EPILEPTOGENIC MODIFICATION OF THE RAT FOREBRAIN

Ph.D. W. McIntyre Burnham Psychology

EPILEPTOGENIC MODIFICATION OF THE RAT FOREBRAIN BY DIRECT AND TRANS-SYNAPTIC STIMULATION

ABSTRACT

An investigation was made both of normal (primary-site) seizure development and of the accelerated development found at secondary stimulation sites (Racine's "transfer effect").

Primary development involved progressive growth in afterdischarge, afterdischarge propagation and convulsive behavior. It was noted that afterdischarge growth took place not gradually but in sudden, large increments.

Transfer was found at all secondary limbic sites after primary limbic stimulation, but not in the amygdala after neocortical stimulation. It was associated with the early appearance of long afterdischarges and super-normal propagation.

Post-transfer suppression of primary site motor seizures (previously reported by Goddard et al.) was found, but only in limbic sites, and only after secondary stimulation of the amygdala. Sometimes during post-transfer stimulation, cortical discharge was seen to produce long "subcortical-type" seizures.

It is argued that both primary seizure development and transfer are related to the development of propagated reactive discharge.

EPILEPTOGENIC MODIFICATION OF THE RAT FOREBRAIN BY DIRECT AND TRANS-SYNAPTIC STIMULATION

by

W. McIntyre Burnham

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Department of Psychology
McGill University
Montreal

July, 1971.

ACKNOWLEDGEMENTS

I am indebted to a number of people for advice and assistance which have materially advanced the research project reported here. Thanks are due to Doctors Ronald Racine and Graham Goddard for valuable advice and discussion, and to Dr. Racine in particular for critical reading of the whole thesis, to Dr. Michael Corballis for statistical consultation, to Dr. Racine, David Kernaghan, Joseph Vanagas and Paul Godbout for technical help with the stimulating and recording equipment, to Ann S. Pellegrino and Jean St. Cyr for assistance with histology, to Mr. Charles Hodge, Mr. Karl Holoczek and Mr. Bruno Klingner for help with the preparation of the figures, and to my wife, Carole, for assistance in collating the data and typing rough drafts.

ABSTRACT

An investigation was made both of normal (primary-site) seizure development and of the accelerated development found at secondary stimulation sites (Racine,s "transfer effect").

Primary development involved progressive growth in afterdischarge, afterdischarge propagation and convulsive behavior. It was noted that afterdischarge growth took place not gradually but in sudden, large increments.

Transfer was found at all secondary limbic sites after primary limbic stimulation, but not in the amygdala after neocortical stimulation. It was associated with the early appearance of long afterdischarges and super-normal propagation.

Post-transfer suppression of primary site motor seizures (previously reported by Goddard et al.) was found, but only in limbic sites, and only after secondary stimulation of the amygdala. Sometimes during post-transfer stimulation, cortical discharge was seen to produce long "subcortical-type" seizures.

It is argued that both primary seizure development and transfer are related to the development of propagated reactive discharge.

TABLE OF CONTENTS

INTRODUCTION

Basic Terms and Definitions

"Epilepsy" is a relatively common pathological state characterized by recurrent episodes of convulsions and/or unconsciousness. The same syndrome created for research purposes in an experimental animal is termed "experimental epilepsy." Experimental epilepsies naturally offer a number of research opportunities which "clinical" (naturally occurrent human) epilepsies do not, and they play a large role in modern investigation of the condition.

The patterns of excessive, hypersynchronous neural firing basic to both clinical and experimental epilepsies are termed "discharges," or, if they occur in response to a specific stimulus, "afterdischarges." In clinical epilepsies, widespread ("generalized") discharge patterns are often found to originate in one particular area of epileptically active tissue, the epileptic "focus." The term "focus" is also applied to the site of experimental "irritation" in an animal preparation.

The spread of discharge from a focus into related tissue is termed "propagation." The propagated discharge which results in secondary sites may be either "projected" (in which

the secondary structure responds passively to volleys from the focus with a series of evoked potentials) or "reactive" (in which the secondary structure is driven to self-sustained independent epileptic activity).

The term "seizure," sometimes applied to a wide variety of epileptic manifestations, will, in this thesis, be applied only to the behavioral convulsions which represent the motor outflow of epileptic discharges ("motor seizures"). Seizures may be described as either "partial" or "generalized" (involving only part or all of the body) and as either "tonic" or "clonic" (involving steady contraction or alternate contraction and relaxation).

