization of the seizure was derived from the study of ictal manifestations.

B. Post-Electroencephalographic Studies

The development of the electroencephalograph by Berger in 1929 enabled researchers to observe the electrical activity of the brain for the first time. With the application of the new recording techniques it then became possible to observe the subclinical epileptogenic process (Lennox, 1936; Lennox, Gibbs, and Gibbs, 1936).

The EEG made possible the study of potential pathways involved in the propagation of seizure discharges to surrounding neural tissue and distant areas of the brain. In the initial stages of these studies, several authors

considered cerebral blood flow to be important in this phenomenon since associated increases in the cerebral blood flow were observed during convulsions (Gibbs, 1933; Gibbs, Lennox, and Gibbs, 1934). It was found that increases in blood flow occurred first in the vicinity of epileptiform foci and then radiated to more distant areas as the clinical seizure generalized (Penfield, 1938; Penfield, von Santha, and Cipriani, 1939). Similar increases in blood flow were also reported following increases in neuronal activity evoked by electrical stimulation of the cortex (von Santha and Cipriani, 1938; Serota and Gerard, 1938). The possibility that hemodynamic and not neuronal changes were responsible for the development of seizures subsequently proved untenable. Kornmuller (1935) concluded that the spread of seizure impulses evoked by electrical stimulation of the rabbit cortex were conducted to more distant areas via neuronal and not hemodynamic pathways. Penfield and Boldrey (1939) later suggested that epileptic spread to distant structures took place over selective neuronal routes that developed from the continual neural bombardment generated by the focus. These sensitized neural circuits, they suggested, could be activated by electrical stimulation of the focal area in human epileptics.

By means of the EEG the contralateral propagation of seizure activity was shown by many authors to depend on the integrity of the forebrain commissures. Gozzano (1936) found that the application of strychnine to the rabbit cortex produced spike activity in homologous areas of the contralateral cortex. He then found that the propagation of these spikes could be blocked by sectioning the corpus callosum. With regard to the clinical generalization of seizures, Voris and Adson (1935) reported that generalized convulsive episodes were still observed in patients suffering an almost

total destruction of the corpus callosum by tumors. A later, more detailed description of seizures in patients with near total agenesis of the corpus callosum indicated that generalized grand mal attacks were rare (Hyndman and Penfield, 1937). The most frequent attacks tended to be hemiconvulsive or petit mal.

Erickson (1940) was the first to conduct a detailed investigation of the clinical and electrographic correlates of seizures in callosal-sectioned acutely prepared cats and monkeys. He observed that bisection of the corpus callosum blocked the spread of electrically induced afterdischarges to the contralateral hemisphere and generalization of the motor seizure. He noted some ipsilateral involvement of the hand, but in general the seizure was unilateral, confined to the contralateral parts of the body. He suggested that the ipsilateral involvement was due to the bilateral representation of these areas in the cortex (Bucy and Fulton, 1933; Wyss, 1938). Erickson concluded his study by further suggesting that certain intracortical association pathways existed that represented a rather elaborate route for the conduction of activity via the callosum.

It was soon discovered that regional differences existed in the callosal representation of particular cortical areas. Some authors reported the inability of strychnine to evoke projected contralateral spikes from various areas of the cortex (Dusser de Barenne and McCulloch, 1938; Dusser de Barenne, McCulloch and Ogawa, 1938). Curtis (1940a,b) found that by electrically stimulating an area of the cortex and simultaneously recording the evoked potentials produced in the contralateral cortex he was able to systematically study the relative callosal representation of each area. He recorded the greatest potentials from homotopic areas but also found several areas that

did not produce potentials. He reported that sectioning the corpus callosum abolished all contralateral potentials. McCulloch and Garol (1941) reported that projected strychnine-evoked potentials recorded in the contralateral hemisphere were dependent on the area stimulated. They observed that strychnization of areas 1,2,4,8,12,17,19, and 22 did not produce contralateral potentials; areas 4,6,7,9,10,18, and 21 did give rise to potentials but only from homotopical areas; and area 9 dorsal to the sulcus principalis and the leg and arm areas 5 and 6 produced potentials diffusely scattered over the contralateral cortex. Bisection of the corpus callosum abolished all of the strychnine spikes in the contralateral cortex except those that had been generated from the temporal lobe. Sectioning of the anterior commissure effectively suppressed contralateral activity arising from these areas.

The clinical generalization of seizures was found to depend on pathways existing within the forebrain commissures. Hoefer and Pool (1943) reported that generalized seizures resulting from either electrical stimulation of the cortex, surface application of strychnine, or picrotoxin could be suppressed by sectioning the corpus callosum. An elevation in the seizure threshold was also observed after sectioning the callosum. They further reported that although the seizure in these animals was typically unilateral, bilateral afterdischarges were observed in most cases. This lead to the suggestion that at least two routes existed that were necessary for the generalization of seizures. The one route, via the corpus callosum, was necessary for the clinical generalization of the seizure, whereas the other route, via extracallosal pathways, was responsible for the electrographic generalization of the afterdischarge to the contralateral hemisphere. An alternate route from the motor cortex to the temporal cortex and then via

the anterior commissure to the other hemisphere was suggested. Considerable anatomical and electrophysiological evidence was then available to indicate the importance of the anterior commissure in the transmission of activity between the temporal lobes (Mettler, 1935; Rundles and Papez, 1938; Bucy and Kluver, 1940; McCulloch and Garol, 1941; Fox and Schmidt, 1943). Furthermore, Alcade (1942) reported that sectioning the corpus callosum in cats failed to suppress the appearance of generalized seizures resulting from electrical stimulation of the cortex. He concluded that the corpus callosum was not an association system essential to the propagation of epileptiform attacks but failed to elaborate which alternate systems might be involved.

Many of the subsequent studies concerned with elaborating the role of the forebrain commissures in epilepsy were done using chronic animal preparations. Kopeloff, Barrera, and Kopeloff (1942) found that the application of aluminum hydroxide gel to the cortex of monkeys resulted in the production of a chronic epileptiform focus. They reported that 3 to 12 weeks after the gel application jacksonian type seizures appeared in the contralateral parts of the body and that these then developed into bilateral generalized recurrent attacks (Pacella, Kopeloff, Barrera, and Kopeloff, 1944). Electrocorticograms indicated focal abnormalities around the site of injection and the appearance of projected activity in the homotopic region of the contralateral cortex (Pope, Morris, Jasper, Elliot, and Penfield, 1946).

Kopeloff, Kennard, Pacella, Kopeloff, and Chusid (1950) examined the effects of corpus callosum bisection on recurrent spontaneous seizures produced by the application of aluminum hydroxide gel to the cortex of monkeys. They observed that bisection of the structure either before or after the

application of the gel resulted in the suppression of generalized seizures. In these monkeys, contralateral hemiconvulsions were most frequently observed. Furthermore, it was found that if the bisection was performed after the development of seizures, the severity of the subsequent hemiconvulsive attacks progressively increased and, in some cases, terminated in status epilepticus. This appeared to suggest that in the intact animal the role of the corpus callosum may in part be concerned with the transmission of inhibitory influences between the hemispheres. They also confirmed the results of previous reports (Hoefer and Pool, 1943) indicating that bisection of the callosum had no effect on the electrographic spread of the seizure to the contralateral hemisphere.

Several explanations have been offered as to why bisection of the corpus callosum in monkeys (Erickson, 1940; Kopeloff *et al.*, 1950) but not cats (Alcade, 1942) effectively suppresses the clinical generalization of seizures. One explanation concerns the relationship that appears to exist between the seizure threshold of an area and its degree of callosal representation. It has been found that the motor cortex of cats possesses a high seizure triggering threshold (Garner and French, 1958) but a low degree of callosal representation (Chang, 1953; Garner and French, 1958). Conversely, the motor cortex of monkeys has a low seizure triggering threshold (French, Gernandt, and Livingston, 1956) and a high degree of callosal representation (Chang, 1953). Due to the decreased callosal coupling of the motor cortices in cats it seems reasonable to assume that the electrographic spread and generalization of the seizure may involve extracallosal pathways. Thus, the increased level of stimulation required to evoke seizures from the motor cortex of cats may be sufficiently high to also activate these extracallosal

links. The reverse would apply to the monkey. Because the motor cortices are extensively coupled by the callosum in this species, an increased number of direct pathways are available for the transmission of activity to the contralateral hemisphere. Likely, the seizure preferentially spreads over these more direct routes. Thus, bisection of this pathway in monkeys would severely disrupt the elaboration of seizures from focal to generalized attacks. In cats, however, the pathway is less critical, therefore making the disruption of the seizure less likely after bisection.

The above perhaps suggest that prefered pathways exist that are able to mediate the propagation of seizure activity from focal areas to more distant brain structures. The first task, however, was to determine which areas of the forebrain were able to support epileptogenic activity. The second task was to investigate the functional and electrophysiological characteristics of the neuroanatomical connections that existed between the focus and distant structures. Many authors felt that by understanding these two aspects of the problem it would then become a much simpler process to determine the prefered pathways for the seizure spread.

The sensorimotor areas of the monkey cortex were found to be the most sensitive structures to the convulsant effects of aluminum hydroxide gel application (Ward, McCulloch, and Kopeloff, 1948; Kopeloff, Chusid, and Kopeloff, 1954). Recurrent spontaneous seizures were also observed in monkeys after application of the gel to parietal areas (Chusid, Kopeloff, and Kopeloff, 1955), preoccipital areas (Chow and Obrist, 1955), and temporal lobe structures (Youmans, 1956) although the reliability of the effect from these areas was somewhat lower than from the sensorimotor areas.

Recurrent spontaneous seizures have also been elicited following the injection of aluminum hydroxide gel into various subcortical structures.

Sloan, Ransohoff, and Pool (1953) found that injections into the amygdala of primates effectively produced a recurrent seizure state. Similar results have also been reported for dogs (Aida, 1956) and cats (Gastaut, Naquet, Meyers, Cavanagh, and Beck, 1959). The thalamus and putamen (Kopeloff, Whittier, Pacella, and Kopeloff, 1950), basal ganglia (Faeth and Walker, 1957), and substantia nigra (Shiroa, 1969) of cats and primates were found sensitive to the convulsant effects of aluminum hydroxide gel. Although the seizure producing effects of aluminum hydroxide gel are less observable in species lower than cats, Servit and Sterc (1958) were able to render rats susceptible to the convulsant effects of auditory stimuli after injections into the cortex.

## Forebrain Commissure Involvement in the Spread of Temporal Lobe and Limbic Seizures

With the advent of chronic recording techniques it became possible to observe and relate the development of clinical manifestations to the electrographic activity of the focus and/or more distant brain structures. For those investigating the electrographic spread and subsequent generalization of seizures, the activity of the contralateral hemisphere during seizure development was studied extensively. This, however, became extremely complex when attempts were made to study the propagation of seizures originating from sites within the temporal lobe or limbic system.

Complex partial seizures resulting from foci located within the temporal lobe have been associated with complex symptomatologies involving autonomic regulation, memory, volitional, and affective behaviours (Schmidt and Wilder, 1968). Electrographically, these seizures have also been associated with a

diffuse spread of afterdischarge activity to both ipsilateral and contralateral structures (Green and Shimamoto, 1953; Gloor, 1957; Walker, 1964). This in turn suggests a marked diversification in the projection pathways from this structure. For example, pathways originating in the temporal cortex and projecting to the brainstem (e.g. Lemmen, 1951; Jasper, Ajmone-marsan, and Stoll, 1952; French, Hernandez-Peon, and Livingston, 1955; Whitlock and Nauta, 1956; Nauta, 1962), and thalamus (e.g. Jasper, Ajmone-Marsan, and Stoll, 1952; Gloor 1955a; Whitlock and Nauta, 1956; Nauta and Valenstein, 1958; Nauta, 1962) have been identified in a number of species. Similarly, cortical association pathways (Adey and Meyer, 1952; Pribram and MacLean, 1953; Bucy and Kluver, 1955; Klingler and Gloor, 1960) and pathways to the hypothalamus (e.g. Auer and di Virgilio, 1953; Gloor, 1955a; Hall, 1959) have also been observed.

The amygdala and hippocampus are limbic structures most frequently associated with the spread of seizure activity from the temporal lobe in both humans (Lichtenstein, Marshall, and Walker, 1959; Jasper, 1964) and laboratory animals (Gloor, 1955a, 1957; Poggio, Walker, and Andy, 1956; Walker and Ribstein, 1957; Guerrero-Figueroa, Barros, Heath, and Gonzalez, 1964; Walker, 1964; Mayangi and Walker, 1974). Some authors have suggested that the tonic component of seizures evoked by electrical stimulation of the temporal pole or hippocampus was due to the activation of brain stem centers (Kaada, Pribram, and Epstein, 1949; Kaada, 1951). Feindel and Penfield (1954) considered the amygdala to be similar to the diffuse projection systems of the reticular formation and non-specific thalamus. They suggested that afterdischarges invading the amygdala from the temporal cortex were propagated diffusely to the contralateral hemisphere, ipsilateral diencephalon, and

parts of the mesencephalon. It was later found that stimulation of the amygdala was also capable of producing cortical desynchronization (Feindel and Gloor, 1954) as well as widespread cortical, subcortical, and brainstem propagation (Gloor, 1955a, 1955b).

There is evidence to suggest that the amygdala and hippocampus are functionally involved in the dissemination of afterdischarges that have originated from other regions of the cortex. Wada and Cornelius (1960) found that the amygdala and hippocampus were involved in the generalization of seizure discharges originating from chronic foci located in the sensorimotor cortex of cats.

Due to the close anatomical and electrophysiological relationship that exists between the temporal neocortex, the structures within it, and the anterior commissure, the anterior commissure has often been viewed as a potentially important pathway for the propagation of temporal lobe activity to the contralateral hemisphere. Studies done in monkeys (McCulloch and Garol, 1941; Fox *et al.*, 1948; Petr, Holden, and Jirout, 1949; Segundo, Naquet, and Arana, 1955; Whitlock and Nauta, 1956), cats (Fox, 1940; Fox and Schmidt, 1943; Gloor, 1955a, 1955b; Ebner and Myers, 1965) and rats (Brodal, 1948; Valverde, 1965; Lammers, 1972; de Olmos, 1972) have demonstrated that temporal lobe fibers pass through the anterior commissure. In general, however, the origin of these fibers within the temporal lobe has been found to vary according to the species studied. For example, in cats (e.g. Fox and Schmidt, 1943) and rats (e.g. Brodal, 1948) the major component of the commissure is the pars olfactoria or anterior limb. The pars interhemispherica or posterior limb is a relatively minor component. In primates (e.g. Bucy and Kluver, 1955) and humans (Klingler and Gloor, 1960) the relation-

ship is reversed. The pars interhemispherica predominates, whereas the contribution of pars olfactoria is relatively minor. Furthermore, Bucy and Kluver (1955) maintain that the anterior commissure in primates does not connect the amygdalae but passes posterolaterally to it and ends in the temporal pole. Frost, Baldwin, and Wood (1958), however, found that afterdischarges evoked by electrical stimulation of the amygdala in monkeys quickly propagated to the contralateral structure. They also reported that afterdischarge associated with that of the amygdala could be observed in the anterior commissure. Similarly, they found that bisection of the commissure suppressed the propagation of afterdischarges to the contralateral amygdala as well as the bilateralization of face and jaw movements often observed following repetitive stimulation.

Klingler and Gloor (1960) reported profuse anterior commissure connections between the amygdaloid nuclei in humans, whereas Ebner and Myers (1965) reported only weak connections in the cat. In the rat, however, the anterior commissure has been found to function as an important interhemispheric connection between the medial, cortical, and some of the basal amygdaloid nuclei (Brodal, 1948).

Extensive monosynaptic connections have been found between the amygdala, surrounding cortical structures, and various olfactory nuclei in a number of species including the rat (Lammers, 1972; de Olmos, 1972), cat (Fox, 1940; Ebner and Myers, 1965), and monkey (Bucy and Kluver, 1955). Species differences regarding the relative contribution that each of the above areas makes to the anterior commissure have been mentioned previously. The point to be made, however, is that even if epileptiform activity was evoked from an area making a small contribution to the anterior commissure, contralateral propa-

gation would still take place due to the extensive ipsilateral connections that the area has with structures that make a large contribution to the anterior commissure.

Poblete, Ruben, and Walker (1959) found that bisection of the anterior commissure in cats prevented the contralateral propagation of afterdischarges produced by electrical stimulation of the temporal pole or second temporal gyrus. Neither the corpus callosum, fornix, massa intermedia, nor posterior commissure appeared to be involved since bisection of these structures had no effect on the propagation. Stimulation of the amygdala produced only weak propagation of afterdischarges to the contralateral structure. They found that only 3 of 43 stimulations of the amygdala evoked afterdischarges in the contralateral amygdala. This in part suggests that weak interamygdala connections exist via the anterior commissure in this species (Ebner and Myers, 1965). Straw and Mitchell (1967) found that bisection of the corpus callosum in cats had no effect on the contralateral propagation of afterdischarges evoked by electrical stimulation of the medial ectosylvian gyrus. They suggested that other subcortical commissural structures must mediate the contralateral transmission of this activity. They felt that the anterior commissure was the most likely candidate.

The hippocampus is a limbic structure that may play a role in the contralateral propagation of temporal lobe seizure activity (Fox *et al.*, 1948; Petr *et al.*, 1949). Adey and Meyer (1952) found that afterdischarges originating from the temporal gyri spread to the hippocampus and subsequently to the contralateral hemisphere via the hippocampal commissure. It was later shown that the hippocampal commissure did indeed function in the contralateral propagation of hippocampal afterdischarges (Simpson,1952;

Creutzfeld and Myer-Mickeleit, 1953), but that the anterior commissure still played a major role (Green and Shimamoto, 1953). Poblete *et al.* (1959) reported that the contralateral propagation of hippocampal afterdischarge in cats was unaffected by sectioning of the hippocampal commissure. Their results suggest that multiple pathways must exist for the contralateral propagation of afterdischarges and that when one is destroyed an alternate pathway may takeover its function.

Due to the diffuse nature of the temporal lobe projections and the connections these make with a variety of subcortical structures that do not cross the midline via the forebrain commissures, many authors have suggested that alternate routes may be used for the propagation of seizure activity to the contralateral hemisphere (e.g. Mettler, 1935; Bailey, von Bonin, Garol, and McCulloch, 1943; Ajmone-Marsan and Stoll, 1951; Segundo *et al.*, 1955; Whitlock and Nauta, 1956). These routes, however, generally tend to be polysynaptic, involving the thalamus, hypothalamus, or reticular formation, and thus seem unlikely candidates for the initial propagation of seizure activity to the contralateral hemisphere. In the early stages of seizure development it seems likely that the direct monosynaptic pathways passing via the forebrain commissures are favoured routes. As seizure development progresses, there can be little doubt that the longer, less direct connections to the contralateral hemisphere become 'sensitized' by the persistent neural bombardment and thus become actively involved in the spread of the seizure discharge. This notion is supported by the work of many researchers (e.g. Ajmone-Marsan and Stoll, 1951; Poggio *et al.*, 1956; Gloor, 1957; Wada and Cornelius, 1960).

Commissural Participation in Secondary Epileptogenesis

Active foci will often generate dependent or in some cases independent spike activity in more distant brain structures. The appearance of these spikes is commonly referred to as secondary epileptogenesis (SE). Studies related to this phenomenon have produced data that are valuable to the understanding of the role played by the forebrain commissures and brainstem structures in the propagation of epileptiform discharges.

An extensive literature exists on the subject of SE in human epileptics (Penfield and Jasper, 1954; Heath and Mickle, 1957; Heath, 1962; Guerrero-Figueroa, Gallant, Robinson, and Heath, 1968), primates (Gozzano, 1936; Erickson, 1940; Pacella *et al.*, 1944; Cure and Rasmussen, 1950; Wada, 1964; Nie, Maccabe, Ettlinger, and Driver, 1974), cats (Wada and Cornelius, 1960; Guerrero-Figueroa *et al.*, 1964), rabbits (Morrell, 1960; Morrell, Proctor, and Prince, 1965; Proctor, Prince, and Morrell, 1966), rats (Isaacson, Schwartz, Persoff, and Pinson, 1971; Ashcroft, Dow, Harris, Hill, Ingleby, McQueen, and Townsend, 1974), and inframammalians (Servit and Strejckova, 1967, 1971).

There appears to be two stages involved in the phenomenon of SE: (1) the appearance of discharges temporally dependent on those from the primary focus; and (2) the appearance of discharges temporally independent from those of the primary focus. Morrell (1960) and later Rutledge and Kennedy (1961) proposed that separate anatomical pathways were responsible for the mediation of these two stages. It was suggested that dependent discharges were mediated via the corpus callosum, whereas brainstem pathways were responsible for the mediation of independent discharges. For example, bisection of the corpus callosum prior to the creation of a primary focus in

the cortex has been found to suppress the appearance of SE in monkeys (Gozzano, 1936; Erickson, 1940), rabbits (Morrell, 1960), and rats (Isaacson *et al.*, 1971; Ashcroft *et al.*, 1974). Similarly, Guerrero-Figueroa *et al.* (1964) found that bisection of the forebrain commissures in the cat prior to implanting alumina gel in various limbic structures prevented the appearance of SE in contralateral structures. In contrast, however, Nie *et al.* (1974) reported that bisection of the corpus callosum in monkeys prior to the creation of a posterior parietal cortex focus only succeeded in slowing but not stopping SE in the contralateral homotopic area. Differences between the results of Nie *et al.* and those of earlier investigators (e.g. Gozzano, 1936; Erickson, 1940) may in part reflect the necessity of doing studies such as these in chronic preparations. Nie *et al.* (1974) studied SE in chronic monkeys whereas the earlier studies were done using acute preparations. It seems reasonable to speculate that over time a number of pathways may develop in the chronic preparation that become capable of establishing areas of SE in either ipsilateral or contralateral structures.

Studies done on species not possessing a corpus callosum (e.g. marsupials and inframammalians) indicate that alternate, extracallosal pathways are capable of establishing areas of SE. For example, Servit and Strejkova (1967, 1971) found that the forebrain of turtles and frogs was capable of supporting SE. Further studies also showed that bisection of all interhemispheric connections in the frog brain did not affect the development of SE (Servit, Strejkova, and Volanschi, 1968). Wilder, King, and Schmidt (1968) observed SE in the forebrain of the opposum, a marsupial lacking a corpus callosum.

Studies related to the effects of forebrain bisection on chronic secondary epileptogenic areas have shown that the discharge activity of these foci is subjected to both callosal and extracallosal influences (Guerrero-Figueroa *et al.*, 1964; Isaacson *et al.*, 1971; Ashcroft *et al.*, 1974). Morrell (1960) found that bisection of the corpus callosum in rabbits blocked the development of synchronous spike discharges between the primary and secondary foci in the cortex. Bisection of the corpus callosum after independent secondary spike discharges had developed, however, produced no subsequent change in the discharge pattern (Morrell, 1960). Morrell suggested that the development of dependent synchronous spike discharges was mediated by the corpus callosum whereas the development of independent spike discharges depended on alternate subcortical pathways. To support his hypothesis he was able to show that the development of independent discharges in secondary epileptogenic areas of the rabbit cortex could be suppressed by isolating the cortex and corpus callosum from the subcortex. The cortex - corpus callosum section, however, did not affect the development of synchronous spike discharges.

## Commissural Participation in the Genesis of Generalized Spike and Wave Activity

The forebrain commissures have been implicated in the interhemispheric generalization of bisynchronous spike and wave activity. The 2.5 to 3.5 per second discharge pattern associated with this activity is often observed in patients exhibiting signs of petit mal epilepsy.

A characteristic EEG feature of petit mal attacks is the simultaneous appearance of generalized bisynchronous spike and wave discharges in most

areas of the cortex. In order to explain the widespread cortical effects associated with this phenomenon, many investigators proposed that these attacks were precipitated by a pathological condition involving either the diffuse thalamic projection system or brainstem reticular formation (e.g. Penfield and Jasper, 1954; Pollen, 1963; Weir, 1964). A large body of both clinical and experimental data, however, has suggested that the phenomenon may also be related to the spread of epileptiform discharges from cortical foci (Bancaud, Talairach, Bonis, Schaub, Szikla, Morel, and Bordas-Ferer, 1965; Marcus and Watson, 1966, 1968; Marcus, Watson, and Simon, 1968; Vioculescu and Popescu-Tisuana, 1969; Mutani, Bergamini, Fariello, and Quattrocolo, 1972, 1973).

Two mechanisms have been proposed to account for the extensive propagation and rapid generalization of spike and wave activity generated by a cortical foci. The one mechanism proposes that discharges arising from cortical foci propagated via intracortical routes to involve ipsilateral structures and transcallosal routes to involve contralateral structures. The other proposal involves the spread of focal cortical discharges to subcortical structures that in turn are capable of projecting the activity to widespread areas of both the ipsilateral and contralateral cortex. Experimental evidence indicates, however, that it is probably a combination of these two that accounts for the widespread bisynchronous activity.

Marcus and Watson (1966, 1968) and Marcus *et al.*, (1968) found that transcallosal and not the cortical-subcortical pathways were responsible for the mediation of generalized bisynchronous spike and wave discharges originating from bilaterally symmetrical foci in the cortex of acute cats and monkeys. Bisection of the corpus callosum was found to disrupt the bilateral synchrony of the discharge although each focus continued to dis-

charge independently. The independent aspect of the focal activity was found to rely on the integrity of the cortical-subcortical systems since isolation of the cortex and corpus callosum resulted in the suppression of independent activity. This procedure, however, did not affect the bilateral synchrony of the spike and wave activity.

Ottino, Meglio Rossi, and Tercero (1971) reported that subcortical structures were capable of mediating the generalized bisynchronous discharges in the absence of the preferred callosal pathways if the convulsant stimulus was sufficiently increased. They found that generalized bisynchrony could still be maintained after bisecting all forebrain commissures to the level of the midbrain if the electrical stimulation of the cortex was increased concomittantly. Generalized bisynchrony could be permanently abolished only after bisection of the midbrain.

It was previously thought that only bilaterally symmetrical cortical foci were capable of generating generalized bisynchronous spike and wave activity. Mutani *et al.* (1973), however, demonstrated that bilaterally asymmetrical foci were equally effective. Furthermore, they found that it was not necessary to create the foci in areas of the cortices extensively coupled by the corpus callosum. Bisection of the corpus callosum, however, disrupted the bilateral synchrony arising from foci created in the sigmoid gyrus of one hemisphere and the lateral gyrus of the other. These two areas have been shown to be markedly deficient in callosal connections (Chodoury, Whitteridge, and Wilson, 1965; Hubel and Wiesel, 1965; Jones and Powell, 1968; Berlucchi, 1972). Isolation of the cortex and corpus callosum did not affect the bisynchrony of the spike and wave discharges.

In view of the above reports, it must be concluded that transcallosal and intracortical pathways function primarily in maintaining the bisynchron-

ous aspects of the discharge whereas subcortical pathways are important for the establishment of independent discharge patterns.

Nature of the Information Transmitted Via the Forebrain Commissures

There have been numerous reports of either enhancement or inhibition of spike discharges in secondary foci following drug-induced inactivation of the primary focus (Rovit, Hardy, and Gloor, 1960; Rovit, Gloor, and Rasmussen, 1961; Gloor, Garretson, and Rasmussen, 1965; Coceani, Libman, and Gloor, 1966). Subsequent investigation has shown that both transcallosal and cortical-subcortical processes are involved in this phenomenon. Mutani *et al.* (1972) observed that bilateral asymmetrical cortical foci often appeared more active than unilateral foci. This led them to suggest that a facilitatory interaction took place between bilateral foci. Sectioning the corpus callosum in cats was found to produce an even further increase in the discharge activity of the bilateral foci. In contrast, cortex-corpus callosum isolation resulted in a marked attenuation in the focal activity. In view of these results, Mutani *et al.* (1972) proposed that transcallosal pathways were responsible for an inhibitory interhemispheric interaction in the intact animal whereas other, subcortical pathways mediated a facilitatory interaction.

There have been few subsequent reports concerning the inhibitory functions of the corpus callosum in seizure activity. It has been shown, however, that bisection of the forebrain commissures in cats (Wada and Sato, 1975) and rats (McCaughran, Corcoran, and Wada, 1976) results in the facilitation of seizure development.