No attempt will be made here to summarize the vast literature on epilepsy. A number of useful reviews are already available. Gastaut and Fischer-Williams, 1959, and Robb, 1965, present concise summaries of basic experimental and clinical research, and Penfield and Jasper, 1954, offer a more extended discussion. Jasper, Ward, and Pope, 1969, present a broad survey of the whole field of modern experimentation.

Epilepsy and Learning

It has recently been suggested (Morrell, 1961b) that the

development of generalized discharge patterns in the brain may be based on a neural reorganization similar to that normally involved in the process of learning. If true, this suggestion would be of particular interest from the learning theorist's point of view since the proposed neural changes could be found in the mammalian forebrain where learning might reasonably be presumed to occur. (Other proposed learning analogs have tended to involve invertebrate preparations or the lower parts of the mammalian nervous system. See Thompson, 1967, or Milner, 1970, for reviews.) Unfortunately, it cannot yet be taken as established either that epilepsy is a progressive condition or that its progress (if such progress exists) is related to the process of learning. Still, there is some suggestive evidence on both these points.

Evidence of the progressive development of epileptic activity has been obtained from experimentation with animal preparations. Several types of experimental focus (e.g. freezing, aluminum hydroxide) cause convulsions not immediately but only days, weeks or months after their creation (see Penfield and Jasper, 1954; Kreindler, 1965). Electrographic recording in brains treated with such irritants shows a progressive development of electrographic discharge (see, for

instance, Morrell, 1960; Wada and Cornelius, 1960) and in some cases, independent secondary foci are even seen to develop outside the area of the original experimental lesion (Morrell, 1960; Wada and Cornelius, 1960; Guerrero-Figueroa et al., 1964; Morrell et al., 1965; Proctor et al., 1966). An experiment by Delgado and Sevillano (1961) in which progressive epileptic development was seen to result from repeated electrical stimulation seems to rule out the possibility that these changes result from further development of the lesion or the spread of epileptogenic material in the brain.

Progressive development is apparently far less evident in clinical epilepsies (perhaps because patients seldom come under careful observation until motor seizures have already developed) and clinically-oriented discussions often ignore the possibility altogether (e.g. Robb, 1965). There are, however, several characteristics of human epilepsy which suggest that it too may be the result of a process of development. There is, for instance, often an "incubation period" of months or years between a brain injury and the onset of subsequent clinical seizures (Penfield and Jasper, 1954; Penfield, 1956). Likewise, secondary foci are sometimes seen to develop in human brains (Hughes, 1966; see Morrell, 1960,

for a bibliography of earlier studies) and partial seizures are sometimes seen to evolve into full scale generalized attacks (Penfield and Jasper, 1954).

Evidence linking the development of epilepsy to the learning process comes from several different lines of research:

1) Experiments with Mirror Foci One line of evidence comes from Morrell's experimental analysis of the "mirror focus" (Morrell, 1960, 1961b). "Mirror focus" is the term applied to the area of secondary discharge which can develop in homologous tissue contralateral to a primary epileptic focus. It had long been believed that such secondary foci could eventually gain independence and continue their activity after the excision of the primary foci. Working with experimental preparations in animals, Morrell was able to show that this was, in fact, the case. The development of such independence in the secondary focus was, he found, associated with a shift towards hyper-excitability in the secondary tissue (evoked potentials were super-normal in the second focus). This hyper-excitability appeared to represent a permanent change in the secondary tissue and seemed to be based on some sort of structural or chemical modification rather than on a process of dynamic reverberation (the secondary focus remained epileptically

hyper-excitable for some months even in an isolated and electrically "silent" cortical slab). In its permanence, this shift towards epileptic hyper-excitibility resembles the neural reorganization which must occur in learning. In Morrell's words, "the mirror focus is a region which has not only 'learned' to behave in terms of paroxysmal discharge, but which 'remembers' this behavior even after months of inactivity" (Morrell, 1961b).