Forebrain Commissurotomy for the Control of Intractible Seizures in Humans

Von Wagenen and Herren (1940) were the first to use forebrain commissurotomy as a surgical treatment for the control of intractible seizures in human epileptics. The surgical procedure was based on a number of clinical reports that indicated that pathological destruction of the corpus callosum often abolished a preexisting seizure disorder. Of the 10 patients who underwent surgery, the corpus callosum and hippocampal commissure were completely bisected in only two cases. These structures were bisected to varying degrees in the other eight patients. The success of the operation was moderate and postoperative recovery was often hampered by neurological complications. Seizures continued in a number of cases although the frequency of the attacks was generally reduced. Typically the attacks were no longer generalized but usually hemiconvulsive and associated with jacksonian type clinical manifestations and no loss of consciousness. Several patients did, however, continue to exhibit generalized seizures. The longterm success of the operation was not reported, although subsequent study was done on the psychological effects of the surgery (Akelaitis, 1942; Bridgman, 1945). It is difficult to ascertain the magnitude of the clinical improvement.

Bogen and Vogel (1963) and Bogen, Fischer, and Vogel (1965) also attempted to control intractible seizures in human epileptics by surgically bisecting the forebrain commissures. In their series of patients, all were subjected to complete transection of the corpus callosum and hippocampal commissure. Some also underwent bisection of the hippocampal commissure and the massa intermedia of the thalamus.

Only one from a group of ten patients failed to show significant reduction in the frequency of attacks after forebrain bisection. Of the nine

showing decreased seizure frequency, all had previously shown a high frequency of generalized attacks prior to surgery. Generalized attacks following surgery were extremely rare over the follow-up period ranging from 2-7 years. The few generalized attacks that were observed were thought to be precipitated by a reduction in anticonvulsant medication. Subsequent increases in medication were reported to suppress these attacks. It was also reported that focal, hemiconvulsive attacks were observed slightly more frequently than generalized attacks but these also responded favorably to medication.

Lussenhop (1970) reported that division of the forebrain commissures was a successful alternative to the more radical hemispherectomy commonly used for the treatment of intractible seizures associated with infantile hemiplegia. Although only two cases were reported and in both of these adequate follow-up information is still lacking, both cases exhibited a marked reduction in generalized seizure frequency. Unilateral attacks were observed although these also decreased in frequency.

Kindling

Electrical stimulation of the cortex is probably one of the oldest techniques used in the study of epilepsy (e.g. Ferrier, 1873; Luciani, 1878). Most of the early knowledge concerning the role of the forebrain commissures in epilepsy was derived from the study of seizures produced by electrical stimulation of the cortex of laboratory animals (for a review see Spiegel, 1931). The convulsant effects of brain stimulation were initially confined to observations regarding the clinical response. It was not until Berger (1929) developed the EEG that the effects of electrical stimulation on the neuron were observed.

It was shortly after the development of the EEG that Adrian (1936) observed the first self-sustained afterdischarges resulting from the electrical stimulation of the cortex. Detailed descriptions of the morphological features of the afterdischarge patterns soon followed (e.g. Rosenbleuth and Cannon, 1941-1942; Jasper, 1954; Kreindler, 1965). Similarly, electrographic studies related to the propagation of afterdischarges from areas of the brain provided a valuable source of information concerning the spread of seizure activity (e.g. Ajmone-Marsan, and Stoll, 1951; Jasper, Ajmone-Marsan, and Stoll, 1952; Poggio *et al.*, 1956; Udvarhelyi and Walker, 1965; Walker and Udvarhelyi, 1965). It was also found that repetitive stimulation of an area resulted in the progressive reduction of its afterdischarge threshold (Pinsky and Burns, 1962; Straw, 1968).

The effects of repeated brain stimulations on freely-moving animals were not known until relatively recently. Alonso-de Florida and Delgado (1958) found that chronic electrical stimulation of the amygdala in cats produced a lasting behavioural change in, in some instances, motor seizures. These results were later confirmed by Fonberg and Delgado (1961) and extended by Delgado and Sevillano (1961), who reported that repetitive stimulation of the hippocampus evoked progressively longer afterdischarges and the frequent appearance of generalized motor seizures. Similar effects were also observed during self-stimulation studies. Wurtz and Olds (1963) observed seizures in animals with self-stimulation electrodes in the amygdala. Seizures resulting from the self-stimulation of hypothalamic sites have also been reported (Bogacz, St. Laurent, and Olds, 1965). However, Goddard (1967) and Goddard, McIntyre, and Leech (1969) were the first to provide detailed information concerning the progressive development of motor seizures evoked

by repeated electrical stimulation of the brain. They reported that once-daily administration of a subconvulsive electrical stimulus to a variety of cortical and subcortical structures in rats, cats, or monkeys resulted in the gradual development of generalized motor seizures. They referred to this phenomenon as the 'kindling' effect.

Kindled seizures have now been confirmed in a number of species including the rat (Burnham, 1971; Racine, 1972a,b; Corcoran, McCaughran, and Wada, 1973; McIntyre and Goddard, 1973; Pinel, Phillips, and MacNeil, 1973), cat (Wada and Sato, 1974 ; Wada, Sato, and Corcoran, 1974), rabbit (Tanaka, 1972), and primate (Wada, Osawa, and Mizoguichi, 1975; Wada and Osawa, 1976). It was once thought that kindling was in part the result of pathological interference of the electrode tip with the surrounding neural tissue. This hypothesis, however, proved to be untenable (Goddard, 1972; Goddard and McIntyre, 1974). It now appears that the development of kindled seizures is characterized in at least four ways: (1) a reduction in the afterdischarge threshold at the site of stimulation; (2) the dependence of motor seizure development on the production of afterdischarge; (3) the elaboration in the morphology of the afterdischarge pattern; and (4) the spread of afterdischarge to more distant, synaptically related structures (e.g. Racine, 1972a,b; Wada and Sato, 1974 ; Wada and Osawa, 1976).

Many studies suggested that kindling was able to produce lasting, if not permanent, widespread alterations in the functioning of the brain. It was found that after generalized motor seizures had been kindled, subsequent seizures following nonstimulated periods of variable duration, usually resulted on the first restimulation (Goddard *et al.*, 1969). Seizures in kindled cats have been reported following nonstimulation intervals of up to one year (Wada, Sato, and Corcoran, 1974). Reports of spontaneous recurrent

seizures in kindled rats (Pinel, Mucha, and Phillips, 1975), cats (Wada *et al.*, 1974), and primates (Wada *et al.*, 1975), and observations that kindling lowers the seizure triggering threshold to a variety of agents (e.g. Pinel and Van Oot, 1975; Pinel, Skelton, and Mucha, 1975; Wada *et al.*, 1974) supports the notion that widespread neuronal changes accompany or result in kindled seizures.

Transsynaptic changes also appear to accompany the development of kindled seizures. For example, increases in the seizure susceptibility of ipsilateral and contralateral structures have been shown to accompany kindling (Goddard *et al.*, 1969; Racine, 1972a; Burnham, 1971, 1975). Similarly, Wada *et al.* (1974) reported that independent interictal discharges persisting for periods up to one year were observed in various subcortical structures of the kindled cat.

Studies have also shown that kindling is able to produce longterm changes in the behaviour of animals. McIntyre and Molino (1972) reported that conditioned emotional response learning in rats was disrupted after kindling. Adamec (1975) also observed changes in the behaviour of cats. He found that a reduction in predatory aggression occurred after elicting amygdaloid afterdischarges.

Repetitive electrical stimulation does not appear to be the only agent capable of kindling seizures. In fact considerable evidence exists which indicates that any stimulus able to cause paroxysmal discharges in areas of the brain may be capable of kindling seizures. Kindled seizures have been reported following injections of carbachol into the amygdala, hippocampus, and caudate nuclei of rats (Vosu and Wise, 1975). Mason and Cooper (1972) reported that repeated injections of initially subconvulsive doses of Metra-

zol in rats will eventually elicit seizures. It has also been shown that repetitive seizures induced by fluorothyl ether (Prichard, Gallagher, and Glaser, 1969) or electroconvulsive shock (Pinel and Van Oot, 1975) result in the eventual reduction in the subsequent seizure threshold.

Little experimental evidence exists as to the possible neurophysiological substrates underlying the kindling phenomenon. As yet, studies have failed to find morphological changes in neurons related to kindling (Goddard and Douglas, 1975; Racine, Tuff, and Zaide, 1975). Although reports that potentiation of neuronal discharge patterns accompanying kindling (Douglas and Goddard, 1975; Racine *et al.*, 1975) have proved intriguing, they are still inconclusive.

## Commissural Participation in Kindling

Racine, Okujava, and Chipashvili (1972) proposed that kindling resulted from the progressive strengthening of interlimbic connections. Afterdischarges generated at the stimulated site, it was proposed, propagated via monosynaptic pathways to reach other limbic structures. Activity in these structures then spread to involve more distant structures and finally much of the limbic system. When this point was reached, there was a further spread of activity to structures associated with the motor system. It was activation of these motor structures that eventually resulted in the clinical manifestations. As support for the hypothesis, Racine *et al.* (1972) showed that simultaneous bilateral stimulation of limbic structures facilitated the development of kindled structures. They also showed that the converse was true. They reported that disruption of the interlimbic connections by transecting the forebrain commissures significantly retarded the development of kindled amygdaloid seizures in the rat.

Wada and Sato (1975) reported that bisection of the forebrain commissures in the cat resulted in the facilitation of kindling elicited by stimulation of the amygdala. They also reported that although bisection of the anterior commissure disrupted the propagation of afterdischarges to the contralateral amygdala in their cats, kindling was still facilitated. This seemed to suggest that the contralateral amygdala played little if any role in the development of kindled amygdaloid seizures. Wada and Sato also reported that since bisection of the forebrain commissures did not disrupt generalization of the seizure other subcortical structures were likely responsible for this aspect of the seizure development. A likely structure, they suggested, was the mesencephalic reticular formation since previous studies (e.g. Wada and Sato, 1974) had implicated this structure in the generalization of kindled amygdaloid seizures. They went on to suggest that kindling may in part be due to the strengthening of limbic-brainstem connections rather than limbic-limbic connections as suggested by Racine *et al.* (1972).

In contrast to the results of Wada *et al.* (1974), McIntyre (1975) reported that bisection of the forebrain commissures in the rat had no effect on the rate of amygdaloid kindling. He also found that the number of stimulations required to kindle the contralateral amygdala after kindling the primary site (ie. the transfer effect) was not significantly different in either the forebrain-bisected group or the intact group. Bisection of the anterior commissure and rostral corpus callosum, however, disrupted propagation of activity to the contralateral amygdala. But, the lack of bilateral amygdaloid afterdischarges in these animals did not affect the transfer phenomenon. This result suggested that structures involved in this phenom-

enon are situated extracallosally. McIntyre also found that forebrain bisection eliminated the interference in seizure expression that is typically observed in intact rats during the first several restimulations of the primary site (ie., after the primary and secondary sites have been kindled).

McIntyre (1975) found that portions of the forebrain commissures participated in the generalization of kindled amygdaloid seizures. He observed that the generalization of seizures was suppressed in rats in which the anterior commissure and rostral corpus callosum were bisected. These animals typically displayed unilateral convulsive manifestations localized to the contralateral extremities of the body.

## The Present Investigation

The experiments reported in this thesis were designed to examine the role played by the various forebrain commissures in the development and maintenance of kindled amygdaloid seizures in the rat. The first two experiments are concerned with the development and electrographic spread of kindled seizures in rats possessing varying degrees of forebrain commissure bisection. The third experiment determines the effects of forebrain bisection on kindled seizures.

# EXPERIMENT 1

Several conflicting reports exist concerning the effects of forebrain bisection on the development of kindled amygdaloid seizures in laboratory animals (Racine *et al.*, 1972; Wada and Sato, 1975; McIntyre, 1975). In view of these results, the present experiment was done in order to reexamine the role played by the forebrain commissures in the development of kindled amygdaloid seizures in the rat. The goals of the study were: (1) to determine the effect that forebrain bisection had on various parameters of the clinical seizure (e.g. rate of development and duration) and (2) an examination of the electrographic spread of the seizure discharge accompanying the various stages of clinical seizure development.

## Method

Subjects. Approximately 25 male hooded rats of the Long-Evans strain weighing between 250-350 g at the time of surgery were used. They were housed individually under *ad-libitum* feeding and drinking conditions, constant room temperature, and a 12 hr light-dark cycle. Rats were allowed 10-14 days to adjust to the colony environment before undergoing surgery.

Surgery. All forebrain bisections were done under visual control. The rats were anaesthetized with interperitoneal injections of sodium pentobarbital (25 mg/kg) and chloral hydrate (300 mg/kg) and a small trephine hole was drilled over the anterior frontal cortex, lateral to the midline. The sagittal sinus was visualized and a slightly curved stylus constructed from a 23 gauge syringe needle was passed through the opening and into the sagittal fissure. The tip of the stylus was then passed caudally until a point marked on the shaft of the instrument indicated

that the most caudal extent of the corpus callosum had been reached. The stylus was then lowered to the base of the forebrain, thus sectioning the corpus callosum, hippocampal commissure, and other midline structures. The tip of the stylus was designed with an upward curve to avoid penetration of the midbrain. In some cases bisection of the anterior commissure was also attempted. In these instances, the tip of the stylus was retracted through the diencephalon to the level of the commissure and then reinserted to the base of the forebrain. A slightly different approach was used, however, if only bisection of the anterior commissure was desired. In this case, the tip of the stylus entered the brain rostral to the corpus callosum and at an oblique angle. This tended to minimize the damage sustained by callosal fibers inadvertently contacted by the stylus. The tip of the stylus was reflected up at a level estimated to be just dorsal to the anterior commissure. The entire stylus was then lowered to the base of the forebrain, thus sectioning the structure.

Control rats were handled similarly except no attempt was made to bisect the forebrain commissures. In these animals a trephine opening was placed over the left frontal cortex just lateral to the midline and the sagittal sinus was visualized. The dura was then cut but no attempt was made to insert the stylus.

Both groups of rats received identical postsurgical treatment. The trephined opening was packed with gelfoam and the scalp inscision was closed with stainless steel wound clips. Postoperative recovery was observed for thirty days. Rats that displayed behavioural evidence suggesting gross neurological dysfunctioning were discarded.

Electrode implantation. Thirty days after surgery all surviving rats were reanaesthetized with an interperitoneal injection of sodium pentobarbital (60 mg/kg) and bipolar stimulating and recording electrodes were implanted. The electrodes were constructed of twisted nichrome wire and had a final diameter of 127 μm. Each also had a tip separation of 0.5 mm and one pole bared of insulation for 0.5 mm along its length. Miniature male connector pins (Amphenol, P202) were soldered to the leads of each electrode.

All rats received electrodes aimed bilaterally at the basolateral nucleus of the amygdala ([AM] 0.4 mm anterior to bregma, 4.3 mm lateral to the midline, 8.5 mm ventral from the surface of the cortex, and with the inscisor bar set at +5.0 mm). In some rats electrodes were also aimed at the left mesencephalic reticular formation (MRF) at the level of the superior colliculus (4.4 mm posterior to bregma, 2.0 mm lateral to the midline, 5.5 mm ventral from the surface of the cortex, and with the inscisor bar set at +5.0 mm). These same rats were also prepared with bipolar cortical electrodes placed over the motor areas 4 and 6 (MC) of the cortex as shown by Skinner (1971). Each pole of the electrode consisted of a coiled loop of nichrome wire that enclosed an area of approximately 1.0 $mm^2$. One pole was placed over Area 4 (1.5 mm posterior to bregma and 1.5 mm lateral to the midline), and the other pole was placed over Area 6 (2.5 mm anterior to bregma and 1.5 mm lateral to the midline). In both cases care was taken not to penetrate the dura. A ground electrode consisting of a bare stainless steel wire, soldered onto a miniature connector pin, and then twisted around the head of a miniature screw, was driven into the frontal bone of each rat.

Electrodes were held in place with dental acrylic cement. The temporal muscles along each side of the head were retracted and screws were driven

into the exposed temporal bone. The screws were then covered with acrylic and served as anchors for the electrode assembly. The connector pins were arranged in a straight line running parallel to the midline (if more than two electrodes and a ground electrode were used, then the pins were arranged in two parallel lines) and held in place by a specially constructed template. The entire assembly was held together with dental acrylic cement. In an effort to protect the pins from being either bent or broken by the rat, a plastic guard constructed from a 10 mm length of 10cc syringe tubing was fitted and then cemented in place around the assembly.

All rats were observed for a minimum of one week following the implantation of electrodes. During this time they were periodically handled and checked for infections.

Testing procedures. Testing was conducted once daily between 1000 and 1200 hr. The rats were transported individually to the testing room and placed in a specially constructed cage shielded with copper mesh. They were allowed several minutes to adapt to the cage and then baseline EEG activity was recorded for 2 minutes. Electrical stimulation consisted of a 1 sec train of 60 Hz constant current sine wave delivered at a fixed current intensity of 160 μa for all rats. Stimulation was initially applied to the right AM in most rats.

Amygdaloid kindling. The progressive development of kindled seizures was classified according to the description by Racine (1972a): C-1, twitching of muscles around the mouth and eyes; C-2, the above as well as head nodding; C-3, the above as well as forelimb clonus; C-4, the above as well as rearing onto the hindlimbs; C-5, the above as well as loss of balance and falling. Seizures were recorded only if the clinical manifestations were sustained for several seconds after the termination of the stimulation.

This criterion was introduced to control for the possibility of stimulus-bound motor movements being included in the clinical progression. Rats were considered kindled upon reaching the C-5 stage in seizure development.

Eight C-5 seizures were evoked from the initial site of stimulation (primary site). On the following session (in most cases this was the following day) the site of stimulation was switched to the contralateral AM (secondary site) in order to study the transfer effect. Transfer refers to the facilitated development of secondary site kindling that is produced as a result of previous kindling at the primary site. Rats were then kindled at the secondary site and allowed to have eight C-5 seizures.

Afterdischarge and seizure duration. The afterdischarge and seizure duration associated with each stage of development were recorded from the start to the finish of all clinical manifestations, except during stages 4 and 5. During these stages the seizure duration from the start to finish of forelimb clonic activity was recorded. Afterdischarge duration, however, was recorded over the entire session.

Histology. Following the completion of the study, rats were killed with an overdose of sodium pentobarbital and perfused intercardially with 0.9% saline followed by 10% formalin. The brain was removed and examined for signs of cortical damage resulting from bisection of the commissures. The brain was then frozen and coronal sections 40 μm in thickness were cut on a sliding microtome. Every fifth section (0.2 mm) was kept and stained with cresyl violet. The electrode placements were examined and the extent of the forebrain bisection was plotted on sections taken from the atlas of Pellegrino and Cushman (1967). Cortical electrode placements were visually determined at the time the brain was removed. Data from animals not having

electrodes in the desired structures were discarded. Tracings were produced of representative forebrain bisections taken from the samples that remained.

Statistical analysis. Statistical analysis of the data was done using standard parametric analysis of variance procedures. All *post hoc* comparisons were achieved using the Scheffé method for multiple comparisons. Significant levels of $p$ were all two-tailed.

Attention was paid to those aspects of the data that dealt with the number of stimulations to kindle, the afterdischarge duration at all recording sites, and seizure duration. Analysis of these various parameters was conducted for both primary and secondary site kindling. A detailed record of the afterdischarge development and propagation from the stimulated site in each rat was also compiled.

## Results

Eighteen of 25 rats survived the forebrain bisection and implantation of the electrodes. All 10 control rats survived the trephination and subsequent implantation of electrodes.

One-way analysis of variance failed to show any significant difference in the rate at which forebrain bisected and control rats kindled ($F$=.11; $df$=1,23; $p$>.05). *Post hoc* histological examination of the brain, however, showed that bisection of the rostral corpus callosum, hippocampal, and anterior commissures caused a significant facilitation in kindling. Bisection of the corpus callosum and hippocampal commissure had no effect. Kindling was retarded only in rats sustaining extensive subcortical, thalamic damage in addition to forebrain bisection.

Propagation of afterdischarges (ADs) to the contralateral AM was disrupted by anterior commissure bisection whereas corpus callosum bisection disrupted propagation of ADs to the contralateral MC.

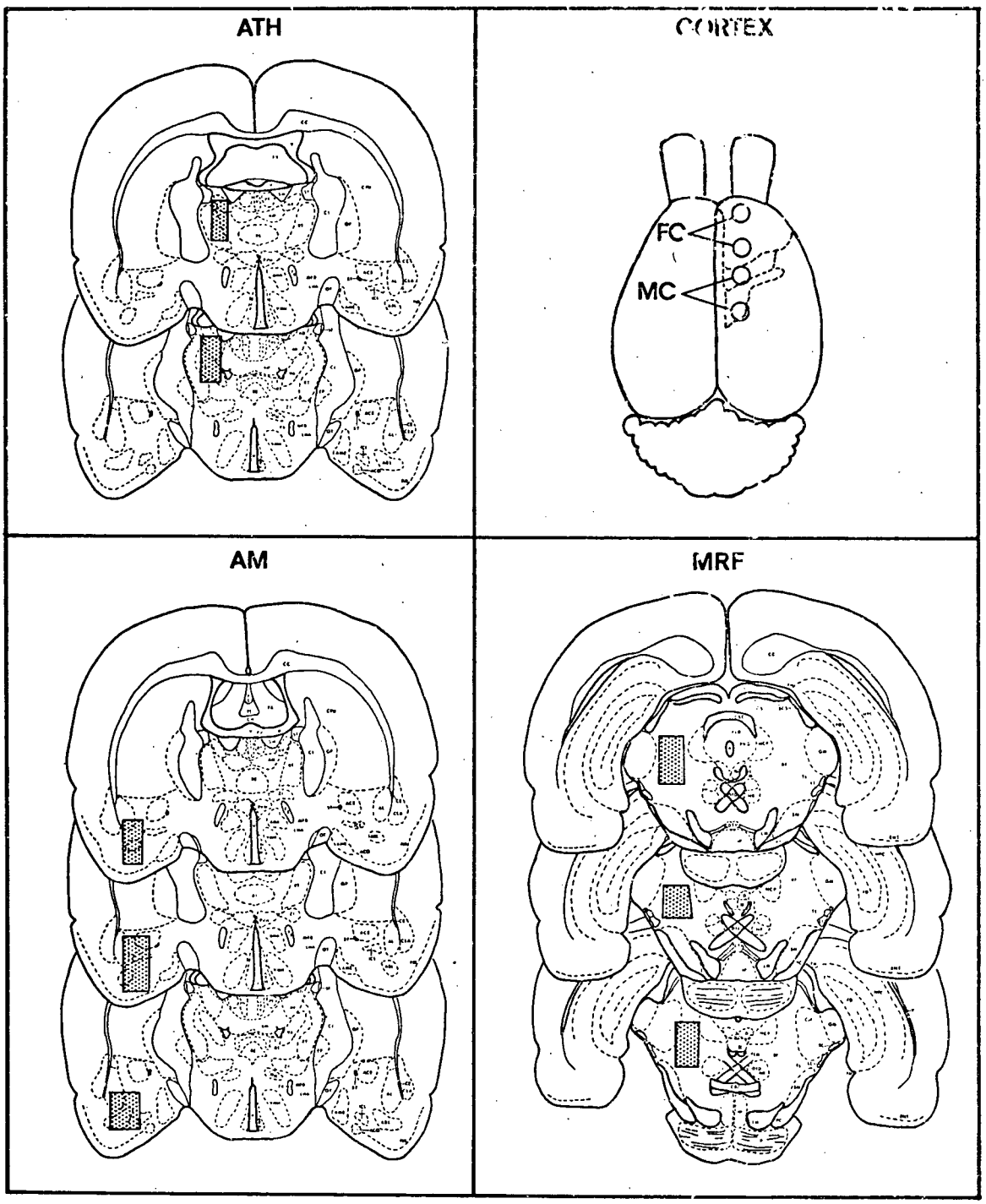
Forebrain bisection had less effect on the rate of secondary site kindling than on primary site kindling. The effects on electrographic spread of the seizure, however, remained essentially the same during primary and secondary kindling.

Histology. The location of electrodes is shown in Fig. 1. All electrode tips were found in or immediately adjacent to the intended structures. AM electrodes were found concentrated in an area surrounding the basolateral nucleus. Electrodes aimed at the MRF were localized to an area immediately lateral to the nucleus of the oculomotor nerve and at the level of the superior colliculus. Visual analysis of the cortical electrode placements found these to be overlying the desired structures: Areas 4 and 6.

*Post hoc* histological examination of the experimental group indicated that the extent of the forebrain bisection was not homogenous. Based on this examination, it was possible to assign each of the experimental rats to one of the 3 following groups: Group CC, bisection of the corpus callosum and hippocampal commissure; Group AC, bisection of the anterior commissure with minimal damage to the rostral corpus callosum; Group TD, partial bisection of the rostral corpus callosum and hippocampal commissure in combination with extensive extracommissural thalamic damage. Representative histology from each of these groups is presented in Fig. 2.

All groups displayed some evidence of extracommissural damage. In group CC, damage to the cortex overlying the corpus callosum appeared to be

Fig. 1. Localization of stimulating and recording electrodes. ATH=anterior thalamus; AM=amygdala; FC=frontal cortex; MC=motor cortex; MRF=mesencephalic reticular formation.

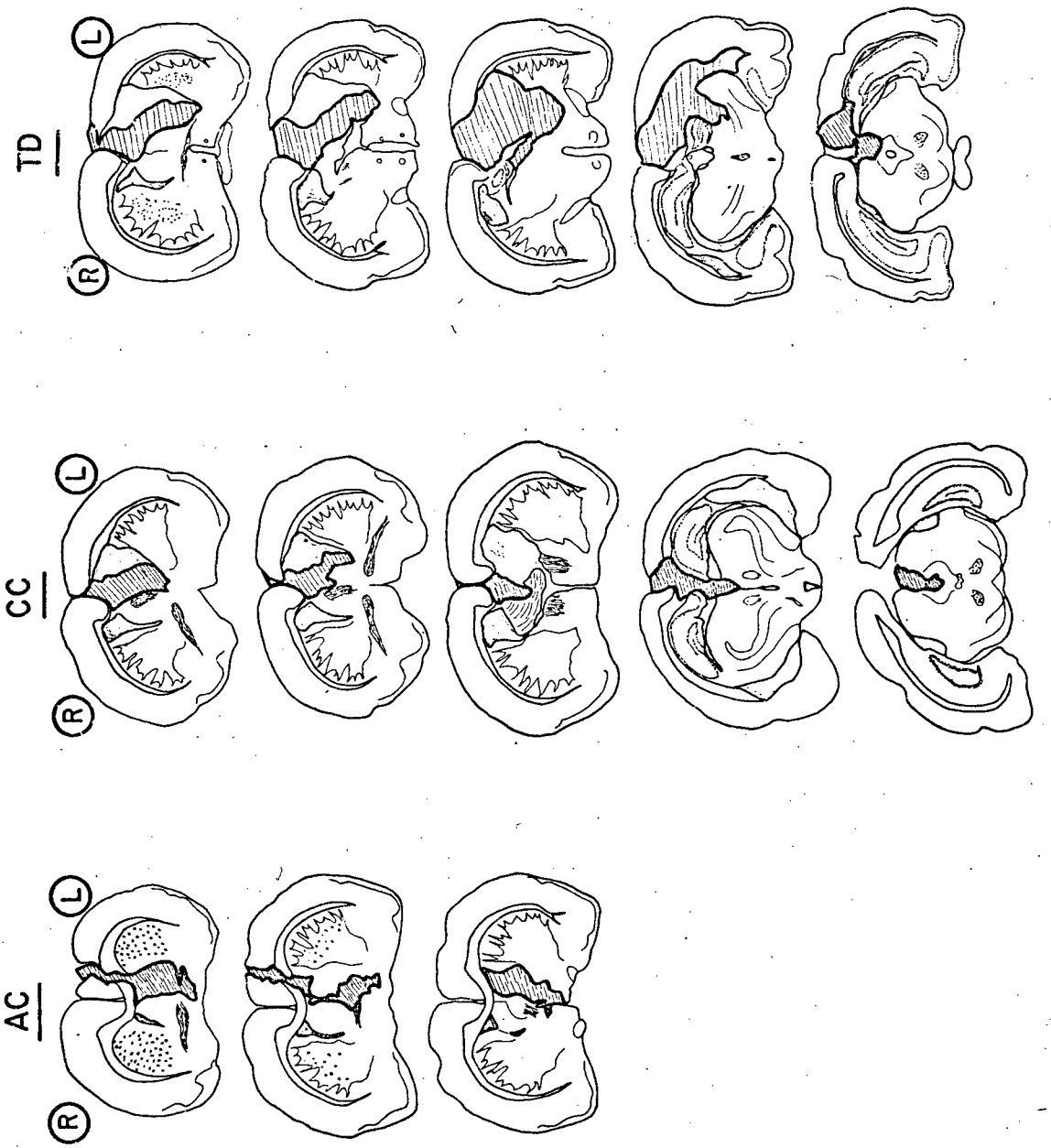

ATH
CORTEX
FC
MC
AM
MRF

slight and in most cases localized to the medial aspects of the rostral forebrain. Subcortically there was a slight dilation of the lateral ventricals but this did not appear to be caused by obstruction of the aqueduct. Damage to the dorsal aspects of the lateral septal nucleus was evident in some rats although this tended to be unilateral and minimal. There was little sign of penetration of the midline thalamic nuclei in this group. Similarly, caudal to the hippocampal commissure the hippocampus appeared undamaged in most rats. The posterior commissure in a number of rats was found to be sectioned whereas the underlying midbrain appeared to be intact.