2) Experiments with Epileptic Conditioning A second line of evidence relating epilepsy to learning comes from studies of the conditioning or extinction of epileptic activity. One group of such studies has grown out of attempts to treat sensory-evoked (reflex) seizures in human patients. The term sensory-evoked is applied to those clinical epilepsies in which attacks are precipitated by more or less specific patterns of sensory input. The possibility has been considered that such seizures are conditional reflexes, and attempts have been made to extinguish them (see Forster, 1969, for a useful review). It has been found that sensory evoked epilepsies can in fact be modified (both worsened and improved) by conditioning techniques. While the worsening of such conditions may be a true example of conditioning, the beneficial effects

of such therapy seem to result from the temporary elevation of seizure thresholds rather than from "extinction" in the classical sense, and it seems unlikely that sensory-evoked epilepsies do in fact represent conditional reflexes (Forster, 1969).

More directly related to the problem of epilepsy and learning, perhaps, are the demonstrations of the conditioned elicitation of epileptic phenomena in experimental animals. Not only has it been reported that the discharge and seizures produced by epileptogenic lesions may be brought under sensory control by conditioning procedures (Morrell and Naquet, 1956; Forster, 1969), it has also been reported that conditioned stimuli may evoke discharge (Ungher and Steriade, 1960; Naquet and Morrell, 1967) and seizures (see reviews by Ungher and Steriade, 1960; Kreindler, 1965) in animals with intact nervous systems.

The results of the experiments on animals with epileptogenic lesions are not surprising in the light of Doty and Giurgea's work on "cortical conditioning" (Doty and Giurgea, 1961). It seems quite reasonable that the activity evoked by sensory input could become associated with activity in an epileptic focus. The results on animals with intact brains are far more

striking. These results seem to indicate that an epileptic discharge pattern can be "learned" by the brain and repeated later in the absence of the original stimulus.

3) Experiments with Threshold Reduction in "Bright" and "Dull" Animals A third line of evidence linking epilepsy and learning comes from some recent experiments on epileptic discharge threshold in rats. Racine (1969) implanted stimulating electrodes in the cortices of 40 rats. He then rated his subjects as "bright" or "dull" on the basis of a successive discrimination task, and as "emotional" or "non-emotional" on the basis of open field scores. Animals at the extremes of both dimensions were then subjected to daily low-level electrical brain stimulation and measurements were taken of the reduction in the threshold for epileptic afterdischarge which resulted. No significant differences in threshold reduction were found between the "emotional" and "non-emotional" subjects, but the "bright" and "dull" groups did differ significantly. More threshold reduction was seen in the "bright" subjects, which seems to suggest a correlation between the neural changes involved in learning and those involved in the development of epileptic discharge.

None of the studies described above can be considered to

offer conclusive proof of a relationship between the mechanisms basic to learning and the development of epilepsy. Morrell's experiments, for instance, apparently lacked controls for the denervation supersensitivity which is said to occur in isolated cortical slabs (Sharpless, 1969), and Forster and his associates (Forster and Chun, 1962; Forster, Chun and Forster, 1963) have been unable to obtain conditioned afterdischarge or seizures in animals with intact nervous systems. Leech, one of Goddard's associates, has recently failed to find differences in rates of seizure development in bright and dull strains of mice (Leech, Personal communication). Still, all of these studies are suggestive of such a relationship and certainly justify the careful scrutiny of epileptic development by researchers concerned with the learning process. Recently several psychologists have undertaken such studies of the epileptic development which results from repeated low-level electrical stimulation.

Recent Psychological Studies of Epilepsy as a Progressive Process

Psychological research on the developmental aspects of epilepsy was pioneered by Graham Goddard and his associates. Goddard's work stemmed from the accidental production of motor seizures in rats that were being subjected to daily electrical

brain stimulation through electrodes chronically implanted in the amygdala (Goddard, Personal communication). Retesting his subjects after a considerable lapse of time, Goddard found the convulsive response to be quite long-lasting and realized that it might be exploited as a learning analog something like Morrell's mirror focus. He chose to call it the "kindling effect" (see Goddard, 1967 a and b; Goddard et al., 1969).

Goddard was not the first experimenter to discover that electrical stimulation could cause seizures (Fritch and Hitzig discovered this effect in 1870; see Ward, Jasper and Pope, 1969) nor even the first to produce seizures through repeated low-level electrical stimulation (see Newman and Feldman, 1964; Herberg and Watkins, 1966; Delgado and Sevillano did a full scale study of the evolution of seizures due to repeated hippocampal stimulation in 1961). Goddard appears, however, to have been the first investigator to appreciate the potential theoretical significance of this preparation and he and his associates have been the first psychologists to explore it extensively. Whether or not the preparation eventually provides a useful learning analog, it will still represent a considerable contribution to the study of the development of epilepsy since, as Morrell has noted, it "substitutes a well controlled and

defined electrical stimulus under precise experimental control for the far more variable, chronic epileptogenic lesion which exerts its effect in its own good time and to its own individual degree," (Morrell, 1969).