Extracommissural damage to the cortex of rats in Group AC was in some cases nearly nonexistent. A number of rats, however, possessed slight damage to the rostral cortex along the medial boundary of Area 10. Subcortical damage was observed mainly in the lateral septal nuclei and anterior hypothalamus. In the septum, it appeared as though involvement of the lateral nuclei caused widespread degeneration throughout the rest of the structure. Penetration of the hypothalamus was most frequently observed in the preoptic area and areas rostral to the anterior commissure.

Rats in Group TD possessed the most extracommissural damage. Damage to the cortex of this group did not appear to be any more extensive than that observed in Groups AC and CC. Similarly, there was some destruction of the dorsomedial aspects of the lateral septal nuclei and a slight ventricular dilation was observed in a minority of rats. By far the most extensive extracommissural damage was in the vicinity of the right rostral thalamus. Damage to this structure appeared to be roughly confined to an area bounded rostrally by the midportion of the anteroventral thalamic nucleus,

Fig. 2. Extent of the forebrain bisection in a representative rat from each group. The bisection is indicated by the crosshatching. Lightly shaded areas represent ventricular spaces. Note the large area of destruction within the rostral thalamic area of Group TD.


TD
L
R
CC
L
R
AC
L
R

medially by the midline, and laterally by the internal capsule. The floor of the right lateral ventricle was the dorsal extreme of the damage, and the medial lemniscus formed the ventral extreme. Caudally, the damage extended to an area approximately at the tip of the dorsomedial nucleus of the thalamus.

Nuclei within this zone of destruction appeared to be involved to varying degrees. The nuclei most affected appeared to be the rostral thalamic nuclei (ie. anterodorsal, anteroventral, and anteromedial nuclei). Also affected, however, were portions of the ventral thalamus including the ventroanterior nucleus and the reticular nucleus. Portions of the midline thalamus were also involved. The dorsomedial nucleus sustained the most extensive damage along the midline.

Fiber bundles coursing through the above areas of the thalamus were also disrupted by the damage. Both the stria medullaris and the stria terminalis were sectioned as a result of the widespread damage.

Primary-site kindling

A. Primary-site clinical seizure development. Little difference between the clinical seizure development of forebrain-bisected rats and control rats (Group C) was observed during the early stages of kindling. All rats displayed the progressive development of seizures commencing with ipsilateral eye closure, gradual appearance of muscle twitches around the mouth (C-1), and finally pronounced head nodding (C-2). With the appearance of C-3, however, clinical differences between the controls and forebrain-bisected rats became evident. Control rats at C-3 normally showed a pattern of alternating forelimb clonus whereas rats in all three bisected groups displayed only unilateral forelimb clonus. Clonic activity in the bisected rats remained localized to the forelimb contralateral to the stimulated

site. These differences between the two persisted throughout the subsequent stages 4 and 5.

The development of C-3 in the control group was typically associated with generalized seizure manifestations but these were usually secondary (ie. clonus appeared first in the contralateral forelimb and then became bilateral). This pattern predominated through the clinical development up to approximately the third or fourth C-5. At this point what can only be called primary generalized C-5 seizures developed. The stimulation triggered an immediated full-blown, bilateral convulsive C-5. This pattern subsequently persisted throughout the following C-5s.

In forebrain-bisected rats, Groups CC and AC, the development of secondary generalization was retarded: usually it did not become evident until several C-4 seizures had been evoked. Similarly, the appearance of primary generalized C-5s was slowed but not stopped. Typically, this pattern did not emerge until the sixth or seventh C-5.

Rats in Group TD seemed to present a special case. These animals failed to display evidence of either primary or secondary generalization. The clinical manifestations in these rats remained asymmetrical, and localized to the contralateral extremities throughout the course of primary site kindling. All of the rats displayed this response regardless of the laterality of the stimulated AM with respect to the extracallosal damage. Three of the 4 rats in this group were initially kindled by stimulation of the AM contralateral to the extracallosal damage.

Two of the 3 rats that were kindled from stimulation of the AM contralateral to the extracallosal damage developed interesting seizure patterns. These consisted of two distinct convulsive episodes within a single session.

This pattern emerged during the later C-4s and persisted throughout the following C-5s. Typically the seizure pattern in these rats began as an asymmetrical C-5 and then terminated with a period of immobility. Following this, however, another asymmetrical C-5 seizure appeared. The distinguishing feature of this attack was that the laterality of the seizure was opposite to that of the first C-5. The electrographic correlates of these seizures are shown in Fig. 3.

B. Primary-site electrographic development and propagation. Bisection of the forebrain commissures was found to exert its major effect on the propagation of afterdischarge (AD) from the primary site to certain contralateral structures. Variations in the propagation of AD to these structures (ie. AM, MRF, and MC) was in turn found to depend on the extent of the bisection.

All groups displayed relatively localized AD in the stimulated site during C-1. It was not until the appearance of C-2 that appreciable propagated activity to the contralateral structures was observed. Group C and rats in Groups CC and TD showed ready propagation of AD into the contralateral AM during stages 2 and 3. Group AC, however, in which the rostral corpus callosum and anterior commissure were sectioned, displayed little if any evidence of contralateral AM activity. Regardless of this, rats in this group displayed no deficit in the clinical development of stages 2 and 3 or subsequent stages.

Stages 2 and 3 were characterized by the propagation of AD into the contralateral MC and MRF of all groups except Group TD (rats in this group possessed bilateral AM electrodes only). A significant feature of this propagation was that bisection of the corpus callosum and hippocampal commis-

sure (Group CC) did not inhibit its spread to the contralateral MC. Similarly, rats in Group AC displayed little, if any, observable contralateral AM AD yet propagation into the contralateral MC and MRF was not affected.

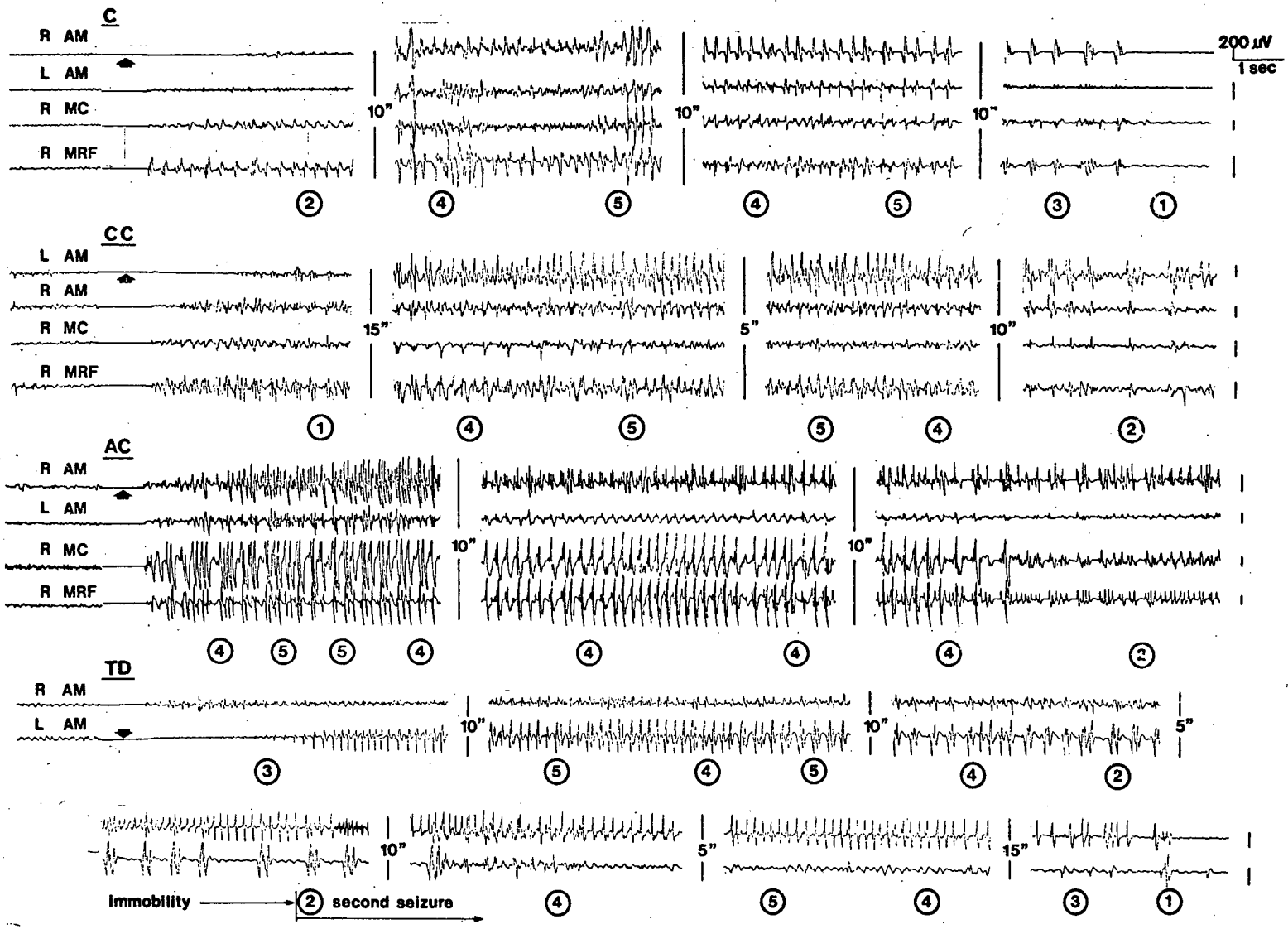
During the early stages of kindling (ie. stages 1, 2, and 3) AD in the contralateral structures was synchronous with that of the stimulated site. AD propagated into these structures was characterized by a moderately high amplitude, 3-6/sec spike and wave discharge. A distinguishing feature of these early stages relates to the appearance of forelimb clonus (C-3) in the bisected and control groups. Although AD readily propagated into the contralateral MRF and MC of all of these groups, the control group displayed bilateral clonus whereas the bisected groups displayed unilateral clonus.

The electrographic correlates of a typical C-5 seizure in each group are shown in Fig. 3. A high amplitude, 6-8/sec polyspike and wave discharge was observed in the contralateral MC of Group C and Group AC with the appearance of C-5 (Fig. 3). Occasionally, a similar pattern was also observed in the contralateral MRF. The appearance of this pattern was characterized by: (1) its independence from that of the stimulated site; (2) its appearance during the stage 4 and stage 5 phase of the seizure; (3) the immediate termination of the pattern with the end of the C-4 or C-5 clinical manifestations. Bisection of the corpus callosum and hippocampal commissure (Group CC) suppressed the appearance of this particular AD pattern in the contralateral MC (Fig. 3). AD in the MC of these rats was instead characterized by a reduced amplitude, 4-6/sec spike and wave pattern with slow background activity. The absence of the polyspike and wave in the contralateral MC of Group CC, however, did not affect the clinical response. Animals in this group eventually displayed a primary generalized C-5 as did those in Groups AC and C, in which the polyspike and wave pattern was evident.

In Groups C and CC little subsequent development in the propagation of AD into the contralateral AM was observed after the appearance of C-5. Eight C-5 seizures were evoked, however, and during this time rats in these two groups displayed a trend towards a complex discharge pattern consisting of irregular, high amplitude, 5-8/sec polyspike and wave activity in both the stimulated and contralateral AM (Fig. 3). Rats in Group AC showed this trend only at the stimulated site. Bisection of the rostral corpus callosum and anterior commissure in this group inhibited the propagation of AD to the contralateral AM (Fig. 3) even after eight C-5s had been evoked. This lack of contralateral AM activity, however, did not disrupt the eventual appearance of primary generalized C-5 seizures.

Propagation of AD into the contralateral AM of Group TD seemed to present a special case. At the stimulated site, the appearance of C-5 was associated with the development of a high amplitude, 5-8/sec polyspike and wave discharge not unlike that observed in the other groups. However, only minimal propagation of AD to the contralateral AM was observed. Following the termination of AD at the stimulated site there was a period of immobility. This in turn was followed by a recruiting-like burst of 7-10/sec, high amplitude spike discharges confined to the contralateral AM. The appearance of this activity was related to a second stage-5 clinical response (Fig. 3). A main feature of this clinical response was that during the primary site AD the seizure was localized in the contralateral extremities whereas during AD in the contralateral AM the seizure was localized to the ipsilateral extremities (ipsilateral to the primary site). This phenomenon was observed in two of the 4 rats in this group. In the remaining 2, similar electrographic features were present but a second clinical seizure was not observed.

Fig. 3. Electrographic correlates of a primary-site C-5 seizure displayed by a typical rat from each group. Arrows indicate the site of stimulation; the circled numbers under each record indicate the clinical response being displayed. R=right; L=left. Note that in Group CC, bisection of the corpus callosum and hippocampal commissure severly disrupts AD propagation into the contralateral R MC but not the R AM or R MRF. In Group AC, propagation of AD to the contralateral AM (L AM) is markedly reduced. AD in R MC and R MRF of this group displays a polyspike and wave configuration typical of these structures. Note the correlation between the end of forelimb clonus and the disappearance of this pattern. The record from Group TD shows the AD correlates of the two seizures displayed by rats of this group. Note the increase in contralateral AM (R AM) activity that is associated with the appearance of the second seizure.


C
R AM
L AM
R MC
R MRF
200 µV
1 sec
10"
10"
10"
CC
L AM
R AM
R MC
R MRF
15"
5"
10"
AC
R AM
L AM
R MC
R MRF
10"
10"
TD
R AM
L AM
10"
10"
5"
10"
5"
15"
immobility
2 second seizure

No evidence of this phenomenon was observed in rats from any of the other bisected groups.

C. Rate of primary-site kindling. Data concerning the rate of primary site kindling in each group are summarized in Table I. One-way analysis of variance indicated that bisection of the forebrain commissures produced an overall significant effect on the rate of primary site kindling ($F$=8.22; $df$=3,21; $p$<.01). Subsequent analysis using the Scheffé method for multiple comparisons indicated that Group AC, in which the rostral corpus callosum and anterior commissure were sectioned, kindled significantly faster than the control group ($F$=2.95; $df$=1,21; $p$<.05). No significant difference in the rate of kindling between Group C and Group CC was found. Group TD, in which partial bisection of the corpus callosum was accompanied by extensive damage to extracommissural structures, kindled significantly slower than controls ($F$=3.31; $df$=1,21; $p$<.05). It was also found that Group TD kindled significantly slower than Group CC ($F$=4.44; $df$=1,21; $p$<.05) and Group AC ($F$=4.21; $df$=1,21; $p$<.05). In Group TD there was no evidence to suggest that the retardation in kindling was related to the stimulation of the AM ipsilateral to the extensive extracommissural damage, and in fact the opposite appeared true. Three of the 4 rats in this group were kindled by stimulating the AM contralateral to the damage.

D. Primary-site seizure duration. Once kindled, each rat was allowed to have an additional eight C-5 seizures. The mean seizure duration of each group is shown in Fig. 4A. It is evident from this figure that bisection of the forebrain commissures had little, if any, effect on the seizure duration. There was a tendency for Group TD to display slightly longer seizures but this was in part due to the inclusion of the second

TABLE I

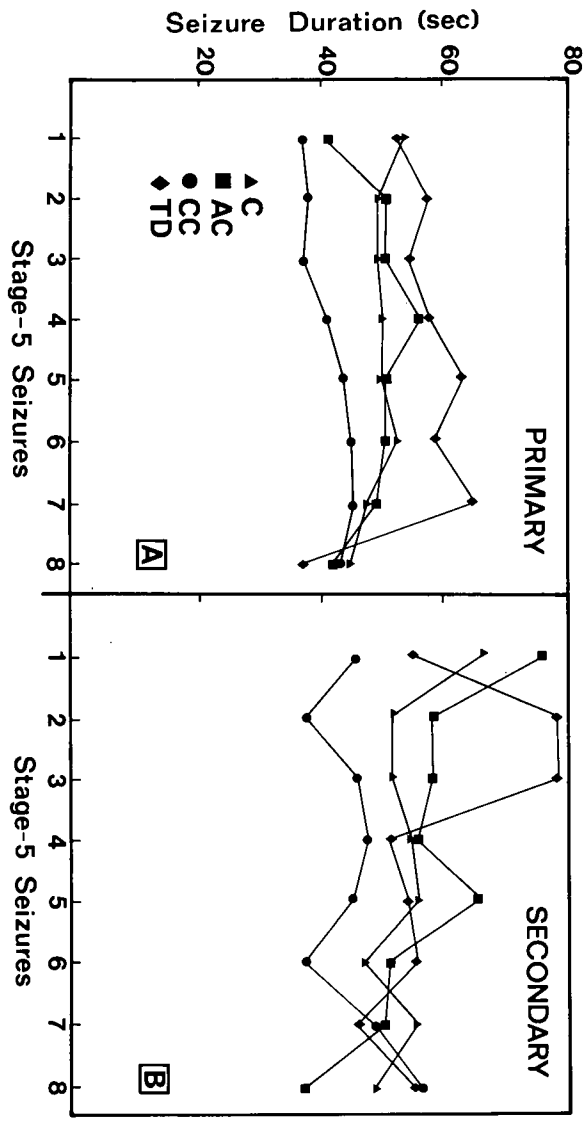
MEAN NUMBER OF SESSIONS TO KINDLE AT EACH SITE

| Group | Sessions to kindle primary site | Sessions to kindle secondary site |
|---|---|---|
| C (control) | 13.3 (10-18) n=7 | 7.6 (4-15) n=5 |
| CC (rostral corpus callosum, hippocampal commissure, and anterior commissure) | 10.0 (4-17) n=10 | 4.5 (1-9) n=10 |
| AC (anterior commissure) | 8.5 * (5-12) n=4 | 8.0 (4-11) n=4 |
| TD (thalamic damage) | 22.0 * (16-27) n=4 | 12.7 † (1-27) n=3 |

* Significantly different from Group C, $p<0.05$
† Significantly different from primary site, $p<0.05$

Fig. 4A. Primary-site kindled seizure duration recorded over eight successive stage-5 seizures.

Fig. 4B. Secondary-site kindled seizure duration recorded over eight successive stage-5 seizures. No significant differences were found between primary-site and secondary-site seizure durations.


Seizure Duration (sec)
20
40
60
80
C
AC
CC
TD
PRIMARY
SECONDARY
A
B
1
2
3
4
5
6
7
8
Stage-5 Seizures
Stage-5 Seizures

seizure duration in the total seizure duration. This effect, however, was not statistically significant. Group CC tended to display the shortest seizures but this also was not significant. No significant effects were noted with respect to either Group AC or Group C.

E. AD duration during primary-site kindled seizures. Fig. 5A shows the AD durations recorded from the stimulated and contralateral AM over the eight C-5 seizures. The duration of the AD at other sites is not shown for reasons of clarity but will be discussed in the text where appropriate.

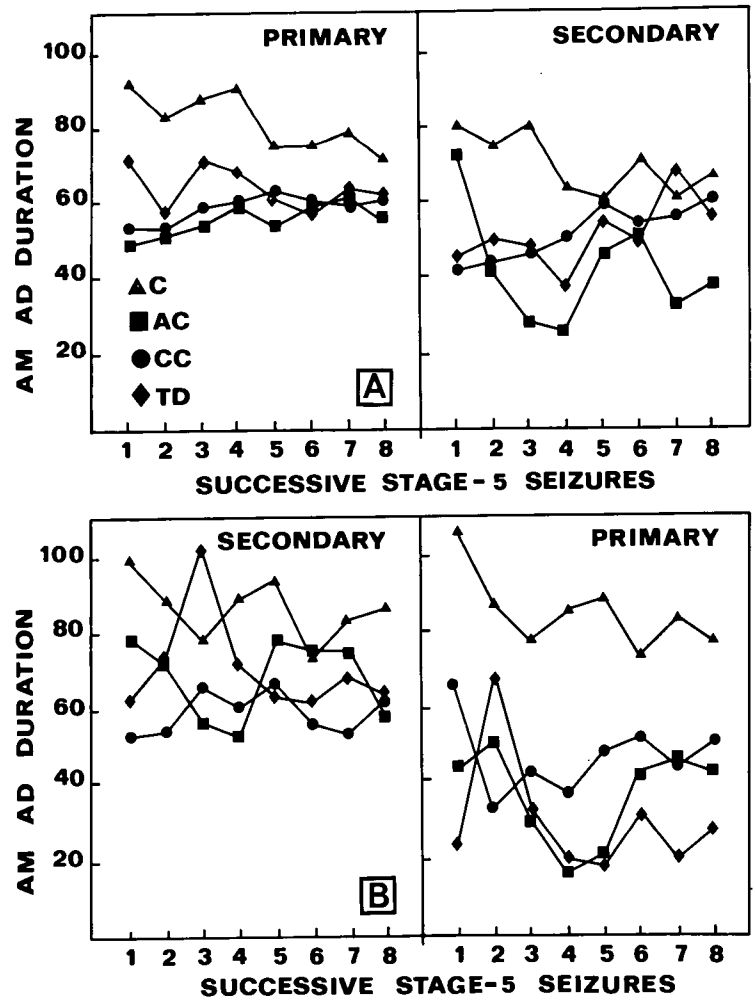
Over the eight sessions there was a marked tendency for the AD of the stimulated AM in the control group to be longer than that of the forebrain-bisected groups. The difference, however, was not consistently significant.

Bisection of the forebrain commissures exerted its major effect on the duration of the AD propagated into the contralateral AM. Overall, bisection of the commissures was associated with a decrease in AD in the contralateral AM. This effect was most obvious in Group AC, in which the rostral corpus callosum and anterior commissure were bisected. In this group the duration of AD in the contralateral AM was consistently shorter than that of the stimulated site. It was also found that the AD duration of the contralateral AM in Group AC was significantly shorter than the AD in the contralateral AM in the control group for the first six sessions ($ps<.05$). No significant differences were found between the duration of AD in the stimulated and contralateral AM in any of these groups and Group AC or C.

Bisection of the forebrain commissures did not affect the duration of AD recorded from the contralateral MRF or MC. This was in contrast to the marked attenuation of AD in contralateral AM that was observed in Group AC. In general, the duration of the AD recorded from either the contralateral

Fig. 5A. Mean AD duration (in secs) recorded from the stimulated (primary) and contralateral (secondary) AM during eight successive primary-site stage-5 seizures. Note the slightly lower duration of the secondary-site AD.

Fig. 5B. Mean AD duration (in secs) recorded from the stimulated (secondary) and contralateral (primary) AM during eight successive secondary-site stage-5 seizures. Note the marked reduction in primary-site AD displayed by rats in Groups AC and TD.


PRIMARY
SECONDARY
AM AD DURATION
100
80
60
40
20
▲C
■AC
●CC
♦TD
A
1 2 3 4 5 6 7 8
SUCCESSIVE STAGE-5 SEIZURES
SECONDARY
PRIMARY
AM AD DURATION
B
SUCCESSIVE STAGE-5 SEIZURES

MRF or MC was only marginally different from that recorded from the stimulated site. In most cases, the duration of AD in these structures was identical to that of the stimulated site.

Secondary-site kindling

Stimulation was switched to the contralateral AM (secondary site) after eight C-5 seizures had been evoked from the primary site. Of the rats that survived and did not dislodge their electrode assemblies, only one failed to kindle with secondary AM stimulation.

A. Secondary-site clinical seizure development. With a few minor exceptions, the clinical development of seizures observed during secondary-site kindling was essentially the same as that observed during primary site kindling. No obvious differences were observed between the control and bisected rats during stages 1 and 2 of secondary-site kindling. With the appearance of C-3, however, evidence of secondary generalization became noticeable in the control group but not the bisected groups. The clonic component of the seizure became bilateral in the control group, spreading from the contralateral forelimb to the ipsilateral forelimb. In the bisected groups, however, the clonic component remained unilateral and localized to the contralateral forelimb. Like primary-site kindling, this pattern persisted up to the development of primary generalized C-5 seizures. Primary generalization in the control group was found to require fewer stimulations to develop during secondary-site kindling than during primary-site kindling. Typically, it occurred after one or two C-5s during secondary-site kindling but not until after three to five C-5s during primary-site kindling. In contrast, the bisected groups required approximately the same number of C-5s (ie. 6-7) during secondary-site kindling as primary-site kindling for the development of primary generalization.

Like primary-site kindling, rats in Group TD also did not develop primary generalized C-5 seizures during secondary-site kindling. In this group, the C-5 was typically of a secondary generalized pattern. In addition, 2 of the 4 rats displaying a second convulsive episode during primary-site kindling failed to do so during secondary-site kindling.

The most obvious difference between primary and secondary-site kindling was related to the progressive clinical development of the seizure. Seizure development during primary-site kindling was characterized by a gradual elaboration and spread of the clinical manifestations. Secondary-site seizures, however, typically developed extremely rapidly and subsequently many of the early clinical events were skipped. For example, it was not unusual to observe rats displaying C-2 on one day and then progress to a C-5 on the following day.

B. Secondary-site electrographic development and propagation. The electrographic correlates of secondary site kindling are shown in Fig. 6. The gradual development and propagation of AD observed during primary-site kindling was absent during secondary-site kindling. Instead, the AD development and spread observed during secondary-site kindling was consistently more elaborate than that observed during the corresponding stages of primary-site kindling. This observation applied to all groups.

AD associated with the appearance of C-1 and C-2 was characterized by a high amplitude, 4-6/sec, spike and wave or polyspike and wave pattern that rapidly propagated from the stimulated AM to the ipsilateral MRF and MC in Groups AC, CC, and C. Propagation of AD into these structures during primary-site kindling (they were then contralateral to the stimulated site) was typically not observed until the later stages of C-2 or the early stages

of C-3. Also in contrast to primary-site propagation, AD spread into the primary site during secondary-site kindling was minimal until the appearance of C-3. This at least applied to the controls and Group CC. Rats in Groups AC and TD failed to show AD in the primary site even with the appearance of C-3. AD activity observed in the primary site of Group CC and C showed a similar discharge pattern to that observed in the secondary site. No disruption in the clinical development of the seizure was observed in any of the groups up to stage 3.

Little subsequent AD development occurred at the secondary site following the appearance of C-4 and C-5. The pattern tended to evolve into a high amplitude, 5-8/sec, polyspike and wave discharge that, towards the beginning of the seizure, displayed considerable irregular activity. A similar pattern gradually emerged from the primary site of the controls although it took several C-5 seizures to fully develop.

Fig. 6 shows the electrographic correlates of a typical C-5 seizure in each group. Bisection of the forebrain commissures exerted a suppressive effect on the propagation of AD into the primary site that was most evident during the early stages of C-5. Group CC appeared least affected, and AD in the primary site consisted of a 5-8/sec, spike and wave or occasionally polyspike and wave pattern synchronous with the secondary site (Fig. 6). Groups AC and TD were most affected, showing very little primary site activity. Most rats in these groups displayed suppressed AD duration characterized by low amplitude spike and wave activity (Fig. 6). In the remaining rats, propagation to the contralateral AM was prevented. These rats displayed primary site activity consisting of slow to fast wave forms and independent spike discharges. Interestingly, towards the sixth to eighth

C-5 some recovery in AD in the primary site was observed in Groups CC and TD. These rats tended to show the emergence of an AD pattern that was similar to the secondary site although it usually lacked the amplitude.