Goddard's basic kindling procedure consisted of the implantation of one chronic stimulating electrode in each subject, a week or more of postoperative recuperation, and then stimulation once each day for one minute with biphasic one millisecond pulses at a rate of 60 Hertz and an intensity of 50 microamperes peak to peak. Both square and sine waves were used and found to be roughly equivalent.

Early kindling stimulations typically had little or no effect on a subject's behaviour. With repetition, however, the same low level of stimulation came to have more and more effect, as behavioral arrest, facial "automatisms" (partial seizures such as eye blinking and chewing movements), and finally full scale generalized clonic convulsions began to occur. Once generalized convulsions had begun, they appeared quite regularly, and not even non-stimulation intervals of up to three months served to seriously diminish the response (Goddard, 1967 a and b; Goddard et al., 1969).

Much of Goddard's basic work was done on the Wistar rat,

but he was also able to kindle other strains of rats, and also cats and monkeys. Likewise, though much of his work was done with amygdaloid stimulation, the basic effect was also obtained from a large number of other forebrain sites including most of the rhinencephalic-limbic structures and the basal ganglia. "Negative" sites (stimulation discontinued after 200 days without eliciting seizures) were found in the cerebellum, midbrain, and most of the neocortex and associated thalamus. One small area in the anterior neocortex did prove to be "positive," though the seizures elicited differed in type from those triggered elsewhere. Goddard et al. termed this area the "anterior limbic field" (Goddard et al., 1969).

The number of stimulations necessary to evoke seizures was found to vary both with the length of the inter-trial interval (intervals shorter than 24 hours were increasingly inefficient and more stimulations were necessary) and with the site of stimulation. Average rates in the different "positive" structures varied from 15 (the amygdala) to 77 days (the hippocampus). In general, Goddard et al. suggested, there was a trend for the number of days to first convulsion in the other sites to correspond roughly to the extent of their anatomical connections to the amygdala.

Although the rate of kindling was affected by site of stimulation and inter-trial interval, it appeared to be relatively independent of other parameters of stimulation. Below a certain threshold for each parameter, no kindling was seen, but above the threshold, different lengths, frequencies and intensities of stimulation all had approximately the same effect.

Although Goddard et al. did not attempt to formulate any complete model of the kindling effect, they did offer some basic suggestions about the neural processes involved. The neural basis of the effect did not seem to be either the sensitization or pathological irritation of tissue near the electrode tip: studies with different types of electrodes and different stimulation schedules had ruled out all the more obvious sorts of local damage, and the finding that even very high levels of stimulation (currents up to 10 milliamperes) did not elicit kindling-type seizures at the start of stimulation seemed to rule out local sensitization (Goddard et al., 1969). Kindling seemed, rather, to result from some sort of neural "reorganization" based upon the repetition of the stimulating current. A study which proved that seizures could still be elicited (at higher threshold), even after electrolytic

destruction of all the tissue near the electrode tip, suggested that the reorganization must be at least in part trans-synaptic.

A second series of studies undertaken by Racine (1969) expanded and extended the scope of Goddard's model by introducing the technique of electrographic recording. Racine's procedure was much like Goddard's except that he took bipolar E.E.G. records before and after each stimulation, stimulated near afterdischarge threshold, and used one second instead of one minute of stimulation (one second proved just as effective). Racine also implanted second or even third electrodes in order to gather data on the trans-synaptic changes that Goddard had postulated.

Racine's studies revealed a number of interesting facts about the electrographic phenomena underlying the kindling effect. The seizures resulting from kindling proved, as expected, to be the result of afterdischarge generated by the stimulating current. Racine, like Goddard et al. found two types of seizure: neocortical, and subcortical (or limbic). The cortical seizures (Goddard et al.'s "anterior limbic field" seizures) could be evoked <u>immediately</u> from a large area of anterior neocortex, provided only that the intensity of stimulation was sufficient to cause afterdischarge. Subcortical

seizures, however, as Goddard had suggested, never occurred immediately, even when discharge was present. They developed only after a period of stimulation. This development, as Racine was able to show, was a direct function of the repetition of afterdischarge. Each discharge contributed the same amount to the onset of seizures regardless of the level of supra-threshold stimulation used to evoke it. Stimulation which did not cause afterdischarge did not advance the process of seizure development. This dependence of seizure development on afterdischarge presumably explains why Goddard et al. found kindling rates to be relatively independent of stimulus intensity, frequency or duration. Pinsky and Burns (1961) have shown afterdischarge to be independent of just the same parameters of suprathreshold stimulation.