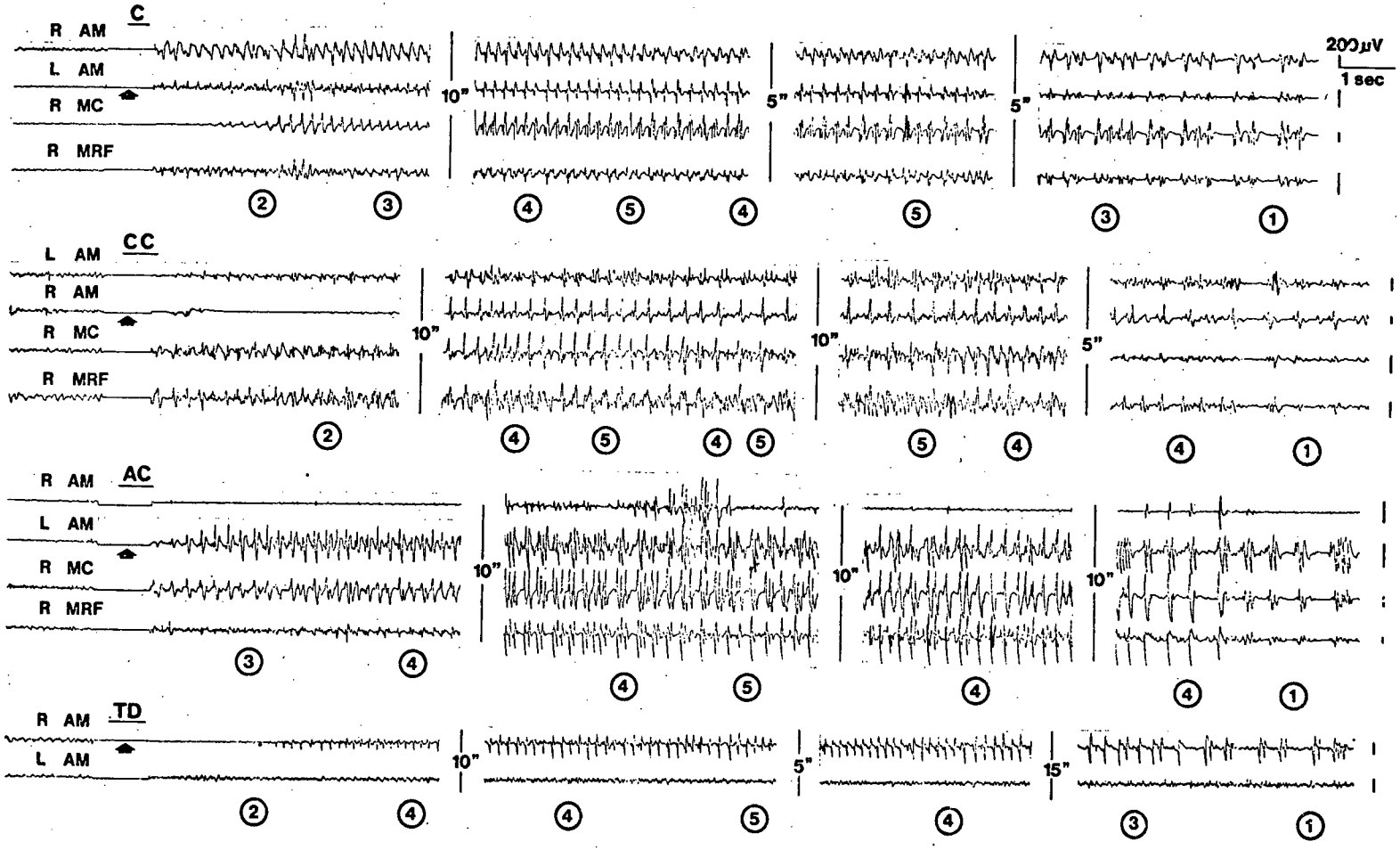
The development of stages 4 and 5 in all groups (except Group TD) was accompanied by a marked increase in the ipsilateral MRF and MC discharge. A high amplitude, independent, 8-14/sec polyspike discharge was observed in the MRF immediately after stimulation. This was accompanied slightly later by a buildup of polyspike and wave activity over the MC. The AD in the MC was typically independent from the stimulated site at the beginning of the seizure but tended towards synchrony as the seizure terminated (Fig. 6). This pattern was similar to that observed during primary-site kindled seizures, with one exception: there was no evidence of the polyspike and wave activity in the contralateral MC in Group CC.

C. Rate of secondary-site kindling. There was no significant difference between the rate at which control and forebrain-bisected rats kindled (Table I). The only significant difference in the rate of secondary-site kindling was observed between Group CC and Group TD. Rats in Group CC were found to kindle significantly faster than those in Group TD ($F$=3.01; $df$=1,39; $p$<.05).

All groups showed a positive transfer effect in that they uniformly required fewer stimulations to kindle the secondary site than the primary site. Group TD, however, was the only group that kindled significantly faster at the secondary site ($F$=2.93; $df$=1,39; $p$<.05).

D. Secondary-site seizure duration. Fig. 4B shows the duration of each C-5 seizure evoked from secondary site stimulation. Bisection of the forebrain commissures produced little effect on the seizure duration. No

Fig. 6. The electrographic correlate of a secondary-site C-5 seizure displayed by a typical rat from each group. Arrows indicate the site of stimulation; the circled numbers under each record indicate the clinical response being displayed. R=right; L=left. Note that in bisected Group CC, propagation to the R MC is unaffected if the stimulated site is ipsilateral to it. In Group AC, bisection of the rostral callosum, hippocampal commissure, and anterior commissure eliminates propagation of AD to the contralateral AM (R AM) but not the R MC or R MRF. Propagation of AD to the contralateral AM (L AM) of Group TD was also disrupted. Note that rats in this group failed to show two seizures during secondary-site kindled seizures.


C
R AM
L AM
R MC
R MRF
10"
5"
5"
200µV
1 sec
CC
L AM
R AM
R MC
R MRF
10"
10"
5"
AC
R AM
L AM
R MC
R MRF
10"
10"
10"
TD
R AM
L AM
10"
5"
15"

significant differences were observed between any of the groups. Similarly, the duration of secondary-site seizures did not differ significantly from the duration of primary-site seizures.

E. AD duration during secondary-site kindled seizures. The AD durations recorded from the stimulated and contralateral AM during the eight secondary-site C-5s are shown in Figure 5B. Details concerning the AD duration at the MC and MRF have been excluded from the figure for the sake of clarity but will be discussed within the text.

Considerably more variation was observed in the duration of the secondary-site AD during secondary-site seizures than during primary-site seizures. There were no significant differences between the groups, however, with regard to the AD duration of the stimulated site during secondary-site kindling. Bisection of the forebrain commissures produced its greatest effect on the propagation of AD into the primary site. The AD in the primary site in Groups AC and TD consistently tended to be shorter than the secondary-site AD over the entire 8 sessions. A similar effect, but of less magnitude, was also observed in Group CC. In all of these groups, however, there were no consistently significant effects.

The effects of forebrain bisection on AD in the primary site were evident in the bisected groups. In Group AC, AD in the primary site was significantly shorter than that of the controls on all but session 2 of the first six sessions ($ps<.05$). A similar but greater effect was noted in Group TD. The AD duration of the primary site in this group was significantly shorter than that of the controls on all sessions but session 2 ($ps<.05$). The AD duration of the primary site in Group CC did not differ significantly from that of the controls ($ps>.05$) or Groups AC and TD ($ps>.05$) on any of the sessions.

No significant differences in the AD duration of the ipsilateral MRF and MC were produced by bisecting the forebrain commissures. Similarly, there were no apparent differences in the AD duration of these structures between any of the groups (except Group TD). In most cases, the AD duration was identical to that of the stimulated site. Therefore, a significant observation was that bisection of the forebrain commissures in Group AC suppresses AD in the primary site but does not affect AD in MC or MRF.

## Discussion

The results of the present study indicate that interhemispheric connections via the corpus callosum and hippocampal and anterior commissures are not critical to the development of generalized kindled amygdaloid convulsions. These results are in agreement with those of McIntyre (1975) and Wada and Sato (1975) but conflict with the earlier report of Racine *et al.* (1972). Racine and colleagues found that bisection of the forebrain commissures in the rat significantly retarded the rate of amygdaloid kindling. Differences in strain, species, stimulus intensity, and waveform at first seem likely explanations for the conflicting results. However, these possibilities were eliminated by the use of an intact control group. The present study suggests that extracommissural thalamic damage like that observed in Group TD may in part explain the differences between the rates of kindling reported here and the earlier report of Racine *et al.* (1972). Racine *et al.* (1972) failed to provide the results of an adequate histologic analysis of the forebrain bisection although he later acknowledged (personal communication, 1974) that damage to the thalamus was observed in some of their rats. Therefore, since rats in Group TD of this study were

the only ones to kindle slower than the controls, it seems reasonable to suggest that the results of Racine *et al.* (1972) may in part have been due to the unintentional destruction of thalamic areas critical for the development of kindled amygdaloid convulsions.

Although a complete study of thalamic involvement in amygdaloid kindling is still lacking, there is some intriguing preliminary evidence which suggests that localized thalamic lesions are able to exert a disruptive effect on the development of these seizures (McCaughran, Corcoran, and Wada, in preparation). Participation of the thalamus in other forms of epileptiform activity and seizure development is well documented. For example, destruction of thalamic nuclei has been found to attenuate epileptiform discharge activity in cats (e.g. Villablanca, Schlag, and Marcus, 1970; Feeney and Gullotta, 1972), and primates (Kusske, Ojemann, and Ward, 1972). Thalamic lesions have also been reported to block or reduce the frequency of seizures in human epileptics (Mullan, Vailati, Karasick, and Mailis, 1967).

Bisection of the rostral corpus callosum and anterior commissure (Group AC) produced a significant facilitation in the rate of seizure development. Bisection of the corpus callosum and hippocampal commissure (Group CC), however, did not significantly facilitate the rate. In view of these results, it would appear that sectioning of the anterior commissure alone may be sufficient to produce this effect. The results of Wada and Sato (1975) in part confirm this. They reported that bisection of the corpus callosum and anterior commissure in the cat produced the greatest facilitation in kindling, although they also observed a facilitated rate of seizure development after bisection of only the corpus callosum. In contrast to the above reports,

McIntyre (1975) found that bisection of the forebrain commissures in the rat did not facilitate the development of kindled amygdaloid convulsions. He reported no significant differences between the rates at which bisected and control groups kindled. Further testing is obviously required in order to develop an explanation that would sufficiently account for the differences between this report and others. Although no concrete explanation can be offered at this time, the possibility is intriguing that the facilitation in the development of kindled seizures following forebrain bisection actually reflects an inhibitory interhemispheric effect transmitted via these structures in the normal animal. Such a possibility is not unprecedented in view of existing data concerning the increase in convulsive behaviour observed in animals following forebrain bisection (e.g. Kopeloff *et al.*, 1950; Stavraky, 1961; Straw and Mitchell, 1967; Mutani *et al.*, 1972).

The present investigation found that the integrity of the forebrain commissures is not essential to the development of bilateral generalized amygdaloid convulsions. Bisection of the commissures retarded but did not stop seizure generalization. McIntyre (1975) reported similar findings in the rat. In view of these results, interhemispheric pathways via the commissures likely participate in seizure generalization, but other, probably subcortical, structures play a critical role. Many previous studies have suggested that brainstem structures, particularly the reticular formation and diffuse thalamic projection system, are critically involved in the generalization of seizures arising from temporal lobe structures (Kaada, 1951; Feindel and Gloor, 1954; Gloor, 1955a,b). With regard to amygdaloid kindling, Wada and Sato (1975) reported that destruction of the MRF in forebrain-bisected cats suppressed the appearance of generalized amygdaloid convulsions. Similarly, McIntyre (1975) found that total forebrain bisection

(including bisection of the thalamus) prevented the development of generalized amygdaloid convulsions in rats. In the present report, only rats in Group TD failed to develop generalized seizures. Histological analysis of the bisection in this group revealed that large areas of the thalamus had sustained extensive damage. These observations add further support to the hypothesis that structures located either in the brainstem reticular formation or thalamus are necessary for the generalization of kindled amygdaloid seizures. Some early evidence, however, does not support this hypotheses. For example, the results of Erickson (1940) and Kopeloff *et al.* (1950) showed that bisection of the forebrain commissures in animals prevented the generalization of seizures. The results reported here, however, do not provide a strong basis of comparison to these earlier reports since the early studies dealt with the effects of forebrain bisection on epileptiform activity originating in the cortex whereas the present report deals with activity originating in the subcortex.

Many previous studies found that the anterior commissure was the major pathway for the interhemispheric spread of seizure activity originating in temporal lobe structures (e.g. McCulloch and Garol, 1941; Frost *et al.*, 1958; Poblete *et al.*, 1959; Wada and Sato, 1975; McIntyre, 1975). In the present study the anterior commissure was found to play a prominent but not exclusive role in the propagation of AD to the contralateral AM. It was found that not only the group in which the anterior commissure was bisected (Group AC) but also the group in which extensive damage to the thalamus was observed (Group TD) showed disruptive effects on the duration of the AD propagated into the contralateral AM. Because no damage to the anterior commissure was observed in Group TD, it must be assumed that the decreased propagation into

the contralateral AM was the result of damage to areas of the thalamus that are involved in this phenomenon. Some propagation of AD to the contralateral AM also occurs via the corpus callosum and hippocampal commissure. It was found that bisection of these structures (e.g. Group CC) had a mildly disruptive effect on AD propagation to the contralateral AM. McIntyre (1975) reported that the most disruptive effects on propagation of AD to the contralateral AM were observed in rats in which the rostral corpus callosum and anterior commissure were sectioned.

Neither the development of bilateral generalized seizures nor the rate of seizure development was affected by the lack of AD in the contralateral AM of Groups AC and TD. In those rats showing the greatest attenuation of AD in the contralateral AM (Group AC), kindling progressed the most rapidly. These results are in contradiction to the interlimbic hypothesis first proposed by Racine *et al.* (1972) that suggested that kindling results from the progressive strengthening of interlimbic connections. This would necessitate the involvement of the contralateral AM. Clearly in view of the present results and the reports of others (Wada and Sato, 1975; McIntyre, 1975) this hypothesis no longer appears tenable. Instead, amygdaloid kindling must now be viewed as a strengthening of connections between limbic and other subcortical, perhaps brainstem, structure(s).

Bisection of the forebrain commissures did not disrupt the transfer effect, in agreement with the results of McIntyre (1975). Furthermore, the results of the present study suggest that involvement of the contralateral AM during primary-site kindling is not necessary for transfer. For example, transfer occurred in Group AC although rats in this group displayed little AD in the contralateral AM. Like kindling itself, the transfer effect must

also make use of some extracommissural structure. Those areas of the thalamus destroyed in Group TD are unlikely candidates since transfer also occurred in this group.

Previous reports have found that the corpus callosum is critical for the interhemispheric propagation of epileptiform activity arising from stimulated areas of the cortex (e.g. Erickson, 1940; McCulloch and Garol, 1941). The callosum has also been implicated in the maintenance of synchronous discharges associated with secondary epileptogenesis (Morrell, 1960; Isaacson *et al.*, 1971) and the mediation of generalized bisynchronous spike and wave patterns arising from bilateral cortical foci (Marcus and Watson, 1966; Marcus *et al.*, 1968; Mutani *et al.*, 1973). The present study found that the corpus callosum and hippocampal commissure were not essential pathways for the interhemispheric transmission of AD in the MC associated with amygdaloid kindling. In a previous study (Wada, Sato, and McCaughran, 1975) a unique independent polyspike and wave pattern was described that emerged bilaterally from the MC of the rats during the development of kindled amygdaloid convulsions. This pattern, it was observed, was closely associated with the final stage of seizure development (ie. C-5). In the present study a similar pattern was observed bilaterally in the control group but only in the MC ipsilateral to the stimulated site in Group CC. Although it has yet to be determined whether this independent activity is originating in the MC or spreading there from some deeper structure, the results of the present study show at least that (1) it relies on the integrity of the corpus callosum and hippocampal commissure for propagation to the contralateral MC; and (2) its absence in one MC does not disrupt the eventual bilateral generalization of the convulsion. It appears likely

that this independent discharge in the MC is a reflection of activity in some deeper structure possibly associated with the motor system. This in part is supported by the report that removal of the MC in rats does not disrupt the development of kindled amygdaloid convulsions in rats (Corcoran, Urstad, McCaughran, and Wada, 1975).

Propagation of AD into the MRF was not affected by the bisection of the forebrain commissures and no evidence of outstanding electrographic development, like that reported by Wada and Sato (1974, 1975), was observed in this structure. In some rats, independent MRF activity was observed during the later stages of kindling but this did not consistently occur. Rats having electrodes in the MRF were also in the minority of the total sample and therefore made the interpretation of the electrographic development difficult. Obviously, more work will be required to define the role played by the MRF in the development of kindled seizures in the rat.

The results of Experiment 1 indicate that the forebrain commissural pathways in the rat are not essential for the development of kindled amygdaloid seizures and that bisection of these structures is, if anything, capable of facilitating the rate of kindling. This may be interpreted to suggest that the forebrain commissures function as inhibitory pathways between the cerebral hemispheres. Existing evidence was reported that supports such a hypothesis (e.g. Mutani *et al.*, 1972; Wada and Sato, 1975).

The original hypothesis of Racine *et al.* (1972) that kindling resulted from the progressive strengthening of interlimbic connections was found to be untenable since the disruption of the majority of these connections did not affect the seizure development. Bisection of the rostral corpus callosum

and anterior commissure also suppressed the propagation of AD into the contralateral AM but did not retard the rate of primary-site kindling or the positive transfer effect to the secondary site. Experiment 1 showed that destruction of areas in the rostral thalamus retarded the rate of kindling and thus indicated that kindling may instead result from the strengthening of limbic-brainstem connections as suggested by Wada and Sato (1974, 1975) and McIntyre (1975).

Although the number of rats having electrodes in structures other than the amygdalae were small (ie. in the MC and MRF), bisection of the corpus callosum and hippocampal commissure disrupted the propagation of AD between the motor cortices in all cases. The significance of the independent polyspike discharge observed in the MC was not determined but previous evidence suggests that it is not involved in kindling (Corcoran *et al.*, 1975) and, therefore, probably reflects activity occurring in deeper structures. Experiment 1 provided little evidence of MRF involvement in kindling. Although this is contrary to previous reports (Wada and Sato, 1974, 1975), the results of Experiment 1 must be interpreted with caution due to the small number of rats having MRF electrodes.

## EXPERIMENT 2

The present experiment was designed to examine the role of specific forebrain commissures in the clinical and electrographic development of kindled amygdaloid seizures. Although Experiment 1 indicated that bisection of the commissures was capable of facilitating the development of kindled seizures, it did not provide information related to which of the commissures was responsible. This was felt to be due, in part, to the inadequate surgical procedure since some rats (e.g. Group TD) displayed evidence of extensive extracommissural damage. A more refined surgical procedure employing stereotaxic control over the bisection was used in the present study. The results of pilot studies indicated that the new technique provided greater control over the extent of the bisection and minimized the chances of producing extracommissural damage.

Experiment 1 indicated that areas of the rostral thalamus participated in the development of kindled amygdaloid convulsions. Corcoran *et al.* (1975) also showed that the frontal cortex of the rat was involved in this process. In view of these data, additional electrographic data were collected from the frontal cortex (FC) and the anterior nuclei of the thalamus (ATH).

### Method

Subjects. Forty-five hooded rats of the Long-Evans strain weighing between 325-375 g at the time of surgery were used. Rats were housed individually in stainless steel mesh cages and maintained in a constant temperature colony room having a 12 hour light-dark cycle. Food and water were provided *ad libitum* except during testing. Rats were also allowed a

minimum of 10-14 days to adjust to the colony environment before undergoing surgery.

Surgery. Bisection of all forebrain commissures, except the anterior commissure, was performed using a stereotaxic technique.

Rats were anaesthetized with sodium pentobarbital (60.0 mg/kg, intraperitoneally) and placed in the stereotax. The coordinates corresponding to the anterior and posterior extremes of the corpus callosum were marked on the surface of the skull, 1.0 mm lateral to the midline. A 1.0 mm wide strip of bone joining these two points was then removed by drilling a series of trephine holes. The dura mater was exposed, dampened periodically with normal saline, and overlying chips of bone were removed. The saggital sinus was visualized and the dura immediately lateral to it reflected. Fine sewing needles (approximately 0.45 mm in diameter) with the eyes of the needles facing downward were mounted in the electrode carriers. One needle was then positioned over the anterior extreme of the callosum and the other was positioned over the posterior extreme. Surgical silk (6-0) was then passed through the eye of each needle. Care was taken to allow enough slack in the silk running between the two needles since insufficient slack was found to produce unwanted tissue destruction when the needles were lowered into the brain. The needles were lowered to points slightly ventral to the extremes of the callosum and the silk was then pulled taut. In this manner, all tissue lying between the needles was sectioned, including the corpus callosum. Following the bisection, the needles were removed from the brain and the thread was extracted. Excessive bleeding was readily controlled by gently applying pressure with a

cotton swab. The strip of exposed cortex was covered by a thin strip of sterile gelfoam soaked in normal saline. The scalp wound was then closed with 9.0 mm stainless steel wound clips and the rats were allowed a minimum of two weeks to recover before implantation of the electrodes.

Bisection of the anterior commissure, either alone or in association with the corpus callosum and hippocampal commissure, was achieved by electrolytic lesioning. An electrode was used that was constructed from 24 guage stainless steel tubing and insulated with Insulex. The cross-sectional diameter of the electrode was left bare. A small hole was drilled in the skull, 1.0 mm lateral to the midline and 1.6 mm anterior to bregma, and the electrode was lowered 7.0 mm at an angle of 7 degrees to the level of the commissure. The anode was then attached to the electrode and the cathode was clipped to the frame of the stereotaxic instrument. A 2.0 ma DC current, generated by a Grass constant current lesion maker, was passed through the tip of the electrode for a duration of 25.0 sec. The hole in the skull was sealed with bone wax and the scalp wound was closed with wound clips. The rats were also allowed a minimum of two weeks to recover before implantation of the electrodes.

Two groups of control rats were prepared. The first group consisted of rats in which the corpus callosum and hippocampal commissure were left intact but the cortex overlying the callosum was sectioned. This was performed in a manner identical to that described for the forebrain bisection except that the ventral penetration of the needles was only to the level of the dorsal surface of the callosum. Thus, when the surgical silk was drawn taut only the cortex overlying the callosum was sectioned. The second group of controls consisted of rats prepared in a manner similar

to the first group except no brain tissue was sectioned. A longitudinal slit was drilled in the skull, the dura mater exposed but left intact. In both control groups, the skull opening was packed with sterile gelfoam soaked in normal saline and the scalp wound was closed with stainless steel clips. These groups were also allowed two weeks to recover before implantation of electrodes.

Electrode implantation. Implantation of electrodes was done under aseptic conditions. Rats were anaesthetized with sodium pentobarbital (60.0 mg/kg) injected intraperitoneally, and bipolar stimulating and recording electrodes of the same type as those used in Experiment 1 were aimed bilaterally at the basolateral nucleus of the AM (0.4 mm anterior to bregma, 4.3 mm lateral to the midline, 8.5 mm ventral from the surface of the skull, and the inscisor bar set at +5.0) of all rats (N=42). Some rats (N=5) were also prepared with electrodes aimed bilaterally at the anteroventral nucleus of the thalamus (0.4 mm posterior to bregma, 1.6 mm lateral to the midline, 5.5 mm ventral from the surface of the cortex, and the inscisor bar set at +5.0) in addition to the bilateral AM electrodes. Other rats (N=7) also had electrodes aimed bilaterally at the MRF (4.4 mm posterior to bregma, 2.0 mm lateral to the midline, 6.0 mm ventral from the surface of the brain, and the inscisor bar set at +5.0), in addition to their amygdaloid electrodes. The remainder of the rats (N=30) had electrodes of similar construction to those used in Experiment 1 placed over areas of the cortex. In these rats electrodes were placed over Area 10 of the FC (3.5 mm and 2.0 mm anterior to bregma and 1.5 mm lateral to the midline) and Areas 4 and 6 ([MC]; 1.5 mm anterior to bregma, 1.0 mm posterior to bregma, and 1.5 mm lateral to the midline). The electrode assembly was then anchored to the skull using a

method identical to that used in Experiment 1.

Rats were allowed a minimum of 10 days to recover from the effects of electrode implantation before being stimulated. During this period they were handled and checked occassionally for infections or neurological impairment. Rats displaying any neurological deficit (e.g. abnormal motor movements were dropped from the study. Those with infections were treated with penicillin (Derafort).

Testing procedures. The testing procedures were the same as those used in Experiment 1. The rats were placed in a shielded wire cage and 2.0 min of baseline EEG activity was recorded. Following this, a 1.0 sec, 160 μa, constant current Hz sine wave stimulus was administered to either the right or left AM of all rats. Rats were stimulated once daily between the hours of 1000 and 1300.

Amygdaloid kindling. Kindled seizure development was classified according to the method of Racine (1972a) outlined in Experiment 1. Rats were considered kindled upon reaching the C-5 stage of seizure development. Eight C-5 seizures were evoked from the primary site and then stimulation was switched to the secondary site in order to study the transfer effect. Eight secondary-site C-5 seizures were evoked before again stimulating the primary site. The primary site was restimulated in order to study the interference phenomenon (McIntyre and Goddard, 1973). Interference refers to the number of stimulations required to evoke a C-5 seizure at the primary site after kindling the secondary site. Rats were allowed to have an additional five C-5 seizures before termination of the study.

Afterdischarge and seizure duration. Criteria identical to those used in Experiment 1 were used in the present study for the purposes of recording

the afterdischarge and seizure duration of the various stages of seizure development.

Histology. Rats were killed with an overdose of sodium pentobarbital, perfused through the heart with 0.9% saline followed by 10% formalin. The brain was removed and frozen coronal sections 40 μm in thickness were taken. Every fifth section (0.2 mm) was kept and stained with cresyl violet. The location of the electrodes and the extent of the forebrain bisection were plotted on sections taken from the atlas of Pelligrino and Cushman (1967). Cortical electrode locations were identified at the time the brain was removed. Tracings of representative histology were prepared.

Statistical analysis. Statistical analysis of the data was done using parametric analysis of variance techniques (ie. one-way and two-way analysis of variance). *Post hoc* comparisons were accomplished using the Scheffé method. Significant levels of $p$ were all two-tailed.

## Results

Forty-two of the 45 rats used in this study survived the forebrain bisection and implantation of electrodes. None of the surviving rats displayed overt evidence of neurological dysfunctioning and it was not possible to distinguish between the bisected and controls rats in terms of general motor behaviour.

Forebrain bisection failed to retard the rate of amygdaloid-kindled seizure development. As in Experiment 1, it was found that bisection of specific commissures actually facilitated kindling. Forebrain-bisected rats, however, did not readily develop primary generalized seizures.

In particular cases, forebrain bisection was able to disrupt the contralateral propagation of AD. The magnitude of the effect was subsequently related to the extent of the bisection.

The transfer effect was not disrupted by forebrain bisection; however, the interference phenomenon was. In forebrain-bisected rats, the interference phenomenon was markedly reduced.

Histology. The tips of all electrodes were found to be in or immediately adjacent to the intended structures. Electrode locations are shown in Fig. 1. AM electrodes were localized to the regions in or surrounding the basolateral and basomedial nuclei. MRF electrodes were concentrated in an area, at the level of the superior colliculus, and approximately 2.0 mm lateral to the nucleus of the oculomotor nerve. Electrodes in the ATH were found slightly lateral to the stria medullaris and in the vicinity of the anterodorsal and anteroventral nuclei. The identification of cortical placements (FC and MC) was done visually at the time the brain was removed from the skull. It appeared that all cortical electrodes were situated over the intended cortical areas (ie. Areas 4, 6, and 10).

Examination of the forebrain bisections and control operations revealed that 5 histologically distinct groups were represented in the sample: Group TSB, bisection of the corpus callosum, hippocampal, and anterior commissures (N=8); Group CC, bisection of the corpus callosum and hippocampal commissure (N=7); Group AC, bisection of the anterior commissure (N=8); Group SBC, sectioning of the cortex to the level of the corpus callosum (N=8); Group C, no cortical damage (N=11).

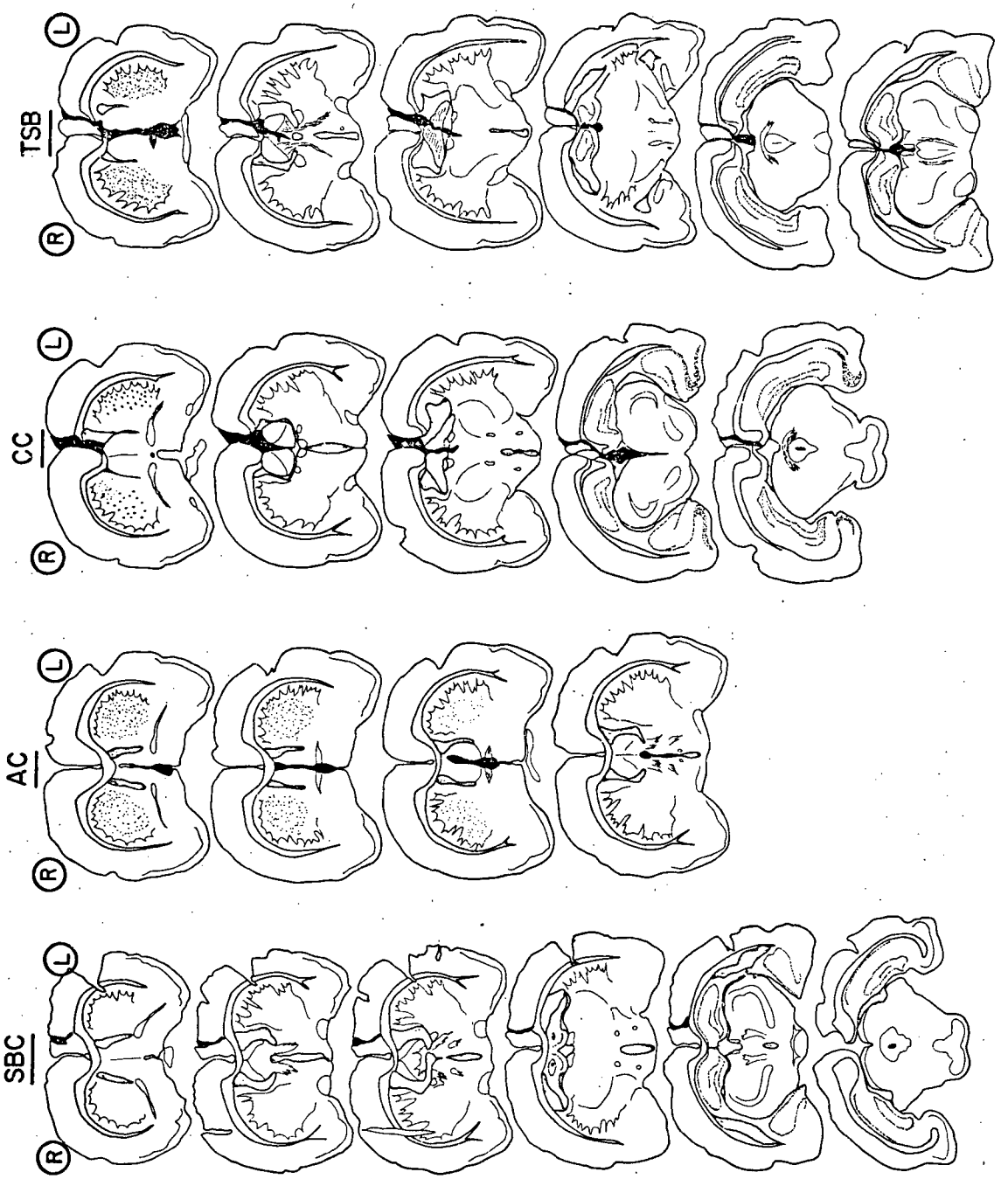
Tracing of histology from a representative rat of each group is presented in Fig. 7. Extracommissural damage in all sectioned groups was min-

imal compared to that in Experiment 1. Group TSB displayed evidence of extracommissural damage localized to the medial aspects of the cerebrum: Areas 24, 25, and 26 of the cingulum. These areas typically sustained some damage due to the passage of the surgical silk. However, signs of gross cell loss were absent except for small areas along the border of the section. Subcortical damage was minimized by the use of the stereotaxic procedure. No ventricular dilation was observed, nor was penetration of the midline thalamus or destruction of the medial aspects of the hippocampus noted. Some cell loss involving anterodorsal portions of the lateral septal nucleus was found. Damage to structures in the vicinity of the electrolytic lesion of the anterior commissure was minimal and typically involving the ventral portions of the medial septal nuclei and the dorsomedial area of the proprius nucleus of the anterior commissure. There was no evidence of the lesion invading the rostral areas of the hypothalamus.

Group CC displayed signs of extracallosal damage similar to those described for Group TSB. Damage to the cortex overlying the callosum was confined to the medial portions of Areas 24, 25, and 26; cell loss was localized to the areas immediately adjacent to the section. Subcortical penetration involved neither the hippocampus nor the midline areas of the thalamus. However, in the rostral area of the forebrain there was a slight penetration of the lateral septal nuclei. Damage to this structure was similar to that described for Group TSB.

Group AC, in which the anterior commissure was bisected, sustained extracommissural damage restricted to a small area surrounding the medial portion of this structure. This included the dorsal portion of the proprius nucleus of the anterior commissure, and the ventromedial areas of the medial

Fig. 7. Extent of the forebrain bisection in a representative rat from each group. Lightly shaded areas represent ventricular spaces. Note that in Group SBC (operated controls) the section extends to the dorsal surface of the corpus callosum only.


TSB
L
R
CC
L
R
AC
L
R
SBC
L
R

septal nuclei. In two cases, the lesion extended caudally to involve the rostral fornix. None of the rats displayed evidence of damage to the anterior hypothalamus.

In Group SBC, damage to the cortex extended the length of the corups callosum, penetrating to the surface of the structure. Damage was confined to the medial boundaries of Areas 24, 25, and 26. In many of the rats it appeared that the silk had been deflected by the surface of the callosum since these cortical areas were 'under-cut' by the section.

Group C showed no signs of cortical damage. The dura had been visualized but not cut in this group.

Primary-site kindling

A. Primary-site clinical seizure development. The appearance of ictal activity associated with C-1 and C-2 was the same for all groups: mouth movements and head nodding. The effects of forebrain bisection did not become apparent until rats began to display C-3. In the control rats, Groups SBC and C, clonus began in the contralateral forelimb, spread to the ipsilateral forelimb, and thus displayed evidence of secondary generalization. Bisection of either the corpus callosum and hippocampal and anterior commissures (Group TSB) or of the corpus callosum and hippocampal commissure (Group CC) prevented the development of secondary generalization. In these groups, the clonic component remained localized to the contralateral forelimb. The development of the secondary generalized pattern was subsequently found to depend on the integrity of the callosal and hippocampal commissural pathways since bisection of the anterior commissure alone (Group AC) did not disrupt its appearance.

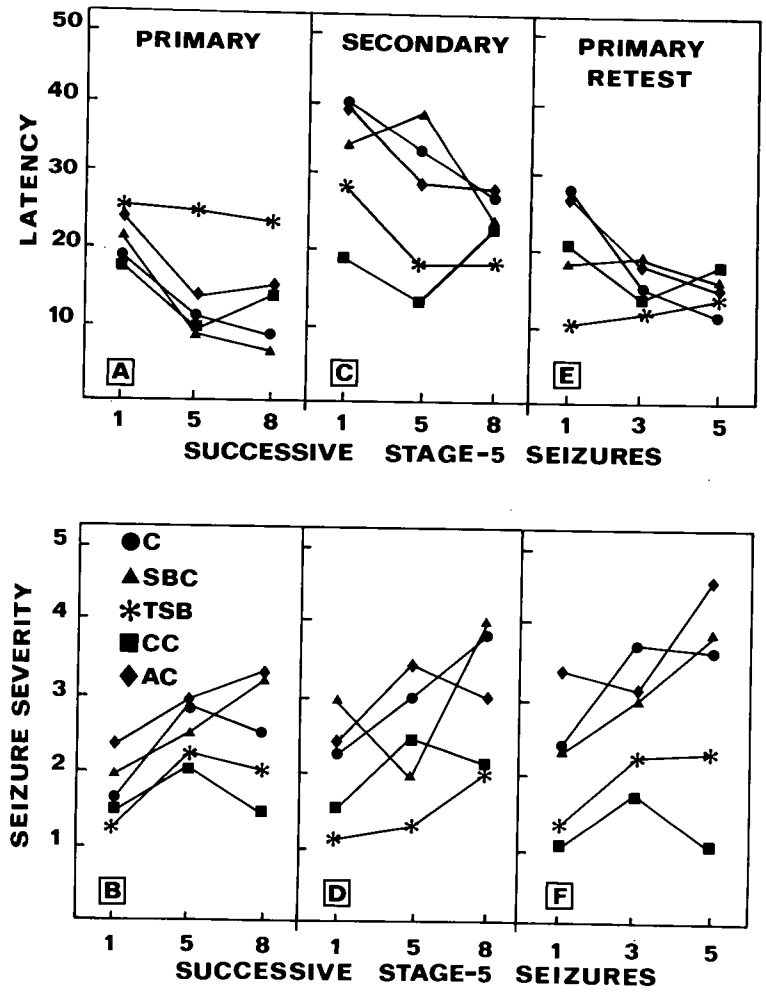
Groups AC, SBC, and C did not differ in clinical development throughout the remaining stages of primary-site kindling. In these groups, seizure development was characterized first by the appearance of secondary-generalized seizures (ie., the spread of ictal activity to the ipsilateral parts of the body). Secondary-generalized seizures were then followed by the appearance of primary-generalized seizures (ie., bilaterally symmetrical seizures from the onset). These bisymmetrical generalized seizures typically occurred after 3 to 4 stage-5 seizures had been evoked.

The asymmetrical seizure development observed in Groups TSB and CC persisted throughout stage 4 and most of stage 5. Rats in these groups often displayed problems in rearing due to the unilateral clonus. A marked deviation in posture was observed towards the side contralateral to the site of stimulation. These rats did, however, begin to show signs of secondary generalized seizures after 3 to 4 C-5s had been evoked; in contrast to the controls and Group AC, however, bisymmetrical primary generalized seizures were not observed until 5 to 7 stage-5 seizures had occurred.

There was a latency from the termination of the stimulation to the appearance of C-5 in all groups of rats. Typically this interval was initially quite long but decreased steadily with subsequent stimulations. By approximately the fifth C-5, the duration of the interval appeared to stabilize. This was observed to varying degrees in all groups except Group TSB (Fig. 8A). In this group, little reduction in the interval occurred throughout the entire C-5 seizures. Furthermore, after reaching stage 5, rats often displayed a number of rearing and falling episodes within a session. The number of such episodes was used as an indication of seizure severity, and is shown in Fig. 8B. It was found that rats in Groups TSB and CC tended to

Fig. 8A,C,E. The mean latency (in secs) from the termination of the stimulation to the appearance of forelimb clonus during successive primary-site, secondary-site, and primary-site rekindled stage-5 seizures.

Fig. 8B,D,F. The mean seizure severity, in terms of the number of rearing and falling episodes, within successive primary-site, secondary-site, and primary-site rekindled stage-5 seizures.


PRIMARY
SECONDARY
PRIMARY RETEST
LATENCY
50
40
30
20
10
A
C
E
1 5 8 1 5 8 1 3 5
SUCCESSIVE STAGE-5 SEIZURES
SEIZURE SEVERITY
5
4
3
2
1
●C
▲SBC
✱TSB
■CC
◆AC
B
D
F
1 5 8 1 5 8 1 3 5
SUCCESSIVE STAGE-5 SEIZURES

display the least severe seizures of any rats. Thus, rats in Group TSB tended to show the greatest seizure latencies and the least severe seizures.

B. Primary-site electrographic development and propagation. Bisection of the forebrain commissures had no observable effect on either the development of primary-site AD or AD propagation to the ipsilateral MRF, ATH, and FC. During C-1 and C-2 all groups displayed a similar high-amplitude, 2-4/sec spike and wave discharge originating in the primary site and readily spreading to these structures. In the control groups, Group SBC and C, similar spread to the contralateral MRF, ATH, FC, and AM was observed. However, all groups characteristically showed little activity in either the ipsilateral or contralateral MC. AD was rarely observed in this structure until several C-2 seizures had been evoked.

The appearance of C-3 or C-4 in Groups SBC and C was associated with a marked increase in the development and propagation of AD. A high-amplitude, 3-6/sec polyspike and wave discharge began to emerge from the primary site and spread to other cortical and subcortical structures. AD in the subcortical structures was typically a lower amplitude but synchronous spike and wave pattern appearing bilaterally. A polyspike and wave configuration was observed only in the ipsilateral and contralateral FC and MC.

The electrographic correlates of a stage-5 seizure in control Group SBC are shown in Fig. 9. Little subsequent development occurred at either the primary or other subcortical sites in groups SBC and C after the appearance of C-5. A notable exception to this was observed in several rats. In these animals, an irregular, 5-8/sec polyspike discharge emerged from the primary site and suddenly spread to the contralateral AM. This event typically required several C-5s to develop and seemed to be associated with the

development of primary generalized seizures. AD in other structures, except FC and MC, usually consisted of polyspike and waves synchronized to the primary site. However, in the FC and MC the development of C-5 was associated with a buildup of independent high-amplitude, 7-8/sec polyspike discharges (Fig. 9). This activity was observed either in the ipsilateral or contralateral FC and MC and disappeared with the termination of the C-5.

There were no observable differences between the control groups (ie., Groups TSB, CC, and AC) in terms of the AD development and spread from the primary site to ipsilateral structures throughout the course of primary-site kindling. Electrographic correlates of a typical C-5 seizure in rats from Groups TSB, CC, and AC are shown in Fig. 9.

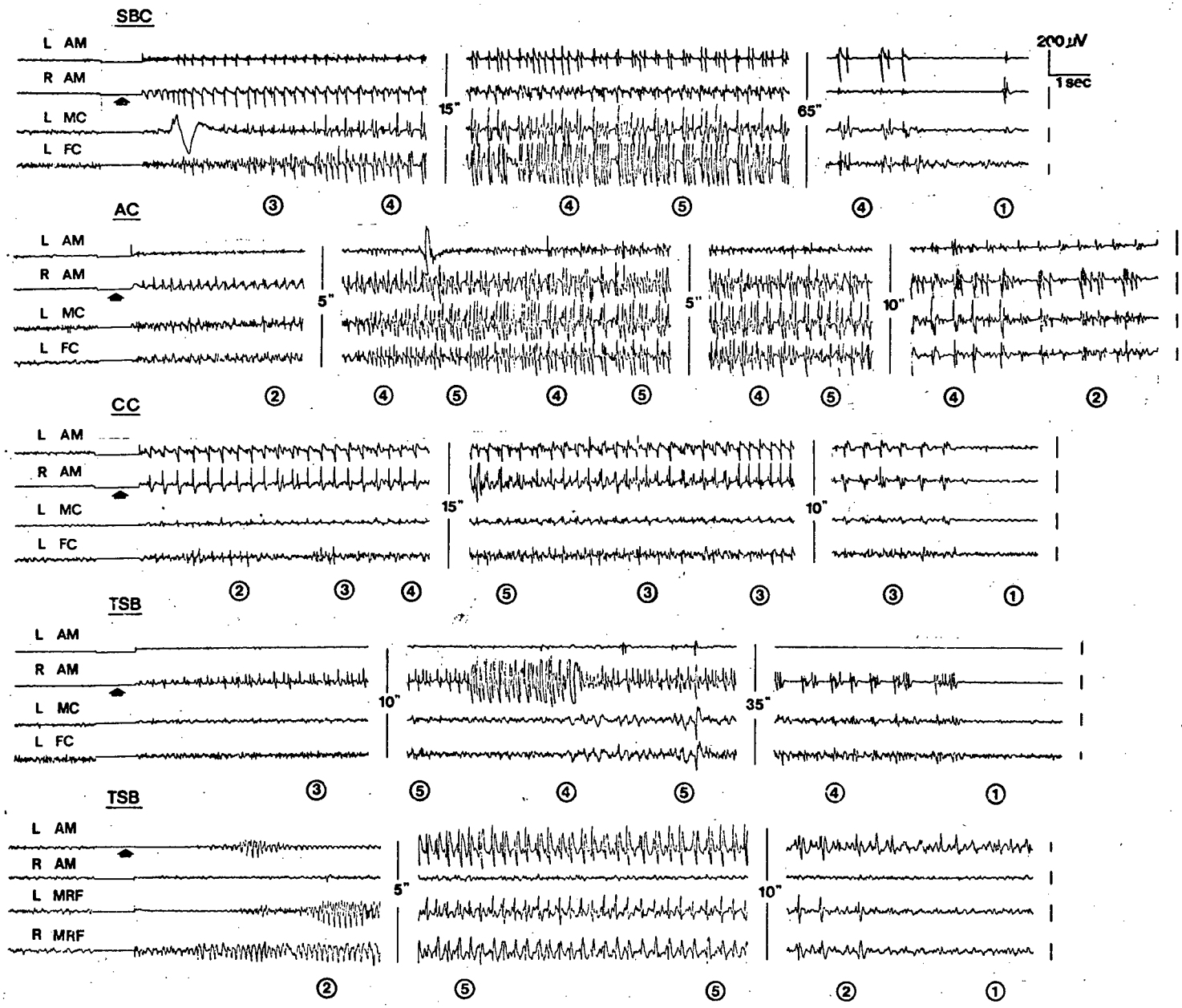
Bisection of the forebrain commissures produced a variety of effects on propagation of AD into contralateral structures during the course of primary-site kindling. Bisection of either the corpus callosum, hippocampal, and anterior commissures (Group TSB) or the anterior commissure (Group AC) disrupted the spread of activity to the secondary site. In Group TSB, AD in the secondary site was absent in all rats during the early stages of kindling (ie. stages 1-3); in Group AC, it was absent in only a few rats during the early stages. Rats in Group AC that displayed AD in the secondary site typically exhibited a pattern that was completely independent of that at the primary site. As kindled seizure development progressed there was a gradual increase in contralateral AM activity in both Group TSB and Group AC. Secondary-site activity, however, never displayed the high-amplitude, polyspike and wave pattern observed in the control groups (Fig. 9). Instead, Groups TSB and AC displayed very low-amplitude, spiky activity that was often independent of the primary site. Occasionally spike and wave activity was observed, but only in Group AC.

Bisection of the corpus callosum and hippocampal commissure (Group CC) did not affect the propagation of AD into the secondary site (Fig. 9). However, propagation of AD into the contralateral FC and MC in both this Group and Group TSB was disrupted. AD activity in the contralateral FC and MC during stages 1-3 in these groups was characterized by low amplitude, sharp waves intermixed with slow activity. No spike and wave discharges, like those observed in the control groups, were noted. In contrast, spike and wave activity not unlike that observed in the control groups was observed over the ipsilateral FC and MC in Groups TSB and CC. The 7-8/sec, high amplitude polyspike discharge observed bilaterally over the FC and MC in the control rats never developed in Groups TSB and CC. AD in the contralateral FC and MC in these groups consisted of moderately high amplitude, sharp waves or spike and waves only occasionally independent of the primary site (Fig. 9). The ipsilateral FC and MC, however, displayed the independent polyspike features like those observed in the control groups. The asymmetry of the pattern in Groups TSB and CC did not affect the eventual development of primary generalized convulsions.

Bisection of the forebrain commissures had its major effect on the morphology of the AD propagated into the contralateral AM, FC, and MC. The duration of the AD in these structures was not permanently disrupted; only during the early stages of kindling was a suppression noted.

Bisection of the forebrain commissures did not disrupt the propagation of AD into other subcortical structures. No apparent differences were noted between the control and bisected rats in terms of AD spread into the ATH and MRF.

Fig. 9. Electrographic correlates of a primary-site C-5 seizure displayed by a typical rat from each group. Arrows indicate the site of stimulation; the circled numbers under each record indicate the clinical response being displayed. R=right; L=left. Bisection of the anterior commissure alone (Group AC) had little effect on the propagation of AD in the contralateral AM (L AM). Note that propagation into the contralateral AM (L AM) was most severely affected in Group TSB. Propagation of AD into the contralateral MRF (R MRF) of this group was not affected. Bisection of the corpus callosum and hippocampal commissure (Groups CC and TSB) markedly reduced the propagation of AD into the contralateral FC (L FC) and MC (L MC).


SBC
L AM
R AM
L MC
L FC
200 µV
1 sec
15"
65"
AC
5"
5"
10"
CC
15"
10"
TSB
10"
35"
TSB
L MRF
R MRF
5"
10"

C. Rate of primary-site kindling. The rate of primary-site kindling for each group is shown in Table II. Bisection of the forebrain commissures was found to have a significant effect on the rate of primary-site kindling ($F$=3.52; $df$=4,37; $p$<.05). *Post hoc* analysis indicated that bisection of the corpus callosum and hippocampal and anterior commissures (Group TSB) caused rats to kindle significantly faster than controls in Group SBC ($F$=12.57; $df$=4,37; $p$<.05) but not in Group C ($F$=3.72; $df$=4,37; $p$>.05). However, no significant difference was found between Group SBC and Group C ($F$=3.57; $df$=4,37; $p$>.05). Similarly, the rate of kindling after bisection of the corpus callosum and hippocampal commissure (Group CC) or the anterior commissure (Group AC) did not differ significantly from either Group TSB, Group SBC, or Group C ($ps$>.05).

D. Primary-site seizure duration. Bisection of the corpus callosum and hippocampal and anterior commissures (Group TSB) caused a trend towards consistently longer C-5 seizures (Fig. 10A). Over the first 4 stage-5 seizures, the duration did not significantly differ from that of the other groups. However, from the fifth to the eighth C-5 the rats in Group TSB displayed consistently longer seizures than those rats in Groups SBC and C ($ps$<.05). Although the seizure duration in Group TSB was consistently longer than that of the other bisected groups (ie., Groups CC and AC), no significant differences were found between Groups CC, AC, SBC, and C.

E. AD duration during primary-site kindled seizures. A total of eight C-5 seizures were evoked from each rat. Fig. 11A shows the AD duration of the primary and secondary site associated with these seizures. Data concerning the duration of the AD at other sites (ie. MRF, ATH, FC, and MC) are not shown for reasons of clarity but will be discussed within the text.

TABLE II

MEAN NUMBER OF SESSIONS TO KINDLE AT EACH SITE

| Group | Primary Site | Secondary Site | Primary Site Retest |
|---|---|---|---|
| C (unoperated controls) | 15.8 (9-29) n=11 | 9.1 ** (4-19) n=10 | 2.9 (1-5) n=10 |
| SBC (operated controls) | 20.5 (14-26) n=8 | 7.9 † (4-11) n=8 | 2.9 (2-4) n=8 |
| TSB (complete bisection) | 11.0 * (7-15) n=8 | 7.8 (1-15) n=5 | 1.3 (1-2) n=3 |
| CC (corpus callosum bisection) | 16.0 (8-17) n=7 | 6.6 ** (4-10) n=5 | 2.0 (1-3) n=3 |
| AC (anterior commissure bisection) | 18.4 (6-31) n=8 | 8.4 (5-13) n=8 | 2.8 (1-6) n=6 |

* Significantly different from operated controls (SBC) $p<0.05$
** Significantly different from primary site $p<0.05$
† Significantly different from primary site $p<0.01$

Fig. 10A. Mean primary-site kindled seizure duration (in secs) recorded over eight successive stage-5 seizures.

Fig. 10B. Mean secondary-site kindled seizure duration (in secs) recorded over eight successive stage-5 seizures.

Fig. 10C. Mean primary-site rekindled seizure duration (in secs) recorded over eight successive stage-5 seizures.

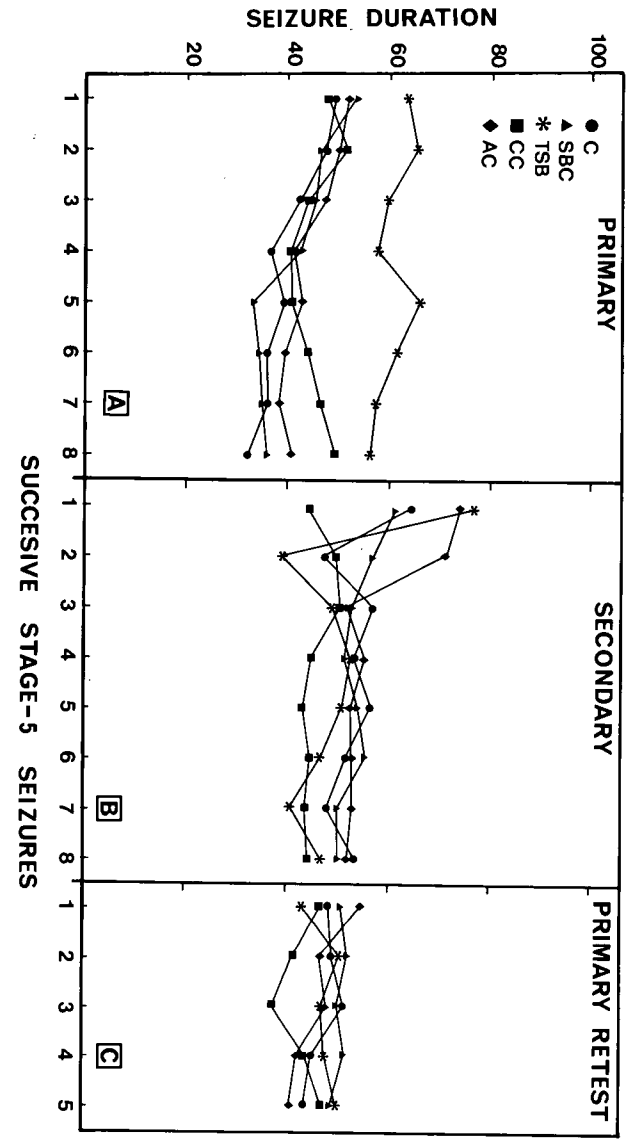
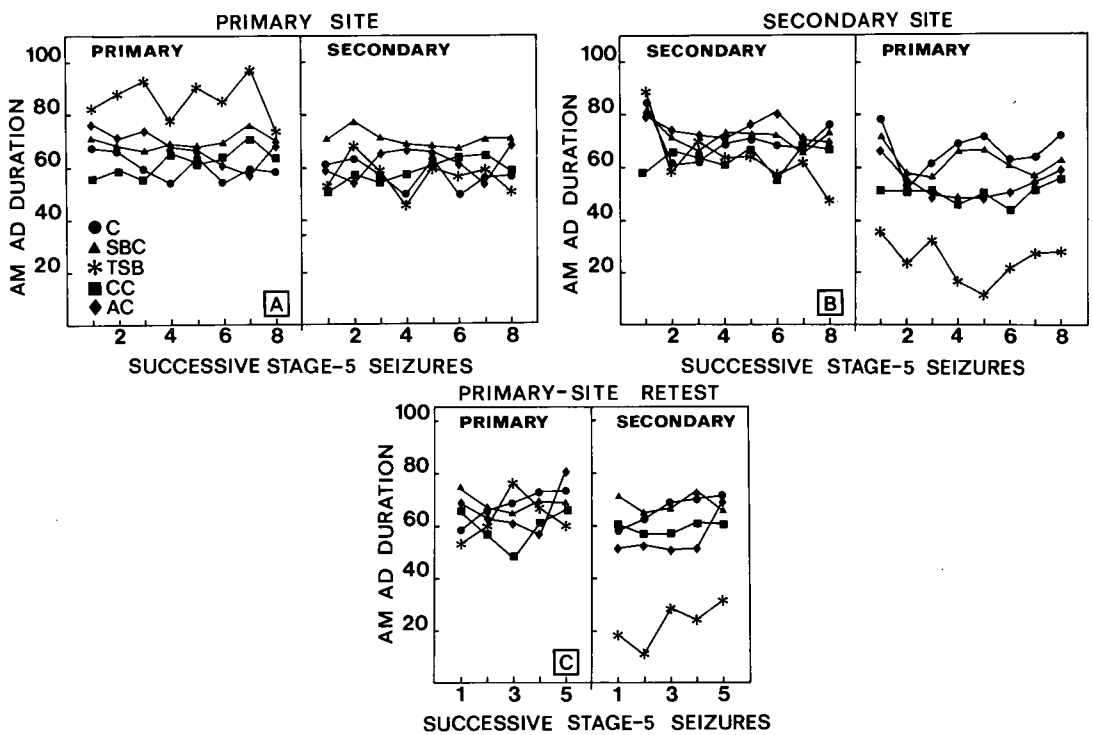

SEIZURE DURATION
20
40
60
80
100
C
SBC
TSB
CC
AC
PRIMARY
SECONDARY
PRIMARY RETEST
A
B
C
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8
1 2 3 4 5
SUCCESIVE STAGE-5 SEIZURES

Fig. 11A. Mean AD duration (in secs) recorded from the stimulated (primary) and contralateral (secondary) AM during eight successive primary-site stage-5 seizures.

Fig. 11B. Mean AD duration (in secs) recorded from the stimulated (secondary) and contralateral (primary) AM during eight successive secondary-site stage-5 seizures. Note the marked reduction in primary-site AD duration in the rats possessing the most extensive bisection (Group TSB).