Like Delgado and Sevillano, Racine noticed several long term changes in afterdischarge which occurred as testing continued. (These were particularly marked in subcortical afterdischarge.) Discharges grew both in duration and in amplitude, frequency of spiking increased, more complex spike forms were seen, and more propagation occurred in secondary sites. Primary site afterdischarge thresholds also dropped regularly, often by as much as 60%. (In the cortex and the

hippocampus short term threshold rises sometimes masked the long term reductions during the actual period of stimulation. These short term rises disappeared, however, after a week's "rest," revealing an actual threshold drop. They were not seen at all when stimulation was given on every second day.)

There appeared to be at least a rough correlation between some of the changes in subcortical afterdischarge and the process of seizure development. Many subjects, for instance, showed a sudden increase in primary site discharge duration and in secondary site discharge amplitude just a few days before the onset of full scale ("Stage 5") seizures. No correlation could be found, however, between seizure development and the reductions which were seen in primary site afterdischarge thresholds. The subjects showing the largest or quickest reductions in afterdischarge threshold were not necessarily the subjects that showed the quickest progression to seizures. Moreover, threshold reduction, unlike seizure development, could be caused by subthreshold stimulation. When low levels of stimulation were used, threshold reduction sometimes played an indirect role in seizure development by causing the eventual onset of afterdischarge. It seemed, however, to be a different neural process. This finding of a difference between threshold

reduction and seizure development is very much in line with Goddard et al.'s conclusion that kindling is not based on local sensitization. As Racine points out, however, it suggests a need for the reassessment of Goddard's data on kindling rates from various brain sites. Because of Goddard's low fixed stimulation, much of his early stimulation probably served only to lower thresholds to the point where afterdischarge began and seizure development started. His measurements therefore may confuse the two processes. This is certainly true in the case of the cortex, where he reports an average kindling rate of 29 days.

Racine's tests of response to stimulation at secondary placements revealed some interesting facts about the trans-synaptic aspects of threshold reduction and seizure development. Threshold reduction seemed, in general, to be confined to the site of actual stimulation. Although he checked in a number of secondary sites after primary site threshold reduction, Racine found only one in which trans-synaptic threshold reduction had taken place, Layer 6 of Area 6 in the anterior neocortex when the contralateral Area 6 was stimulated. In other secondary sites threshold changes were usually trivial, and threshold rises were seen as often as threshold reductions. In one instance, the hippocampus after contralateral hippocampal stimulation, a <u>significant</u>

rise in threshold was recorded.

Unlike threshold reduction, seizure development did appear to involve trans-synaptic changes. After seizures had been developed at one site, other sites also tended to show a greatly enhanced potential for triggering them. In subcortical structures this enhanced potential was reflected in shorter than normal rates of seizure onset, with seizures sometimes occurring even on the first afterdischarge. In the anterior cortical placements, where seizure always accompanied afterdischarge, the enhanced triggering potential took the form of unexpectedly strong seizures with early tonic extension. Racine termed this spread of enhanced seizure triggering potential the "transfer effect." Transfer was found both between contralateral homologous structures (the amygdala, the hippocampus and the anterior cortex) and contralateral non-homologous structures (the septal area after contralateral amygdaloid seizure development, and cortical Area 40 after seizures had been evoked in the contralateral Area 6). Racine failed to find transfer, however, between the amygdala and the contralateral hippocampus.

The trans-synaptic nature of the neural reorganization involved in transfer was indicated by the fact that the phenomenon

occurred full strength even after the primary focus had been destroyed before the start of secondary site stimulation. Racine suggests that this reorganization might result from the propagation of reactive discharges into secondary sites, each reactive secondary discharge acting like an electrically evoked discharge to promote secondary site seizure development (Racine, 1969).

Goddard was originally somewhat skeptical about the transfer effect (Goddard, 1967a), but eventually he and his group were able to demonstrate it in their own laboratory using their own technique (Goddard et al., 1969). In their experiments transfer was demonstrated between the contralateral amygdalae and between the amygdala and the ipsilateral septal area (Goddard et al., 1969). They also discovered a further aspect of the phenomenon. After a few seizures had been evoked at the secondary site, stimulation of the first site no longer evoked seizures. A few primary site stimulations were necessary to re-establish them. Subjects left unstimulated even for long periods do not show such a failure in seizures, so the effect appears to have resulted from the secondary stimulation rather than from the mere passage of time.

Goddard et al. found this post-transfer suppression of primary

site seizures between the contralateral amygdalae, and between the ipsilateral septal area and amygdala. They called it "retroactive inhibition" (in reference to the learning analogy) and suggested that during transfer testing, the "convulsive circuits" might partially lose their "connection" with the first site (Goddard et al., 1969). Racine (1969) has suggested the alternative hypothesis that nothing more is involved than an inhibition of primary site discharge due to the sort of trans-synaptic threshold elevation he had demonstrated in the hippocampus. Actually, Racine had not demonstrated significant threshold rises at the sites where Goddard et al. found "retroactive inhibition," but since Goddard et al. did not do electrographic recording, the problem remains unsettled.

The Present Problem

The present study represents a further exploration of the progressive development of epileptic activity as it is seen in Goddard's electrical stimulation preparation. Particular attention was given to the phenomenon of transfer, the accelerated seizure development seen at secondary sites, in the hope of learning more about the trans-synaptic aspects of seizure development. As in Racine's studies, extensive use was made of electrographic recording.

Previous studies had already provided a good deal of data on contralateral homologous transfer, so the present study concentrated on transfer between non-homologous, ipsilateral sites. Transfer was tested between several different types of structure (see Table 1) in order to give as complete a picture of the phenomenon as possible. Careful comparisons were made between the afterdischarges and seizures evoked from the various sites during transfer testing and those evoked during normal primary stimulation and records were also kept of the previous occurrence of reactive discharge at the transfer sites since Racine has suggested that such secondary reactive discharge may be basic to the phenomenon.

An attempt was made to correct certain methodological faults of previous transfer studies: all subjects were given the same number of seizures before transfer (not done by Racine) and electrographic records were always taken (not done by Goddard et al.). A good number (10) of primary site seizures were administered to ensure that transfer would be seen clearly if it were present.

Although transfer provided the main center of interest for the study, primary site seizure development was not neglected. Careful records were also taken of the development of primary

site epileptic activity and these are reported fully below both for purposes of comparison and because they are of interest in their own right. Primary site response was also investigated after the period of transfer testing in order to provide electrographic data on the phenomenon of post-transfer seizure suppression reported by Goddard et al.

METHODS

Subjects Seventy-eight male, black-hooded rats of the Royal Victoria Hospital strain served as the subjects of the present experiments. They were obtained from the Quebec Breeding Farm (Sainte Eustache, Quebec), housed two or three to a cage in 12" x 14" x 7" clear plastic colony cages, maintained on "ad lib" water and Purina Rat Chow, and handled regularly. Each subject was chronically implanted with stimulating-recording electrodes in two homolateral forebrain sites. Subjects' weights ranged from 240 to 280 grams at the time of surgery.

Electrode Placements The majority of implantations were made in three subcortical structures: the amygdala, the septal area, and the hippocampus. Among them, these three structures allowed the testing of several different types of transfer: transfer between directly and non-directly connected structures; transfer between structures with strong and weak propagation; and transfer between "old" cortex and subcortical structures. (Table 1 indicates the pairs of structures used in transfer testing and briefly summarizes their relationships.) Special attention was given to the hippocampus, where Racine had previously failed to find transfer. Its dorsal and ventral parts were tested separately, since they

are known to have different patterns of afterdischarge and afterdischarge propagation, (Elul, 1964 a and b).

Plans to examine subcortical-cortical transfer were abandoned when it proved too difficult to distinguish "strong" and "weak" cortical seizures. One cortical-subcortical group (motor cortex to amygdala) was tested, however, to try for transfer between the two different "seizure systems."

Electrodes Electrodes were made of two strands of 0.01 inch insulated nichrome wire twisted together to form a straight, relatively stiff shaft. One end of the electrode was prepared for receiving leads by soldering a male connector (Winchester Plugs, SMRE-P) to each strand and fixing the two connectors half a centimeter apart with a small application of dental cement. The other end of the electrode was cut to a length appropriate to its intended site, leaving the uninsulated tips about 0.25 mm. apart. Each electrode was checked for shorts and leaks in the insulation before it was implanted.