Fig. 11C. Mean AD duration (in secs) recorded from the stimulated (primary) and contralateral (secondary) AM during eight successive primary-site rekindled stage-5 seizures. Note that in Group TSB the secondary-site AD duration is considerably shortened during primary-site rekindled seizures.


PRIMARY SITE
PRIMARY
SECONDARY
AM AD DURATION
100
80
60
40
20
● C
▲ SBC
✱ TSB
■ CC
◆ AC
A
2 4 6 8
SUCCESSIVE STAGE-5 SEIZURES
SECONDARY SITE
SECONDARY
PRIMARY
B
PRIMARY-SITE RETEST
C
1 3 5

Bisection of the forebrain commissures produced no consistently significant effects on the duration of the AD recorded from the secondary site. Furthermore, forebrain bisection did not appear to affect the AD duration of either the MRF, ATH, FC, or MC. In these structures, whether ipsilateral or contralateral to the site of stimulation, the duration of the AD was typically similar if not identical to that of the primary site. Although in Groups TSB and CC the propagation of AD into the contralateral FC and MC was affected by the bisection, only the morphology of the AD was changed.

Secondary-site kindling

A. Secondary-site clinical seizure development. Secondary-site kindling was in part characterized by an acceleration in the clinical development of seizures in all groups. Unlike the progressive ictal development displayed by the groups during primary-site kindling, stages in seizure development during kindling of the secondary site were often missed. Rats often displayed C-3 seizures on the first secondary-site stimulation or 'skipped' from C-2 to C-5 from one session to the next.

Rats in Groups AC, SBC, and C showed a rapid secondary generalization of the clonic component associated with C-3: clonus initially appeared in the contralateral forelimb but subsequently generalized to also include the ipsilateral forelimb. Groups TSB and CC also developed secondary generalized clinical manifestations but, like primary-site kindling, they were slower to appear. Secondary generalized characteristics typically did not develop until the later stages of C-4 or early C-5. Up to this point, the clonic component of the seizure was localized to the contralateral extremities. It was found, however, that the development of secondary generalized characteristics was, overall, slightly faster during secondary-site kindling than during primary-site kindling.

The development of primary generalized convulsions appeared in Groups AC, SBC, and C after one or two C-5 seizures had been evoked. This was slightly faster than that observed during primary-site kindling (e.g., during primary-site kindling this development usually occurred after 3 to 5 stage-5 seizures). Groups TSB and CC also displayed a slightly accelerated rate of primary generalized seizure development with the appearance of C-5. Typically by the appearance of the first C-5, secondary generalization of clonus to the ipsilateral extremities was observed. Primary generalized seizures usually followed this by one or two sessions. Thus, primary generalized seizures in these groups developed after 3 to 4 C-5 seizures: slightly faster than during primary-site kindling.

Most groups displayed a much longer latency from the termination of the stimulation to the appearance of the C-5 during secondary-site kindled seizures than during primary-site kindled seizures (Fig. 8C). However, the notable exceptions were Groups TSB and CC. In these groups, the latency did not appear to differ greatly between primary and secondary-site C-5s. The other groups (ie. Groups AC, SBC, and C) showed a gradual reduction in latency over the eight C-5s; but even by the eighth C-5, the latency in these groups was approximately twice that observed after a comparable number of primary site C-5s.

Secondary-site C-5 seizure severity in all groups, except Group TSB, was slightly greater than primary-site C-5 severity. In Group TSB, seizure severity was reduced slightly during secondary-site C-5s (Fig. 8D). However, like primary-site C-5s the trend towards increased severity with successive stage-5 seizures was observed in all groups, including Group TSB, during secondary-site C-5s.

B. Secondary-site electrographic development and propagation. The development and spread of AD associated with the early stages of secondary-site kindling (ie., C-1 and C-2) was considerably more advanced than that observed during similar stages of primary-site kindling. All groups displayed a high amplitude, 3-4/sec spike and wave or polyspike and wave discharge appearing first in the secondary site and then rapidly spreading to the ipsilateral MRF, ATH, FC, MC, and the contralateral MRF and ATH. Groups AC, SBC, and C, but not Groups TSB and CC, also exhibited a rapid propagation of this pattern into the contralateral FC and MC. In Groups TSB and CC, contralateral cortical activity usually consisted of low amplitude slow waves. Spread of AD into the primary site of Groups CC, SBC, and C was unaffected but of very low amplitude, much lower than that observed during similar stages of primary-site kindling. Many of the rats in Group CC displayed no AD in contralateral AM. However, the most striking effect on propagation of AD into the primary site was observed in Groups TSB and AC. None of the rats in these groups exhibited AD spread into this structure.

The later stages of secondary-site kindling (ie., C-3, C-4, and C-5) were marked by the gradual emergence, from the secondary site in all groups, of a high amplitude, high frequency, irregular polyspike pattern. This pattern first became evident during C-3 and was fully developed by the appearance of C-5. All groups also showed evidence of the bilateral propagation of this AD pattern into the ATH and MRF. In these structures, however, the pattern was more regular and consisted of polyspike and wave discharges.

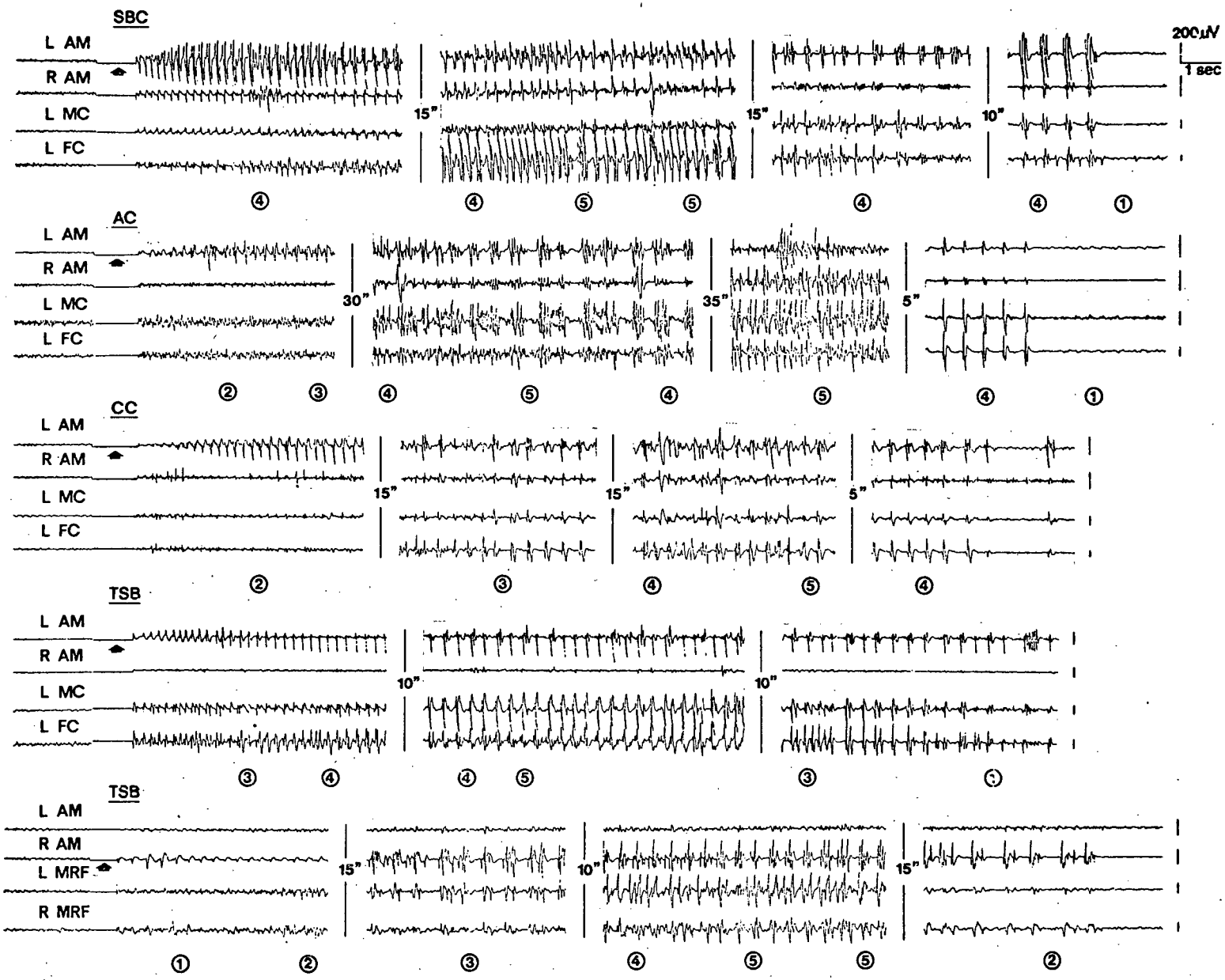
During C-4 and C-5, an independent polyspike pattern, like that observed during primary-site kindling, was observed bilaterally over the FC and MC in Groups AC, SBC, and C (Fig. 12). The discharge appeared with the start of

the C-4 or C-5 and gradually ceased with the termination of the seizure. Groups TSB and CC displayed a similar development but only unilaterally over the FC and MC ipsilateral to the stimulated AM (Fig. 12). The contralateral FC and MC AD failed to exhibit a polyspike pattern and instead displayed mainly lower frequency spike and waves. This asymmetry, however, did not disrupt the appearance of bisymmetrical generalized convulsions.

Propagation of AD into the 'primary' site appeared most affected by secondary-site kindling. Even Groups CC, SBC, and C showed a marked suppression in propagated activity into this structure. Typically, the duration of AD in the contralateral AM in these groups was not as affected as the amplitude of the AD. Unlike the relatively high amplitude spike and wave or polyspike and wave pattern that evolved during stages 3-5 of primary-site kindling, the 'primary' site during similar stages of secondary-site kindling displayed a very low amplitude sharp wave or spiky discharge accompanied by fast background activity. This pattern dominated the primary site until several C-5 seizures had been evoked. Associated with these seizures there was a rapid development in primary site activity and a gradual emergence of the irregular spike and wave or polyspike and wave pattern observed in the primary site (Fig. 12). The development of AD in the contralateral AM in rats of Group AC was similar to that described for Groups CC, SBC, and C. However, the amplitude of AD in the contralateral AM in Group AC failed to develop with the appearance of C-5. Instead, the amplitude remained low and consisted of high frequency spiky activity (Fig. 12).

Rats in Group TSB displayed a lack of AD in the primary site which persisted throughout the course of secondary-site kindling. The duration increased slightly during the appearance of C-5 but it was often only half

Fig. 12. Electrographic correlate of a secondary-site C-5 seizure displayed by a typical rat from each group. Arrows indicate the site of stimulation; the circled numbers under each record indicate the clinical response being displayed. R=right; L=left. Note that in Group AC, bisection of the anterior commissure had little effect on the propagation of AD into the contralateral AM (R AM). In Group TSB, bisection of the corpus callosum, hippocampal commissure, and anterior commissure severely disrupted propagation of AD into the contralateral AM. Propagation into the contralateral MRF (L MRF) in this group was unaffected. Note also in Groups CC and TSB propagation of AD into the MC and FC ipsilateral to the stimulated AM is unaffected.


SBC
L AM
R AM
L MC
L FC
200μV
1 sec
15"
15"
10"
④ ④ ⑤ ⑤ ④ ④ ①
AC
L AM
R AM
L MC
L FC
30"
35"
5"
② ③ ④ ⑤ ④ ⑤ ④ ①
CC
L AM
R AM
L MC
L FC
15"
15"
5"
② ③ ④ ⑤ ④
TSB
L AM
R AM
L MC
L FC
10"
10"
③ ④ ④ ⑤ ③ ①
TSB
L AM
R AM
L MRF
R MRF
15"
10"
15"
① ② ③ ④ ⑤ ⑤ ②

of that recorded from the secondary site. Rats in this group also failed to develop any high amplitude AD in the primary site (Fig. 12). AD activity recorded from this structure typically consisted of independent spiky activity or slow waves.

C. Rate of secondary-site kindling. No significant difference in the rate of secondary-site kindling was observed between any of the groups ($F$=.36; $df$=4,31; $p$>.05). However, all groups required fewer stimulations to kindle seizures during secondary-site kindling than during primary-site kindling and thus showed a positive transfer effect (Table II). In all groups, except Group TSB, the rate of secondary-site kindling was significantly faster than primary site: Group TSB - $F$=1.19; $df$=4,72; $p$>.05; Group CC - $F$=3.38; $df$=4,72; $p$<.05; Group AC - $F$=4.64; $df$=4,72; $p$<.01; Group SBC - $F$=5.32; $df$=4,72; $p$<.01; Group C - $F$=3.24; $df$=4,72; $p$<.05. Group TSB presumably did not display a significant transfer effect because the rate of primary-site kindling was also facilitated.

D. Secondary-site seizure duration. Fig. 10B shows the duration of the eight successive stage-5 seizures evoked by secondary-site kindling. Little variability in seizure duration between the groups was observed and no significant differences were found. Although secondary-site seizures tended to be longer than primary-site seizures, no significant differences were found.

E. AD duration during secondary-site kindled seizures. The AD duration recorded from the secondary and primary site during the 8 secondary-site C-5s is shown in Fig. 11B. For reasons of clarity the duration of the AD recorded from the MRF,ATH, FC, and MC is not shown but will be discussed within the text.

Bisection of the forebrain commissures produced variable effects on the duration of the AD recorded from the primary site. The duration of AD propagated into the primary site in all groups, except Group TSB, was not significantly different from that of the secondary site. In Group TSB, the duration of AD in the primary site was significantly shorter than that of the secondary site ($ps<.05$) on all but the third, seventh, and eighth sessions.

The duration of the AD recorded from the primary site of Groups CC, AC, SBC, and C was not significantly different. However, the duration of AD in the primary site of Group TSB was significantly shorter than that of control Group SBC on all sessions ($ps<.05$) and control group C on all sessions ($ps<.05$) but the first, third, and seventh. The duration of the AD recorded from the primary site of Group TSB was not consistently shorter than that of the other bisected groups (ie., Groups CC and AC).

Bisection of the forebrain commissures did not disrupt either the ipsilateral or contralateral propagation of AD into the MRF, ATH, MC, or FC. The AD duration recorded from these sites did not differ greatly from that recorded from the stimulated site. In many cases, the durations were identical. Therefore, the duration of the AD recorded from the primary site in Group TSB was often significantly shorter than that recorded from any of these structures.

Rekindling of the primary site

A. Clinical seizure development. Primary generalized seizures occurred very rapidly in all groups when the primary site was again stimulated. All groups, but particularly Groups TSB and CC, possessed a majority of rats that displayed either C-4 or C-5 seizures on the first stimulation. It was rare to observe rats exhibiting less than a C-3 on the first stimulation.

Signs of secondary generalization were absent in all rats except for a few in Groups TSB and CC. Typically, most rats displayed a primary generalized seizure on the first C-5. Some rats in Groups TSB and CC, however, required one, but rarely more than two, C-5s in order to develop this pattern.

In all groups but Group TSB, the latency from the termination of the stimulation to the appearance of the C-5 was initially quite long but steadily decreased with subsequent C-5s. The latency in Group TSB was initially quite short and changed very little with subsequent C-5s (Fig. 8E). A similar effect was observed during primary-site C-5 seizures. However, during these the latencies in Group TSB were initially longer than the other groups and remained so throughout the subsequent C-5s (Fig. 8A). In general, the latencies recorded during rekindling of the primary site were similar to those recorded during secondary site kindling (Fig. 8C).

Rats in Groups TSB and CC showed less severe seizures than other rats during rekindling of the primary site (Fig. 8F). Furthermore, rats in Groups TSB and CC showed little difference between the severity of primary-site, secondary-site, and primary-site-retest C-5s. In contrast, rats in the other groups showed a trend towards increased severity over these phases of the study (e.g. Figs. 8B, 8D, and 8F).

B. Electrographic development and propagation. The development and spread of AD evoked by restimulation of the primary site was in general similar to that observed during the later stages (ie. C-4 and C-5) of secondary-site kindling. All groups initially developed a high amplitude, 3-4/sec, spike and wave discharge that subsequently evolved into a complex, 4-6/sec, irregular spike and wave or polyspike and wave with the appearance of C-5 seizures.

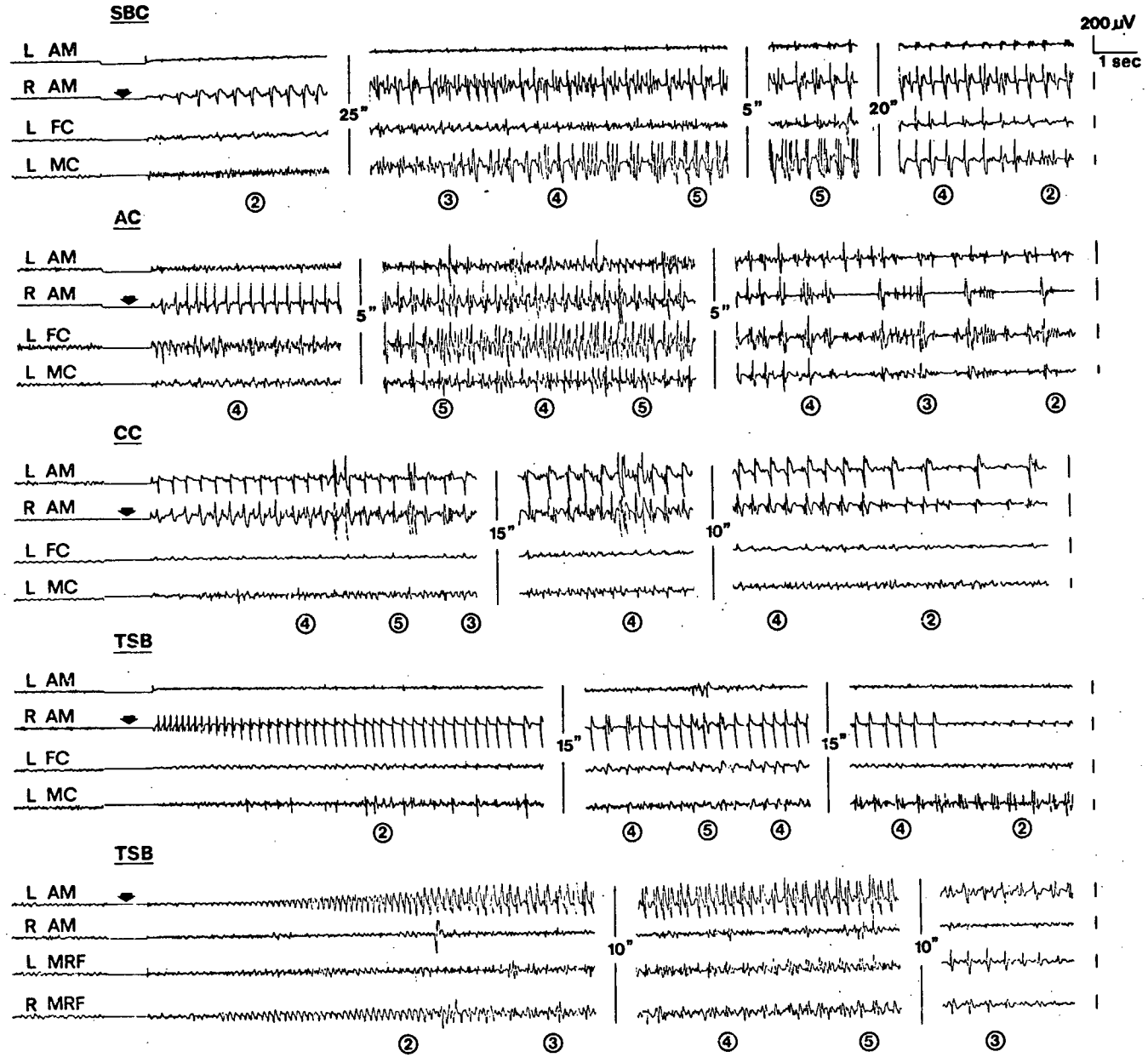
During C-5, an independent, irregular polyspike and wave discharge was observed bilaterally over the FC and MC of Groups AC, SBC, and C (Fig. 13). In Groups TSB and CC a similar pattern was observed but was restricted to the cortical areas ipsilateral to the stimulated AM (Fig. 13). The contralateral FC and MC in these groups was characterized by a low frequency spike and wave discharge with high amplitude slow wave background activity.

Rats in Groups CC, SBC, and C initially displayed a suppression in AD propagation into the secondary site. However, the suppression did not appear in the duration of AD but rather in the amplitude of AD. The secondary site was dominated by very low amplitude spiky activity with intermixed low amplitude sharp waves or spikes. This pattern often persisted up until several C-5 seizures had been evoked, at which time it rapidly assumed the characteristics of the stimulated site (Fig. 13).

Propagation of AD into the secondary site of Group TSB was severely disrupted by the forebrain bisection. Contralateral AM activity in this group usually consisted of independent low amplitude spike discharges of short duration (Fig. 13). The duration increased slightly during the appearance of C-5 but overall it remained very short. Rats in Group AC initially displayed a similar pattern of development (Fig. 13) except that the duration of the AD recorded from the secondary site gradually increased. During the appearance of C-5, the morphology of the AD pattern in the secondary site was like that observed in Groups CC, SBC, and C except there appeared to be a tendency towards more independent activity.

Propagation of AD into the ipsilateral and contralateral ATH and MRF did not vary between the groups (Fig. 13). In most cases the discharge morphology in these structures was similar to the stimulated site.

Fig. 13. Electrographic correlates of a primary-site rekindled C-5 seizure displayed by a typical rat from each group. Arrows indicate the site of stimulation; the circled numbers under each record indicate the clinical response being displayed. R=right; L=left. Bisection of the anterior commissure caused a slight reduction in the AD duration of the contralateral AM (L AM). Note that in Groups CC and TSB propagation to the contralateral MC (L MC) and FC (L FC) has been severely disrupted by bisection of the corpus callosum and hippocampal commissure. Similarly, in Group TSB, propagation of AD into the contralateral AM (R AM) was disrupted. Propagation of AD into the contralateral MRF (R MRF) in this group was not affected.


SBC
200 µV
1 sec
L AM
R AM
L FC
L MC
25"
5"
20"
AC
5"
5"
CC
15"
10"
TSB
15"
15"
TSB
L AM
R AM
L MRF
R MRF
10"
10"

C. Rate of rekindling. The rate at which the groups rekindled when the primary site was again stimulated is shown in Table II. The magnitude of the interference effect was determined by the number of stimulations required to evoke a C-5. For example, the greatest number of stimulations required signified the greatest interference effect. As can be seen in Table 2, rats in Groups TSB and CC kindled the fastest and thus showed the least interference. Groups AC, SBC, and C showed the greatest interference. However, no statistically significant differences in the rate of kindling were found ($F$=1.04; $df$=4,25; $p$>.05). This in part may have been due to the small number of rats in Groups TSB and CC that progressed to this stage.

D. Seizure duration. Five C-5 seizures were evoked from the primary site before termination of the experiment. Fig. 10C shows the seizure duration of the group on each of these sessions. No significant differences in the seizure duration were found between any of the groups on any of the five C-5s. Furthermore, the duration of these seizures did not differ significantly from those recorded during either primary or secondary-site kindling.

E. AD duration. Fig. 11C shows the AD duration recorded at the primary and secondary site during the five C-5 seizures evoked by stimulation of the primary site. The duration of AD recorded from sites other than the AM is not shown for the sake of clarity. Relevant data concerning these structures will be presented in the text.

No significant differences in the duration of the primary site AD were found between any of the groups. Similarly, in all groups except TSB the duration of AD in the secondary site was not significantly different from that of the primary site. In Group TSB, the duration of AD in the secondary site was significantly shorter ($ps$<.05) than that of the stimulated AM on

all sessions. It was also found to be consistently shorter that that of the secondary site in any of the other groups ($ps<.05$).

Bisection of the forebrain commissures did not affect the duration of the AD propagated into either the ipsilateral or contralateral MRF, ATH, FC, and MC. In most cases, the duration of the AD recorded from these structures was similar if not identical to that recorded from the stimulated site.

## Discussion

The results of the present study complement and extend those of Experiment 1. It is evident that the forebrain commissural pathways in the rat are not critical for the development of bisymmetrical generalized convulsions evoked by kindling of the amygdala. In view of these results, the possibility must be considered that other, extracommissural structures may be either critical for or at least capable of mediating the development of kindled seizures.

Bisection of the corpus callosum and hippocampal and anterior commissures (Group TSB) was found to significantly facilitate the development of primary-site kindled seizures when compared to the appropriate control group, one in which the cortex overlying the callosum had been sectioned (Group SBC) in order to control for the effects of cortical damage.

The present experiment also succeeded in delineating which of the forebrain commissures were responsible for the facilitation in primary-site kindling. The results indicated that bisection of the corpus callosum and hippocampal and anterior commissures (Group TSB) was critical since bisection of the corpus callosum and hippocampal commissure (Group CC) or the anterior commissure alone (Group AC) did not affect the rate of seizure

development. In Experiment 1, bisection of the rostral corpus callosum and hippocampal and anterior commissures significantly facilitated kindling. Therefore, if the results of the two experiments are combined it becomes apparent that bisection of the rostral corpus callosum and hippocampal and anterior commissures is all that is necessary for the effect. It further shows that the entire corpus callosum is not involved but only those areas of the structure rostral to Area 4.

Interhemispheric pathways via the forebrain commissures were not significantly involved in determining the rate of secondary-site kindling since it was found that bisected rats kindled at approximately the same rate as the intact controls. However, the commissural pathways appeared to partake in the mediation of the interference effect that is commonly observed during rekindling of the primary site (e.g., McIntyre and Goddard, 1973). The present results indicate that bisected Groups TSB and CC displayed a reduction in interference. Bisection of the anterior commissure alone (Group AC) had no effect on interference. In view of these data, it is evident that the interhemispheric pathways responsible for the mediation of the interference effect are contained within the corpus callosum or hippocampal commissure but not within the anterior commissure. Previous results (e.g. McIntyre, 1975) have led to similar conclusions.

The results presented here also show that collectively the corpus callosum, hippocampal commissure, and anterior commissure play a significant role in determining the primary-site AD and seizure duration. However, there was no suggestion of their involvement in either secondary-site kindling or rekindling of the primary site. Bisection of these structures, as possessed by rats in Group TSB, significantly increased the duration of

the primary-site AD and seizure. Other bisections were without effect.

Although the present study indicates that the integrity of the forebrain commissures is not essential for the development of kindled convulsions, there are strong indications that access of structures in one hemisphere to those in the other hemisphere (via the forebrain commissures) is important for determining (1) the latency to the onset of the seizure; (2) the severity of the ictal episode; and (3) the mediation of an 'interference-type' effect acting on the latency to seizure onset during secondary-site C-5s. All groups except Groups TSB and CC showed an inverse relationship between the seizure severity and the latency to onset of the seizure: as the latency decreased the severity increased. Bisected rats in Groups TSB and CC consistently displayed little change in latency or seizure severity during the primary, secondary, and primary retest phases of the study; in contrast, the other groups showed a progressively more severe seizure but a decreasing latency only during the primary and primary retest phases. In these groups, the latency during secondary-site kindled seizures was typically longer than that recorded during primary-site kindled or primary-site rekindled seizures. This effect was not observed in Groups TSB and CC, suggesting that it is mediated by either the corpus callosum, hippocampal commissure, or both. Similarly, the decreased seizure severity observed in Groups TSB and CC strongly suggests that interhemispheric pathways via the corpus callosum and hippocampal commissures are essential in determining the severity of the convulsive attack.

The present study indicates that the corpus callosum, hippocampal commissure, and anterior commissure play a significant role in the propagation of AD into the contralateral AM. Previous reports have found that

bisection of the anterior commissure alone is sufficient to block the spread of AD between the amygdalae (e.g., Frost *et al.*, 1958; Poblete *et al.*, 1959). However, the data reported here suggest that alternate routes are available through which the AD may spread to the contralateral AM since bisection of this structure alone (rats in Group AC) did not affect the duration of AD in the contralateral AM. The present report suggests that rather than serving as a critical route for AD propagation, the anterior commissure functions mainly as a structure involved in maintaining the synchrony of the AD between the two amygdalae. Bisection of this structure blocked the development of bisynchronous AD between the amygdalae.

Propagation of AD into the contralateral AM was most disrupted by the extensive bisection of the forebrain commissures (Group TSB). If these data are considered along with those from Experiment 1, it becomes apparent that bisection of the rostral corpus callosum, hippocampal commissure, and anterior commissure is sufficient to produce the effect. McIntyre (1975) arrived at a similar conclusion. In spite of the depression in contralateral AM activity that was observed in Group TSB during primary-site kindling, no significant effect in the rate of secondary-site transfer was found between this group and any of the other groups. These results indicate, as do the previous results of Experiment 1 and those of McIntyre (1975), that the appearance of AD in the contralateral AM during primary-site kindling is not critical for the transfer effect and that the transfer effect must therefore be mediated by some extracommissural structure. Furthermore, the bisynchronous discharge of the amygdalae was not found to be critical to the development of primary generalized seizures since these developed in all groups regardless of the state of the AD in the contralateral AM.

An interesting effect was observed throughout this study with regard to the duration of AD in the contralateral AM of Group TSB. It appeared as though the depression in propagation to the contralateral AM increased with subsequent phases of the study. For example, the depression appeared greatest during the secondary-site and primary-site retest phases of the study. A similar observation was made during secondary-site kindling in Experiment 1.

The corpus callosum and hippocampal commissure were found to be critical for the bilateral propagation of a polyspike and wave discharge pattern that was observed in the FC and MC. In Groups TSB and CC this pattern was localized to the FC and MC ipsilateral to the stimulated site, whereas in the other groups the pattern was observed bilaterally. Although this pattern is closely associated with the appearance of C-5 seizures, its importance in the expression of these seizures remains uncertain. As suggested in Experiment 1, the pattern is likely a reflection of activity occurring in some lower structure. However, in the present study the asymmetrical nature of this pattern in Groups TSB and CC did not disrupt the eventual generalization of the seizure.

Bisection of the forebrain commissures did not disrupt the bilateral propagation of AD into the ATH and MRF. No difference in AD spread to these structures was observed between any of the groups. In Experiment 1, the data suggested that areas of the rostral thalamus were critically involved in the development of kindled seizures; yet, in the present study, no outstanding electrographic features were noted in this structure. Admittedly, however, only a small area of the rostral thalamus was monitored in the present study, which may suggest that larger areas of the structure are

involved in kindling. Furthermore, if brainstem structures are critical to kindling, as has been hypothesized, then perhaps recordings from the MRF would have provided an indication. Clearly, in the present study no signs of outstanding electrographic activity were observed in the MRF, contrary to observations made in cats (Wada and Sato, 1974, 1975). Two possibilities may account for this discrepency: (1) species differences with regard to MRF participation in kindling; and (2) the areas of the MRF monitored were not comparable. Of the two possibilities the latter is favoured since MRF electrode placements in the present study were quite rostral to those of Wada and Sato (1974). This in turn may indicate that only particular areas of the MRF participate in kindling.

The forebrain commissures participate in, but are not critical for, the development of bisymmetrical generalized convulsions. Bisection of the corpus callosum and hippocampal commissure retards but does not stop the development of bisymmetrical generalization. The present results indicate that alternate extracommissural pathways are capable of mediating this particular aspect of seizure development. The question that must be asked is, What role do these alternate routes play in the intact rat? Unfortunately, this cannot be ascertained on the basis of the data contained within the present study.

## EXPERIMENT 3

The two previous experiments have indicated that the forebrain comissures in the rat are not essential for the development of kindled amygdaloid seizures. The results of these studies show, in fact, that bisection of these pathways is capable of facilitating the rate of primary-site kindling, increasing the duration of the stimulated site AD, and increasing the seizure duration. Furthermore, bisymmetrical generalized convulsions were shown to develop in the bisected rats, although the rate of development was retarded in the absence of the commissural pathways.

There are several reports that bisection of the forebrain commissures in humans suffering from intractible seizures is a beneficial therapeutic technique (Bogen and Vogel, 1963; Bogen *et al.*, 1965; Lussenhop, 1970). The reported beneficial effects range from an enhanced ability to control the seizure with anticonvulsant medication, to the lateralization of the seizure and subsequent retention of consciousness. To my knowledge none of the authors have reported an increase in seizure activity, as might be suggested by the results of Experiments 1 and 2. It may, however, be significant to note that a reduction in postoperative medication has been associated with the appearance of generalized seizures in some of these patients (Bogen, Sperry, and Vogel, 1969). This in part supports the suggestion made earlier that the commissural pathways are involved in, but not essential to, the development of generalized seizures.

The point at which the forebrain commissures are sectioned, in relation to the development of the epileptogenic process, may be an important factor in explaining the incongruity that exists between the results of the human

clinical studies and Experiments 1 and 2. In the human clinical studies, bisection of the commissures was performed following the maturation of the epileptic process, whereas in Experiments 1 and 2 bisection was done prior to the development of the process. Perhaps in the intact brain an interhemispheric inhibitory influence, like that suggested by Mutani *et al.* (1972), is maintained by the forebrain commissures and this in turn functions in the control of abnormal electrical activity in the brain (ie., paroxysmal discharges). The sectioning of the forebrain commissures would remove the inhibitory effect thereby facilitating the development of seizure activity. Kopeloff *et al.* (1950) found that bisection of the forebrain commissures after the maturation of a cortical focus in the monkey resulted in an increased state of seizure susceptibility. Alternatively, in the intact brain the commissural pathways might be the pathways critically involved in the maintenance of seizure activity after the epileptogenic process has matured. A mutually facilitatory effect may occur between the hemispheres that is mediated via the forebrain commissures. If these connections are then severed the result may be a severe disruption in the seizure. In order to clarify the various issues, the present experiment was designed to examine the effects of forebrain bisection on secondary-site kindling in rats already kindled from a primary site. If these pathways are involved in the mediation of an interhemispheric inhibition, bisection of the commissures after primary-site kindling should result in facilitated secondary-site kindling. On the other hand, if the forebrain commissural pathways function in the mediation of a mutual facilitation between hemispheres, by sectioning them secondary-site kindling should be retarded.

It was decided that rather than examining the role played by all the forebrain commissures, only the effects of bisecting the corpus callosum

and hippocampal commissure would be examined. These two connections were chosen for a variety of reasons. Firstly, it was felt that since these structures are most frequently sectioned in human patients, it would be appropriate to do the same in this study. Secondly, there are many technical considerations involved in the bisection of these structures in the rat. For example, pilot studies indicated that selective bisection of the anterior commissure in a kindled rat would be extremely difficult and impossible to achieve on a consistent basis. However, bisection of the corpus callosum and hippocampal commissure was consistently achieved.

## Methods

Subjects. Seventeen male hooded rats of the Long-Evans strain weighing between 300-350 g were used. Rats were housed individually in a temperature controlled colony room with a 12 hour light-dark cycle. They had free access to food and water except during testing and were allowed 10-14 days to adjust to the colony environment before undergoing surgery.

Electrode implantation. Rats were anaesthetized with sodium pentobarbital (60.0 mg/kg, intraperitoneally) and bipolar nichrome electrodes were aimed bilaterally at the basolateral nucleus of the amygdala (0.4 mm anterior to bregma, 4.3 mm lateral to the midline, 8.5 mm ventral from the surface of the skull, and the inscisor bar set at +5.0) of all rats. Details concerning the construction of electrodes, their implantation, and postoperative care of rats has been outlined in Experiments 1 and 2.

Testing procedures. The testing procedure used in this study was identical to that used in the previous experiments, 1 and 2. Rats were placed in a shielded wire cage and 2.0 min of baseline EEG activity was

recorded. A 1.0 sec, 160 μa constant current 60-Hz sine wave stimulus was then administered to either the right or left amygdala of each rat. The stimulation was delivered once daily between the hours of 1000 and 1300.

Amygdaloid kindling and forebrain bisection. Kindled seizure development was classified according to the method of Racine (1972a) outlined in Experiment 1. Rats were considered kindled after reaching the C-5 stage in seizure development. Eight stage-5 seizures were evoked from the primary site. Following the eighth C-5, rats were anaesthetized with sodium pentobarbital (60 mg/kg, intraperitoneally), fixed in the stereotax, and a midline craniotomy was performed. The saggital sinus was visualized and the forebrain commissures were bisected using the method described in Experiment 2. Eight of the 15 rats were randomly chosen for bisection. No record was kept of which rats had undergone bisection in order to reduce experimenter bias. The remaining rats were treated in a similar manner, but instead of bisecting the commissures only the cortex overlying the corpus callosum was sectioned. These rats served as a control group. Following surgery the craniotomy was packed with sterile gelfoam soaked in normal saline, and the skull was then covered with a thin layer of dental acrylic.

Rats were allowed a minimum of 10 days to recover from surgery before being stimulated. Following recovery, the site of stimulation was switched to the secondary site in order to study the effects of forebrain commissurotomy on transfer. Rats were then kindled and eight C-5 seizures were evoked. Following the eighth C-5, stimulation was then switched back to the original site (primary site) and the effects of forebrain bisection on the interference phenomenon was examined. Eight C-5 seizures were evoked by stimulating the primary site. The site of stimulation was then again

switched back to the secondary site where eight C-5 seizures were evoked prior to the termination of the experiment.

Afterdischarge and seizure duration. The criteria used in the present study for the recording of afterdischarge and seizure duration associated with the various stages of kindling were the same as those used in Experiments 1 and 2.

Additional parameters of the kindled seizure. The results of Experiments 1 and 2 suggested that a record of several additional aspects of the kindled seizure would be helpful in determining the effects of forebrain bisection. Thus, a record was made of the latency from the termination of the stimulation to the appearance of the C-5 ictal manifestations for each session. Similarly, the number of C-5 seizures evoked prior to the bilateral generalization of the response were also noted. A measure of the severity of the seizure was also attempted on each session; this was estimated by recording the number of rearing and falling episodes exhibited by each rat on each session.

Histology. Rats were killed with an overdose of sodium pentobarbital, perfused through the heart with 0.9% saline that was followed by 10% formalin. The brain was removed and stored in 10% formalin. Frozen coronal sections 40 μa in thickness were taken. Every fifth section (0.2 mm) was kept and stained with cresyl violet in order to identify the electrode location and extent of the bisection. The electrode location and extent of the bisection were then plotted on sections taken from the stereotaxic atlas of Pelligrino and Cushman (1967). Tracings of representative histology were prepared.

Results

Because no record was kept concerning which rats had undergone commissurotomy, the experimental and control groups were not assembled until a histological analysis of the brain had been made. All rats were intact during primary-site kindling; therefore, the division of the primary-site kindling data into experimental and control sections was done in order to show that effects observed between these groups in subsequent phases of the study were not due to inherent differences.

Bisection of the corpus callosum and hippocampal commissure facilitated the rate of secondary-site kindling. Forebrain bisection was also found to disrupt the development of primary generalized motor seizures. AD duration was not affected by forebrain bisection; however, secondary-site kindled seizures were typically less severe and of longer latency to onset. Interference was also markedly reduced by the bisection.

Histology. All electrode tips were found in or immediately adjacent to the basolateral nucleus of the AM (Fig. 1). Bisection of the forebrain commissures in the experimental group ([CC]; N=8) appeared relatively constant, with most rats possessing a complete bisection of the corpus callosum and hippocampal commissure. To be included in the experimental group rats had to possess a complete bisection of the hippocampal commissure and at least the rostral half of the callosum: the results of Experiment 1 and 2 suggested that the rostral aspects of the callosum were most involved in kindling. Extracommissural damage in the experimental group was minimal. In most rats it was confined to the tissue overlying the callosum (ie., cingulate cortex). Subcortical damage also appeared negligible. The hippocampus appeared relatively free of destruction, although some rats displayed

minor damage to the medial aspects of Ammons Horn. No evidence of midline thalamic damage was observed, nor was any obvious disturbance of the ventricular system apparent. Overall, the bisection was very clean. Representative sections are shown in Fig. 14.

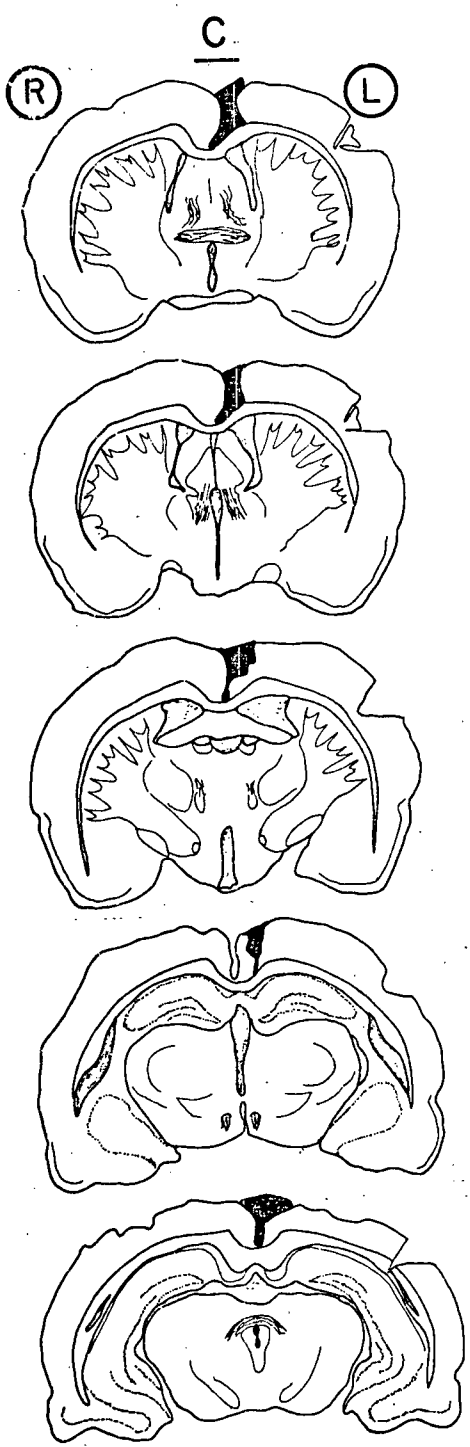
There were no signs of callosal damage in the control group ([C]; N=7). The transection in this group was confined to a small strip of cingulate cortex, adjacent to the midline. In a few rats the location and extent of the transection were similar to the above except that some 'undercutting' of the cortex was noted, apparently resulting from the deflection of the surgical silk by the fibers of the callosum. Representative control sections are shown in Fig. 14.

Primary-site kindling

A. Primary-site electroclinical development and propagation. There were no outstanding differences between the control and experimental groups with regard to the electroclinical development of primary-site kindled seizures. The progressive elaboration of seizures in both groups followed a pattern similar to that described for the control rats of Experiments 1 and 2. By the eighth C-5 all but one rat from each group had developed primary generalized seizures (Table III). Typically this pattern emerged around the fourth or fifth C-5 and remained throughout subsequent sessions. Both groups also displayed marked but similar reductions in the C-5 latencies over the first to eighth seizures (Fig. 15A). Similarly, both groups showed a progressive increase in seizure severity over the eight C-5 sessions (Fig. 15B).

The overall pattern of AD development and propagation was similar in both groups. Perhaps the most evident electrographic feature was the some-

Fig. 14. Extent of the forebrain bisection on a representative rat from each group. Lightly shaded areas represent ventricular spaces. In Group C, the section extends to the dorsal surface of the corpus callosum only.


C
R
L

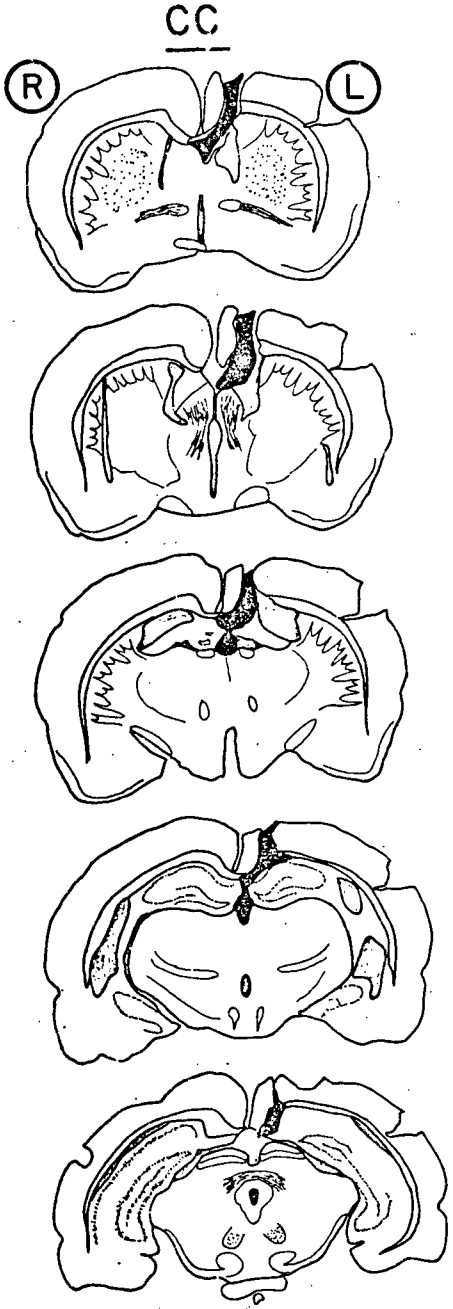

CC
R
L

TABLE III

EFFECT OF FOREBRAIN BISECTION ON THE DEVELOPMENT OF PRIMARY GENERALIZED MOTOR SEIZURES

| | Primary | Secondary | Primary Retest | Secondary Retest |
|---|---|---|---|---|
| Group CC | | | | |
| No. showing primary generalized seizure | 7 | 1 | 4 | 3 |
| Total | 8 | 8 † | 7 | 7 * |
| Group C | | | | |
| No. showing primary generalized seizure | 6 | 7 | 7 | 7 |
| Total | 7 | 7 | 7 | 7 |

* Significantly different from Group C (controls) $p<0.05$
† Significantly different from Group C (controls) $p<0.01$

Fig. 15A,C,E,G. Mean latency (in secs) from the termination of the stimulation to the appearance of forelimb clonus during successive primary-site kindled, secondary-site kindled, primary-site rekindled, and secondary-site rekindled stage-5 seizures.

Fig. 15B,D,F,H. Mean seizure severity in terms of the number of rearing and falling episodes, within successive primary-site kindled, secondary-site kindled, primary-site rekindled, and secondary-site rekindled stage-5 seizures.

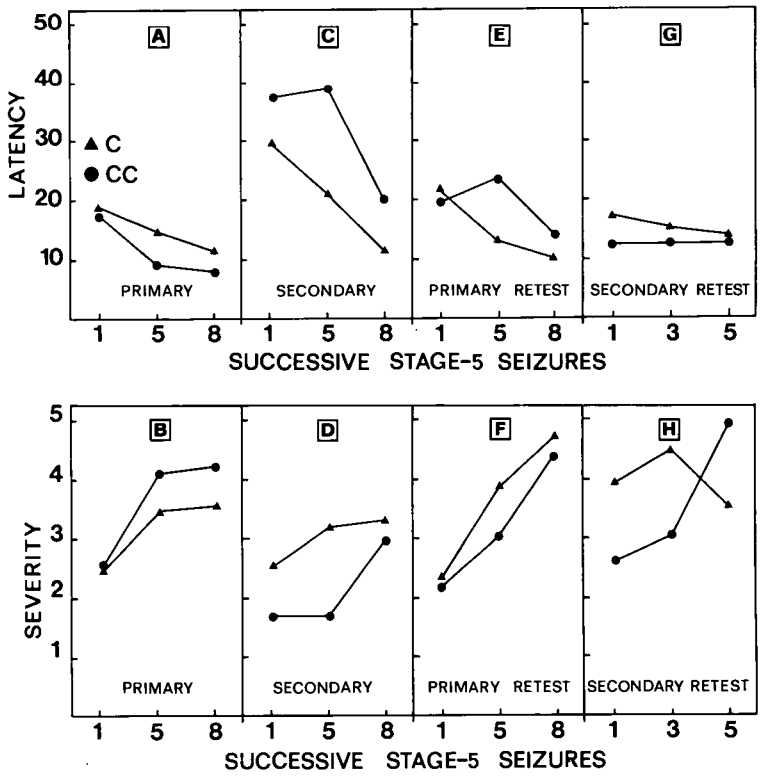
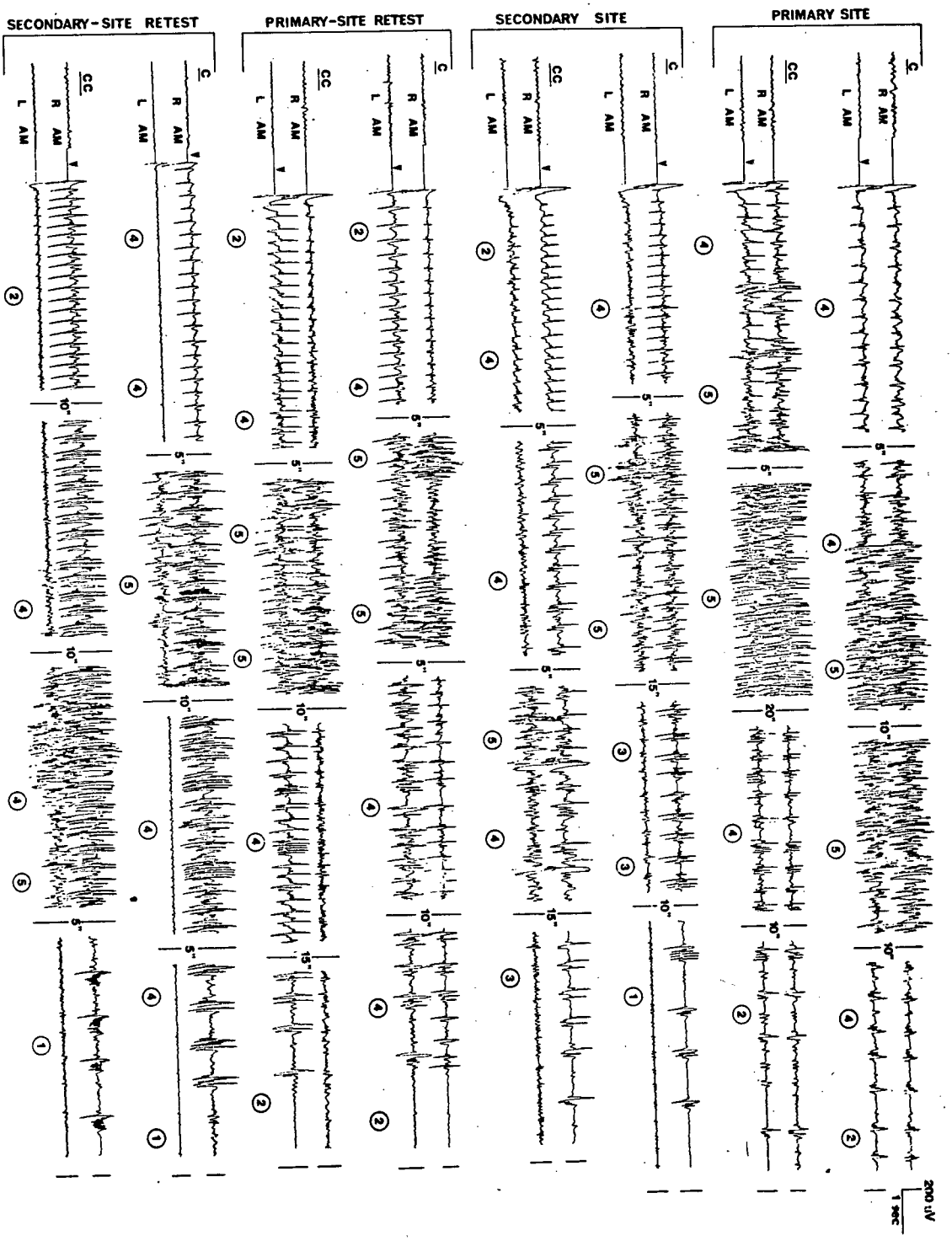

A
C
E
G
LATENCY
50
40
30
20
10
▲ C
● CC
PRIMARY
SECONDARY
PRIMARY RETEST
SECONDARY RETEST
1 5 8 1 5 8 1 5 8 1 3 5
SUCCESSIVE STAGE-5 SEIZURES
B
D
F
H
SEVERITY
5
4
3
2
1
PRIMARY
SECONDARY
PRIMARY RETEST
SECONDARY RETEST
1 5 8 1 5 8 1 5 8 1 3 5
SUCCESSIVE STAGE-5 SEIZURES

Fig. 16. Records from a representative rat in each group showing the electrographic correlates of a stage-5 seizure during the various sections of the experiment. Arrows indicate the site of stimulation; the circled numbers under each record indicate the clinical response being displayed. R=right; L=left.


SECONDARY-SITE RETEST
PRIMARY-SITE RETEST
SECONDARY SITE
PRIMARY SITE
C
CC
R AM
L AM
200 µV
1 sec

what slow development of propagated activity in the contralateral AM. Although the AD pattern in this structure was typically synchronous with that of the stimulated site, the amplitude of the discharge was considerably lower. The activity of the contralateral AM in both groups did not usually mature (ie., assume the same high amplitude characteristics of the stimulated site) until several stage-5 seizures had been evoked. Fig. 16 shows the electrographic correlates of a primary-site C-5 seizure for each group.

B. Rate of primary-site kindling. Table IV shows the rate of primary-site kindling for each group. As expected, there was no significant difference between the rate at which the control and experimental groups kindled ($F$=.29; $df$=1,13; $p$>.05).

C. Primary-site seizure duration. The primary-site seizure duration observed during each of the eight C-5s is shown in Fig. 17A. No significant differences were found between the two groups over these eight sessions. Both groups tended to display longer seizures during the first several C-5s but with subsequent stimulations the durations appeared to stabilize.

D. AD duration during primary-site kindled seizures. Fig. 18A displays the AD duration recorded from the primary and secondary sites during the eight primary-site C-5 seizures. As is evident, little difference between the stimulated and contralateral AM AD duration in either group existed. Furthermore, no significant differences were found between either group with regard to the duration of the primary or secondary-site AD.

Secondary-site kindling

A. Secondary-site electroclinical development and propagation. Bisection of the corpus callosum and hippocampal commissure was found to severely disrupt the development of primary generalized C-5 seizures. This final

TABLE IV

MEAN NUMBER OF SESSIONS TO KINDLE AT EACH SITE

| Group | Primary Site | Secondary Site | Primary Site Retest | Secondary Site Retest |
|---|---|---|---|---|
| CC | 14.6 | 4.0 * | 1.6 | 1.3 † |
| | (11-20) | (2-9) | (1-4) | (1-2) |
| | n=8 | n=8 | n=8 | n=7 |
| C | 15.9 | 7.0 | 2.4 | 2.4 |
| | (8-26) | (6-9) | (1-4) | (2-3) |
| | n=7 | n=7 | n=7 | n=7 |

* Significantly different from the rate of secondary-site kindling of the controls (Group C) $p<0.05$

† Significantly different from the rate of secondary-site rekindling of the controls (Group C) $p<0.01$

Fig. 17A. Mean seizure duration (in secs) of eight successive stage-5 primary-site seizures.

Fig. 17B. Mean seizure duration (in secs) of eight successive stage-5 secondary-site seizures.

Fig. 17C. Mean primary-site rekindled seizure duration (in secs) recorded over eight successive stage-5 seizures.

Fig. 17D. Mean secondary-site rekindled seizure duration (in secs) recorded over eight successive stage-5 seizures.