Surgical Implantation of Electrodes Twelve hours before surgery, each subject was moved from its colony cage into a 13" x 8" x 5" individual cage which was supplied with water but no food. An injection of atropine was administered one-half hour before anesthetization to reduce the chances of respiratory congestion.

Anesthesia was induced through an intraperitoneal injection

of 40 mg/kg sodium pentobarbital (Nembutal), additional injections of chloral hydrate being administered as needed during the course of the operation to maintain a steady level of anesthesia. After anesthesia had been established, the subject was ear-marked and injected intramuscularly with 30,000 units of penicillin (Bicillin 300 LA). Its scalp was shaved and painted with tincture of merthiolate, its head fixed in a stereotaxic instrument (Kopf, Model 900), and its skull exposed by a mid-line incision of the scalp. Holes for the electrodes were drilled at appropriate sites and four jewellers' screws were inserted into the skull to provide anchorage for the emplacement. One of these had a male connector attached to serve as the ground electrode. The electrodes were then stereotaxically lowered to an appropriate depth in the brain, and, after the skull had been thoroughly dried with a stream of filtered compressed air, were fixed in place with an application of dental cement which also covered the jewellers' screws. The wound was closed either by a second application of dental cement or by suturing with surgical silk. The external surfaces of the wound were dusted with a topical antibacterial powder (Furacin).

After the incision had been closed, the subject was injected intraperitoneally with Mikedimide, a barbiturate

antagonist, and returned to an individual cage where it was maintained for a week without handling, on ad lib food and water. At the end of the week, it was given a second injection of penicillin (30,000 i.u.) and returned to a colony cage, where regular handling was resumed. Two weeks of post-operative recovery were allowed before stimulation was begun. Superficial infections which sometimes appeared about the emplacement were treated with topical applications of a 1:1000 aqueous solution of zephiran chloride or of ointment containing the antibiotic Bacitracin.

Apparatus for Stimulating and Recording Stimulation and recording took place in a room shielded to minimize electrical interference in the records. The subject was tested in a box 12" wide, 12" deep and 20" high which was constructed of wire mesh. Three walls and the floor of the box were lined with thick cardboard to reduce static electricity. Observation took place through the fourth side, which was unlined. A 7" x 9" mirror attached to one of the cardboard sides assisted observation. The top of the box was open to provide for free movement of the leads from the recording and stimulating equipment.

All recording was bipolar. Two pairs of light-weight, low-noise, shielded cables (Microdot, Inc.) led the signals

from the subject to a Grass Model 7 Polygraph, where they were amplified by Wide Band A.C. Preamplifiers and recorded by an ink-writer.

Stimulation was applied to the brain through the same leads used for recording, the Polygraph connection being switched off by an automatic relay during the period of stimulation. Two Grass SD5 Stimulators, co-ordinated to provide the biphasic pulses and feeding a constant current adapter, supplied the current. A relay timer determined the duration of the pulse train. The intensity of stimulation was monitored on a Tektronix Type 502 Dual Beam Oscilloscope.

Stimulation Parameters The standard stimulation used in all experiments was a one second train of bipolar, bisymmetrical 60 Hz square wave pulses. Each pulse consisted of one millisecond of negative stimulation followed, after a tenth of a millisecond interval, by one millisecond of positive stimulation. Intensity varied from subject to subject and from condition to condition as described below.

Data Recording and Scoring E.E.G. records were taken for 20 seconds before and 2½ minutes after each stimulation. Short-hand notes were made on the records describing the subjects' behavior. When seizures occurred, their onset and duration were indicated by means of a remote control polygraph

marking pen.

"Discharge" was scored whenever clear-cut spiking could be seen above the normal background activity. Propagated discharge was scored as "reactive" whenever clear, site-typical spikes as large as those resulting from direct stimulation appeared. (Each subject's records contained examples of the response of each site to direct stimulation.) This criterion of reactive discharge differed somewhat from the criterion previously used by Delgado and Sevillano. Delgado and Sevillano (1961) scored propagated discharge as "reactive" when they observed a site-typical discharge rhythm in the secondary structure (e.g. 4-6 per second in the amygdala). In the present study, clear-cut site-typical rhythms were not seen (see the second section of Results and Discussion) and so amplitude was used as a criterion instead. This criterion, like any criterion based on gross recording, should probably be considered as only an estimate of reactive discharge.