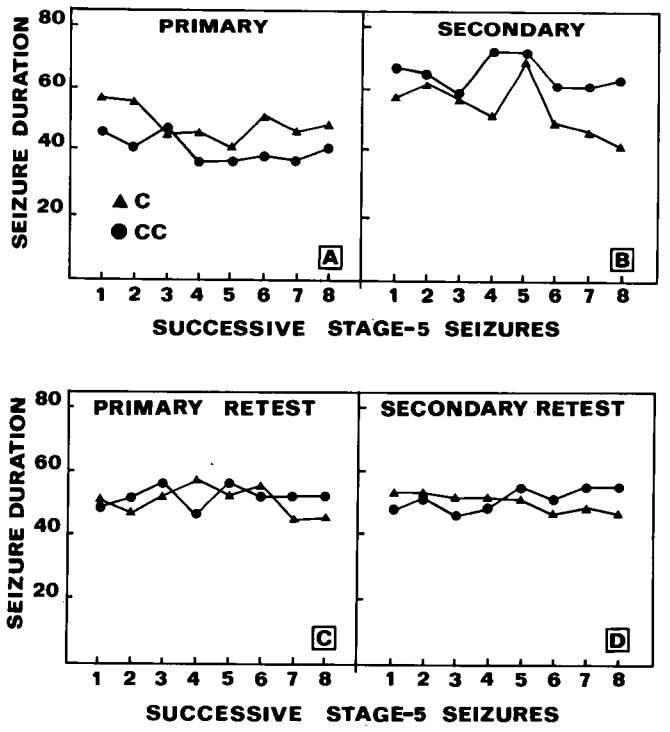
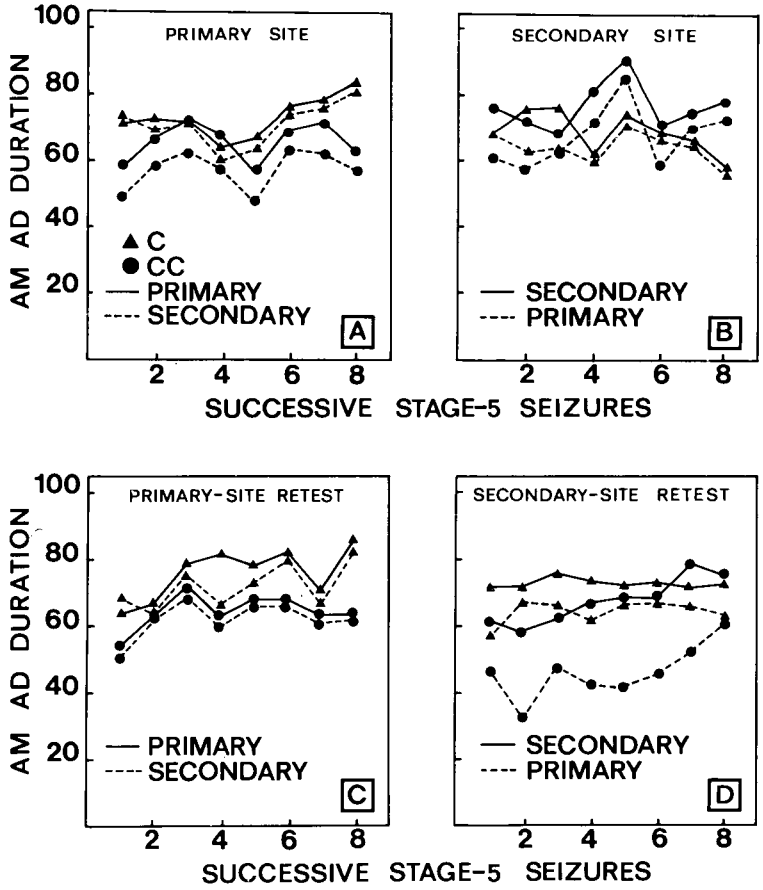

PRIMARY
SECONDARY
SEIZURE DURATION
80
60
40
20
▲ C
● CC
A
B
1 2 3 4 5 6 7 8
SUCCESSIVE STAGE-5 SEIZURES
PRIMARY RETEST
SECONDARY RETEST
SEIZURE DURATION
80
60
40
20
C
D
1 2 3 4 5 6 7 8
SUCCESSIVE STAGE-5 SEIZURES

Fig. 18A. Mean AD duration (in secs) recorded from the stimulated (primary) and contralateral (secondary) AM during eight successive primary-site stage-5 seizures.

Fig. 18B. Mean AD duration (in secs) recorded from the stimulated (secondary) and contralateral (primary) AM during eight successive secondary-site stage-5 seizures.

Fig. 18C. Mean AD duration (in secs) recorded from the stimulated (primary) and contralateral (secondary) AM during eight successive primary-site rekindled stage-5 seizures.

Fig. 18D. Mean AD duration (in secs) recorded from the stimulated (secondary) and contralateral (primary) AM during eight successive secondary-site rekindled stage-5 seizures.


PRIMARY SITE
SECONDARY SITE
AM AD DURATION
100
80
60
40
20
▲ C
● CC
— PRIMARY
---- SECONDARY
A
— SECONDARY
---- PRIMARY
B
2
4
6
8
SUCCESSIVE STAGE-5 SEIZURES
PRIMARY-SITE RETEST
SECONDARY-SITE RETEST
— PRIMARY
---- SECONDARY
C
— SECONDARY
---- PRIMARY
D
SUCCESSIVE STAGE-5 SEIZURES

stage in development was displayed by all control rats by the eighth C-5; in contrast, primary generalization was evident in only one of the 8 rats in the experimental group (Table 3). This difference was found to be highly significant ($\chi$=8.24; $df$=1; $p$<.01). Experimental and control groups both showed similar effects on the C-5 seizure latencies. Secondary-site seizures were typically accompanied by much longer latencies to develop. The major difference, however, was that forebrain-bisected rats displayed consistently longer latencies than those of the control group (Fig. 15C). Furthermore, forebrain bisection also produced a marked reduction in the severity of the secondary-site seizure (Fig. 15D). However, the effect was not permanent and tended to dissipate by the eighth C-5. Therefore, in summary, secondary-site clinical seizures may be characterized by: (1) lack of primary generalization; (2) longer latency to appear; and (3) a marked reduction in seizure severity.

Bisection of the forebrain commissures had very little effect on the electrographic correlates of secondary-site kindling. Experimental and control groups both showed a similar facilitation in the development of secondary-site AD that has proved to be a characteristic of secondary-site kindling (e.g., Experiments 1 and 2). Similarly, both groups showed a retardation in the propagation of AD into the primary site. The duration of AD in the primary site was disrupted only during the initial stages of kindling (ie. C-1 to C-3). As kindling progressed, the duration of the AD approached that of the secondary site, but the amplitude and complexity of the discharge remained depressed. This effect appeared most evident in the bisected group but persisted throughout many of the initial C-5s in both groups. AD morphology in the secondary site did not approach that of the primary site (ie., 4-6/sec, high amplitude, polyspike and wave or irregular

polyspike) until approximately five C-5 seizures had been evoked. Electrographic features of a typical C-5 seizure for each group are shown in Fig. 16.

B. Rate of secondary-site kindling. The rate of secondary site kindling in each group is shown in Table IV. Bisection of the corpus callosum and hippocampal commissure significantly facilitated the rate of secondary-site kindling ($F$=8.83; $df$=1,13; $p$<.05). The control group did, however, show a significant transfer effect ($F$=5.05; $df$=1,13; $p$<.05).

C. Secondary-site seizure duration. The duration associated with each of the secondary-site C-5 seizures is shown in Fig. 17B. Both groups displayed similar increases in seizure duration as compared to those of primary-site seizures. Although the bisected rats displayed longer secondary-site seizures than the controls, no consistently significant differences between the groups were found.

D. AD duration during secondary-site kindled seizures. Bisection of the forebrain commissures had little effect on the duration of the AD recorded from the secondary and primary site. Fig. 18B shows the duration of the AD recorded from AM during the 8 secondary-site C-5 seizures in each group. Although the AD duration at the secondary site in the bisected group tended to be longer than that of the controls, no significant differences were found. Similarly, no differences were found between the duration of AD in the primary site and the secondary site in either group.

Rekindling of the primary site

A. Electroclinical development and propagation. The effects of forebrain bisection on the development of seizures was less apparent during rekindling of the primary site than during secondary-site kindling. Both

groups displayed similar seizure latencies that were, in general, shorter than those observed during secondary-site kindling (Fig. 15E). No significant differences were found between the groups, although bisected rats continued to display longer latencies than the controls (Fig. 15E). Severity of the seizure was also unaffected by the forebrain bisection (Fig. 15F).

Bisection of the corpus callosum and hippocampal commissure disrupted the development of primary generalized C-5 seizures. Only 4 of the 8 rats in the experimental group eventually developed this type of C-5; in contrast, all rats in the control group exhibited primary generalized C-5 seizures (Table III). No statistically significant difference was found between the groups with regard to this particular aspect of seizure development. Also, more rats in the experimental group developed primary generalized C-5s during rekindling of the primary site than during kindling of the secondary site.

Very few contrasting electrographic features were observed between the experimental and control group during primary-site rekindling. The electrographic correlates of a typical C-5 seizure are shown in Fig. 16. Both groups showed a rapid development of seizures. This was accompanied by a facilitated development in the overall morphology of the stimulated site. Most rats displayed high amplitude, 4-6/sec, polyspike and wave discharges that became progressively more irregular with subsequent C-5 seizures. Propagation into the secondary site of both groups initially consisted of very low amplitude spike and wave or sharp wave discharges synchronized with the primary site. However, after four to five C-5 seizures had been evoked, this pattern gradually evolved into a high amplitude irregular discharge similar to that observed at the primary site.

B. Rate of primary-site rekindling. The rate of primary-site rekindling is shown in Table IV. Bisection of the corpus callosum and hippocampal commissure produced a reduction in the interference effect that is commonly observed when a site is rekindled (e.g., Experiments 1 and 2). However, due to the variability within the two groups, the effect was not statistically significant.

C. Rekindled primary-site seizure duration. No significant differences were found between the C-5 seizure duration of either group. The duration in both groups appeared to stabilize during this phase of the study (Fig. 17C). Both groups showed a nonsignificant reduction in seizure duration as compared to secondary-site C-5s.

D. AD duration during primary-site rekindled seizures. Fig. 18C shows the duration of AD in the primary and secondary site associated with each of the primary-site rekindled C-5 seizures. Bisection of the forebrain commissures did not affect the AD duration. No significant differences were found in the AD duration of primary or secondary sites either within or between the two groups.

Rekindling of the secondary site

A. Electroclinical development and AD propagation. Significantly fewer rats in the experimental group developed primary generalized C-5 seizures during secondary-site rekindling ($\chi$=3.22; $df$=1; $p$<.05). Only 3 of the 7 rats in the forebrain-bisected group developed this type of seizure; all of the rats in the control group, however, exhibited the eventual development of this pattern (Table III). Bisection of the forebrain commissures was found to have little effect on the severity or latency of the seizure. Although the seizure latency in previous phases of the study typically decreased as

a function of the number of C-5 seizures, it appeared to stabilize during secondary-site kindled seizures (Fig. 15G). The seizure severity in the control group appeared to stabilize, whereas in the experimental group the characteristic increase with subsequent C-5 seizures was observed (Fig. 15H).

The electrographic correlates of a secondary-site rekindled C-5 are shown in Fig. 16. There was no difference between the groups in terms of stimulated-site AD development. Both groups displayed well developed, high amplitude, 4-6/sec, polyspike and wave configurations with the first stimulation. An outstanding feature of secondary-site rekindling was the lack of propagation into the primary site observed in the forebrain-bisected group. Not only was the amplitude of the discharge drastically reduced in this group but the duration of the discharge was also severely affected. This lack of primary-site activity was most evident during the first several C-5 seizures. Some signs of recovery were noted with subsequent sessions. Usually by the sixth to eighth C-5, a pattern similar to that recorded from the primary site was observed in this structure. A similar but less consistent effect was also observed in the control group. In the control group, propagation into the primary site was sometimes depressed during the early C-5s but in all cases it rapidly recovered. Primary-site activity in both groups was characterized by extremely low amplitude sharp wave discharges imposed on a background of fast activity. These discharges, however, were only rarely independent from those of the stimulated site.

B. Rate of secondary-site rekindling. Bisection of the corpus callosum and hippocampal commissure significantly reduced the interference effect associated with the rekindling of the secondary site ($F$=17.65; $df$=1,12; $p$<.01). The rate of secondary site rekindling is shown in Table IV. No significant

differences were observed between the rates of primary and secondary-site rekindling in either group.

C. Rekindled secondary-site seizure duration. The stabilization in seizure duration noted during primary-site rekindled C-5s was also evident during secondary-site C-5s. The duration of these secondary-site rekindled seizures is shown in Fig. 17D. No significant differences in seizure duration were found between either the control or forebrain-bisected groups.

D. AD duration during secondary-site rekindled seizures. Bisection of the forebrain commissures caused a consistent reduction in the duration of AD in the primary site (Fig. 18D). A significant reduction from that of the stimulated site was found on session 2, 4, 5, 6, and 7 ($ps<.05$). No significant differences were found in AD durations of the control group primary and secondary site. Furthermore, the AD durations of the secondary site in the control and experimental group were not significantly different.

## Discussion

The results of the present study again confirmed that the corpus callosum and hippocampal commissure in the rat are not essential pathways for the development of kindled amygdala seizures. Bisection of these structures, following primary-site kindling, produced a significant facilitation in the rate of secondary-site kindling (ie., transfer effect). These data suggest that in the intact animal the commissural connections interfere with or inhibit the interhemispheric transfer of seizure susceptibility.

The present results also indicate that although the integrity of the forebrain commissures is not necessary for the development of seizures, these structures do participate in determining several clinical aspects of

the kindled seizure. Firstly, the forebrain commissural pathways are involved in determining the latency from termination of the stimulation to C-5 clinical manifestations. Bisection of these pathways produced much longer latencies. Secondly, since the severity of the kindled seizure was markedly reduced in the bisected rats, commissural pathways providing access to the contralateral hemisphere must be viewed as important links for the transmission of activity concerned with determining the severity of the convulsive attack. The disruptive effects that forebrain bisection has on latency and severity of the attack are most evident during secondary-site kindling. The disruptive effects diminished with subsequent phases of the study: primary- and secondary-site rekindling. In view of these data, it is worthwhile considering the possibility that this diminuation in the disruptive effects is a reflection of the establishment of alternate, extracommissural routes which in turn are able to support these two aspects of kindled seizure expression. Finally, in the intact rat the neuronal mechanisms responsible for the development of primary-site primary generalized seizures are likely to involve the forebrain commissures. Furthermore, if rats are kindled prior to forebrain bisection, these commissural connections may become the preferred, if not permanent, pathways concerned with the primary generalization of the seizure. This is supported by the present finding that bisection of the commissures produces a longterm disruption in the expression of this type of seizure.

The present results indicate that perhaps both inhibitory and facilitory processes are evoked during kindling and that bisection of the forebrain commissures can successfully separate these. For example, an interhemispheric inhibitory effect, mediated via the commissures, may be actively

involved in the suppression of epileptogenecity in the intact animal. Bisection of the commissures would eliminate this influence and may thus explain the facilitated rate of secondary-site kindling that was observed in the experimental group. As kindled seizure development progresses in the intact animal, an interhemispheric facilitatory interaction may be evoked that also is mediated via the forebrain commissures. This in turn may influence such aspects of the seizure as severity and latency to expression. This would account for the decreased severity and increased latency observed in the bisected rats. Whether or not this is an active process cannot be deduced at this time. It is possible that a facilitatory interaction is not actually occurring, and the effects on latency and seizure severity noted in the bisected group are due to a disruption in the spread to, and subsequent recruitment of, a greater number of contralateral structures (e.g., areas of the contralateral cortex).

The forebrain commissures were also found to be involved in the mediation of the interference effect observed during the rekindling of the primary structure. The results showed that bisection of the commissures significantly reduced the interference effect (ie., bisected rats required fewer stimulations than controls to rekindle a site). These data may also be viewed as support for the hypothesis that forebrain bisection disrupts the manifestation of an interhemispheric inhibitory process.

Participation of the forebrain commissures in determining the C-5 seizure duration was not indicated by the present results. No differences were observed between the experimental and control groups. However, some evidence of commissural involvement in the propagation of AD into the contralateral AM was observed, but only during the rekindling of the secondary site.

It was found that the AD duration in the contralateral AM during this phase of the study was significantly reduced on many of the sessions. An explanation for this effect is lacking for the moment.

# GENERAL DISCUSSION

Racine *et al.* (1972) proposed that kindling resulted from the progressive strengthening of interlimbic connections. To support this hypothesis, they showed that if the majority of the interlimbic connections were severed by transecting the forebrain commissures, the rate of amygdaloid kindling was retarded. The present series of experiments shows, however, that the forebrain commissures of the rat are not critical pathways for the development of seizures evoked by repetitive stimulation of the amygdala. This finding is not unprecedented and has been observed in previous studies (McIntyre, 1975; Wada and Sato, 1975). The results of Racine *et al.* (1972) may in part have been due to the unintentional damage of extracommissural structures as suggested by Experiment 1.

Although present and previous results (ie., McIntyre, 1975; Wada and Sato, 1975) indicate that the interlimbic hypothesis of Racine does not adequately account for amygdaloid kindling, the hypothesis cannot be totally discarded; even in the forebrain-bisected animal many alternate interlimbic and potential interlimbic routes exist via structures such as the thalamus and hypothalamus (e.g., Bucy and Kluver, 1955; Nauta, 1962; Lammers, 1972; de Olmos, 1972). Nevertheless, the acceptance of the interlimbic hypothesis should remain guarded. In view of the present results, an alternate explanation is advanced. This hypothesis proposes that amygdaloid kindling is a function of the strengthening of limbic-brainstem connections. It has been proposed that the repetitive elicitation of AD results in the progressive potentiation of particular pathways (e.g., Goddard and Douglas, 1975; Racine *et al.*, 1975). It is possible that some of these pathways may involve routes to the brainstem. Many early reports suggested that reticular

and thalamic elements of the brainstem are important for the development of seizures arising from the temporal lobe structures (Kaada, 1951; Feindel and Gloor, 1954; Gloor, 1955a,b). Wada and Sato (1974, 1975) have also demonstrated the participation of the MRF in amygdaloid kindling. Brainstem involvement in other aspects of convulsive behaviour such as secondary epileptogenesis (e.g., Morrell, 1960; Isaacson *et al.*, 1971; Nie *et al.*, 1974) and bisymmetrical generalization of discharges arising from bilateral cortical foci (e.g., Marcus and Watson, 1966; Ottino *et al.*, 1971; Mutani *et al.*, 1973) has also been shown. Furthermore, in Experiment 1 of this thesis, destruction of large areas of the thalamus significantly retarded amygdaloid kindling.

Bisection of the corpus callosum, hippocampal commissure, and anterior commissure significantly facilitated the rate of primary-site kindling (Experiments 1 and 2); bisection of the corpus callosum and hippocampal commissure significantly facilitated the rate of secondary-site kindling (Experiment 3). Wada and Sato (1975) also found that bisection of these structures facilitated the rate of amygdaloid kindling in the cat. These results support the hypothesis that within the intact animal one hemisphere is able to exert an inhibitory influence on the development of epileptiform activity in the other. In addition, this influence appears to be mediated via the forebrain commissures. This hypothesis does not go unsupported by earlier investigations. For example, a number of studies have shown that either enhancement or inhibition of spike discharges in secondary foci can occur following the inactivation of primary foci (e.g., Rovit *et al.*, 1960; Morrell, 1960; Gloor *et al.*, 1965; Coceani *et al.*, 1966). These studies demonstrate the fact that bilateral foci possess the ability to interact.

Mutani *et al.* (1972) later showed that the activity of bilateral cortical foci is enhanced following the sectioning of commissural connections and reduced following cortex-corpus callosum isolation from the subcortex. This led to the suggestion that transcallosal pathways were responsible for the transmission of an interhemispheric inhibitory influence and that brainstem pathways mediated a similar but facilitatory effect. Although Mutani's hypothesis was derived from observations of cortical epileptogenic processes in acutely prepared animals, the results presented in this thesis suggest that the same is true for subcortical processes in chronic preparations.

The present results suggest that the facilitated rate of kindled seizure development may in part be the reflection of the precoccious development of limbic-brainstem pathways in the bisected rat. The facilitative nature of these pathways and the importance of brainstem structures has already been discussed (ie., Mutani *et al.*, 1972; Wada and Sato, 1974, 1975). Therefore, the following hypothesis is advanced: In the intact animal, shorter monosynaptic and often commissural routes are the preferred routes for the early spread of epileptiform activity originating in the amygdala. For example, Frost *et al.* (1958) showed that the importance of the anterior commissure in monkeys for the early spread of amygdaloid AD to the contralateral amygdala. However, these are not critical pathways for the development of kindled seizures and function mainly as avenues for the dissemination of the discharge to other nonessential structures. The critical pathways for kindling are those connecting the limbic-brainstem structures. Because these routes are often long and polysynaptic, they are slow to develop in the intact animal; and do so only through the repeated bombardment by AD from the AM. In the early stages of kindling, AD propagation likely occurs first over

the short monosynaptic routes since these are more accessible. As kindling progresses, however, the less accessible brainstem pathways are gradually 'sensitized' by the repeated invasion of AD activity. Therefore, kindled seizure development in the intact animal is a reflection of the gradual 'sensitization' of these limbic-brainstem connections. In the bisected animal, many of the shorter, more accessible monosynaptic routes are severed. Thus, AD in these animals is unable to make use of these pathways. Instead, AD that would normally use these routes is, in a sense, 'funnelled' into the brainstem circuits. This increased level of AD bombardment in turn results in an increased rate of 'sensitization'. The increased rate of limbic-brainstem 'sensitization', therefore, is reflected as an increase in the rate of amygdaloid kindling.

One might alternatively explain the facilitation in kindling as a manifestation of denervation supersensitivity and not the removal of transcomissural inhibition and potentiation of limbic-brainstem connections, since the effect was observed in completely bisected (ie., bisected in the corpus callosum, hippocampal commissure and anterior commissure) rats of Experiments 1 and 2 and callosotomized rats of Experiment 3. This indicates that only those rats with the most extensive bisections show the effect. Stavraky (1961) found an increase in the susceptibility of callosomotized rats and cats to the convulsive effects of pentylenetetrazol. Similarly, Sharpless (1969) has suggested that denervation supersensitivity is capable of producing increases in seizure susceptibility. The results presented here, however, contraindicate supersensitivity as a cause for the facilitated kindling. Firstly, only primary-site kindling in Experiments 1 and 2 and secondary-site kindling in Experiment 3 were facilitated. If denervation

supersensitivity were the explanation for this increase in seizure susceptibility, a facilitation in secondary-site kindling in Experiments 1 and 2 might also have been expected. Secondly, in Experiments 1 and 2 the seizure severity in the rats with bisections in either the corpus callosum, anterior commissure, and hippocampal commissure or corpus callosum and hippocampal commissure did not appreciably increase through subsequent phases of the studies, unlike the other bisected and control rats. Furthermore, in Experiment 3 the seizure severity during secondary-site kindling actually decreased. An overall increase in seizure severity would presumably be indicated if denervation supersensitivity were the cause of the facilitated seizure development. Finally, Wada and Sato (1975) found no difference in the generalized seizure triggering threshold of forebrain-bisected kindled cats and intact kindled cats.

The forebrain commissures are implicated in the mediation of the interference effect. However, only bisections involving at least the corpus callosum and hippocampal commissure disrupted this effect, suggesting that these structures and not the anterior commissure are critical. McIntyre (1975) reported a similar result.

Although the results of Experiments 1, 2, and 3 indicate that bisection of the forebrain commissures either before or after kindling produces many similar effects, they further indicate that quite different effects can be produced. The most obvious differences were noted with regard to the development of primary generalized convulsions. The results of Experiments 1 and 2 showed that the corpus callosum and hippocampal commissure participated in but were not critical for the development of primary generalization. Bisection of these structures retarded but did not stop the gradual emergence of

this convulsion. However, bisection of these structures after kindling rendered the animals incapable of developing primary generalized convulsions during subsequent phases of kindling (ie., secondary site, etc.). These contrasting results may illustrate an inherent property of the central nervous system: neural plasticity. Because the development of primary generalized convulsions is severely disrupted by forebrain commissurotomy after kindling, the forebrain commissures appear critically involved in this phenomenon in the intact rat. On the other hand, if the commissural pathways are severed prior to kindling the results support the neural plasticity suggestion in that alternate, subcortical pathways are able to assume the functions of the commissures and thus mediate the development of primary generalized convulsions. In the kindled rat, the commissural connections appear to be the major routes for primary generalization of the seizure and the 'potential' alternate pathways are presumably involved in some other aspect of kindling (e.g., propagation of AD). Therefore, the number of 'potential' alternate pathways in the kindled rat are necessarily fewer than in the nonkindled rat. As a result, forebrain bisection has a considerably greater, if not permanent, effect on primary generalization of the seizure in kindled as opposed to nonkindled rats.

Most of the reports concerning the effects of forebrain bisection in humans suffering from intractible seizures have indicated therapeutic benefits ranging from enhanced ability to control seizures with anticonvulsant drugs to a reduction in generalized seizure frequency, lateralization of the clinical manifestations and a retention of consciousness (Bogen and Vogel, 1963; Bogen *et al.*, 1965; Lussenhop, 1970). None of the authors have thus far reported an increase in seizure activity as might be suggested by

the results of the present studies (ie., Experiments 1 and 2). However, the only fair test of this was represented by Experiment 3, in which the effects of forebrain bisection on the mature epileptiform process were tested. The results of this study indicate that bisection of the forebrain commissures was indeed capable of exerting a degree of control over subsequent seizure development. Although the bisected rats in this study displayed a significant facilitation in secondary-site kindling, it is important to note that the clinical aspects of these seizures indicated that an overall decrease in the intensity of the evoked seizures had occurred. This decrease in seizure intensity was manifest as: (1) a significant reduction in the number of rats displaying primary generalization; (2) a marked increase in the latency to convulsion; and (3) a reduction in the seizure severity. An explanation as to why the rats displayed facilitated seizure development and the human patients did not may be a function of: (1) a difference in species; or (2) the maintenance of the human patitents on a postoperative regimen of anticonvulsant medication. In the human patient, bisection of the forebrain commissures may increase the seizure triggering threshold to the point where anticonvulsant medication becomes effective. With regard to the generalized seizure, Bogen *et al.* (1969) have reported that generalized seizures have occurred in patients following a reduction in medication. This supports the suggestion that the forebrain commissures are the principal mediators in this phenomenon, but that alternate pathways are also able to serve as mediators.

The electrographic observations seemed to bear no relationship to the clinical aspects of kindling, although the importance of particular pathways for the interhemispheric propagation of AD was indicated. In contrast to

many of the early reports (e.g., McCulloch and Garol, 1941; Frost *et al.*, 1958; Poblete *et al.*, 1959) the anterior commissure was found not to be the major pathway for the spread of AD between the amygdalae. Experiments 1 and 2 showed that bisection of the anterior commissure alone had little longterm effect on propagation into the contralateral AM. Because propagation was most disrupted by sectioning of the corpus callosum, hippocampal commissure and anterior commissure, the importance of these additional routes was clearly indicated. Furthermore, the participation of thalamic areas in this phenomenon was indicated by Experiment 1.

The lack of AD activity in the contralateral AM had no effect on (1) transfer; (2) interference; or (3) generalization. In view of these data, not only does the interlimbic hypothesis of kindling become less tenable but the importance of contralateral limbic structures in kindling becomes questionable. Further studies should be done to determine their participation.

The corpus callosum and hippocampal commissure are involved in the bilateral propagation of an independent polyspike discharge observed in the MC. This pattern of activity has been described previously (Wada *et al.*, 1975) and typically occurs in association with the appearance of C-5 seizures. It was not possible to determine whether this activity originated in the MC or was a reflection of activity occurring in some deeper structure. However, the asymmetrical appearance of this pattern in the bisected rats did not appear to affect the clinical development. For example, the pattern was present in these animals even after generalized seizures had developed.

Forebrain bisection had no effect on the bilateral propagation of AD into the MRF and ATH. Similarly, no outstanding electrographic features

were observed during kindling in either of these structures. Wada and Sato (1974, 1975) showed that the MRF in cats displayed a unique electrographic pattern of development, associated with the bilateral generalization of the convulsion and the appearance of spontaneous recurrent seizures. The lack of such development in the present Experiments 1 and 2 is likely in part due to a difference in electrode location within the MRF.

## SUMMARY

The role of the forebrain commissures in the development of kindled amygdaloid seizures in the rat was investigated in the first two experiments. Bisection of the corpus callosum, hippocampal commissure, and anterior commissure significantly facilitated the rate of primary-site siezure development. The results suggest that interhemispheric connections via the forebrain commissures are able to inhibit the devleopment of kindled seizures. In the bisected rat, an increase in the rate of formation of limbic-brainstem pathways critical to kindling was suggested as a further explanation for the facilitated seizure development. The present studies also found that the forebrain commissures participate in the interference phenomenon but not in the transer effect.

In the last experiment, the role of the corpus callosum and hippocampal commissure in the kindled rat was investigated. Bisection of these structures caused a significant facilitation in secondary-site kindling but a marked reduction in the intensity of the seizure.

The results of the present studies suggest that the corpus callosum and hippocampal commissure are likely the principle routes used in the development of generalized kindled motor seizures. Bisection of these pathways after kindling renders a significant number of rats subsequently incapable of displaying this type of seizure. However, if these structures are bisected prior to kindling, the development of generalized convulsions is retarded but not stopped. These differences are presumably attributable to the establishment of alternate routes for seizure generalization, in the rat that has undergone forebrain bisection prior to kindling.

Bisection of the anterior commissure alone was not sufficient to disrupt the propagation of afterdischarge into the contralateral amygdala (Experiments 1 and 2). The rostral corpus callosum and hippocampal commissure are additional pathways for the interamygdaloid propagation of afterdischarge. Furthermore, the lack of afterdischarge in the contralateral amygdala did not disrupt the transfer effect.

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