Workers in this field have varied somewhat as to what they have scored as a seizure. In the present study, a seizure was scored whenever clear-cut convulsive jerking was present not only in the face and head but also in some other part of the limbs or body. A seizure was scored, in other words, when partial seizures of the face and head were seen

to generalize. This criterion is probably fairly close to that used by Goddard et al., (1969), but is somewhat less stringent than that used by Racine (1969). (Racine's "full" motor seizure had to involve both rearing and falling.) The latency of a seizure was scored as the interval between the offset of stimulation and the start of generalized seizure activity, and its duration was scored as the period during which generalized seizure activity persisted. Strength of seizure was scored in terms of Racine's "seizure stages":

Stage 3 - forelimb clonus

Stage 4 - rearing

Stage 5 - rearing and falling

(Racine's Stages 1 and 2 describe partial seizures.)

Test Procedures At the start of testing, all the subjects with electrodes in a given pair of structures were sorted randomly into two groups of equal size. Stimulation was begun in one of the structures in the first group and in the other structure in the second. Transfer was always tested in both directions between a given pair of structures, so that each group could serve as the other group's control.

Testing involved five different steps:

1) Afterdischarge Threshold Testing at the Primary Site

Afterdischarge threshold testing at the primary site was begun

on the fourteenth day after surgery and took from one to two weeks. Racine's (1969) method was adapted for the purpose. Stimulation was started at the expected lower end of the range of effective currents for the structure involved. (Racine's work provided a basis for this estimate.) If no afterdischarge occurred on the first stimulation, the intensity was doubled and doubled again on subsequent stimulation days until an afterdischarge did result. If an afterdischarge occurred immediately, intensity was halved and halved again on subsequent days until afterdischarge failed to occur. Both of the above procedures served to establish the threshold as falling within a given interval. When this interval had been established, it was reduced on subsequent stimulation days by the "half-split" method until it was no larger than one-fifth of its upper limit. The midpoint of the remaining interval was designated as the afterdischarge threshold.

Stimulation was given on every second day (6 days a week). This schedule was used during threshold testing and during several other crucial test periods to eliminate the "fatigue" effects (threshold elevation, afterdischarge shortening) that Racine (1969) found to result from daily suprathreshold stimulation.

2) Stimulation of the Primary Site (Seizure Development)

Stimulation of the primary site was begun on the day after the completion of threshold testing and was continued until ten generalized motor seizures had been evoked. This period varied, according to the subject, from several weeks to several months. The intensity of stimulation used was calculated separately for each subject by adding 30% to its afterdischarge threshold. This slightly elevated intensity was used in order to minimize the effects of "fatigue" or threshold oscillation. Occasionally "no discharge" days occurred even at this level of stimulation. If three such days occurred in a row, or if six occurred in the course of a test series, the subject's stimulation intensity was increased by 50%. Daily stimulation (5 days a week) was employed until seizure onset, after which the 48 hour schedule was resumed. The daily schedule was adopted to economize on time during the long period of primary stimulation. It seemed justified by Goddard's finding that the rate of seizure development is independent of intertrial interval provided that the intervals are over 12 hours.

3) Stimulation of the Secondary Site (Test for Transfer)

Stimulation of the secondary site was begun two days after the elicitation of the tenth primary site seizure and was

continued until five generalized motor seizures had been evoked from the second site. The period of stimulation varied according to the subject from under two weeks to over two months. Since no afterdischarge threshold testing was done at secondary sites, a standard secondary intensity was calculated for each structure by doubling the average threshold found in primary subjects at that site. This intensity caused immediate afterdischarge in most subjects. If afterdischarge did not occur on the first secondary stimulation, increments of 50% were made in stimulation intensity on subsequent stimulation days until it appeared. Stimulation was normally administered on every second day. If no generalized motor seizure had occurred by the third day of stimulation, however, subjects were switched to a daily stimulation schedule in order to equate conditions to those of primary site seizure development. Daily stimulation was continued until the occurrence of the first secondary-site seizure.

4) Resumption of Stimulation at the Primary Site (Test of Afterdischarge Duration) This test was given to five subjects from each primary group and was designed to see whether the brief afterdischarges seen at certain previous stages of testing might be characteristic of "near threshold" levels of stimulation. Testing was begun two days after the

last test in the series described above and usually took several weeks. Stimulation was administered every second day. Starting at its standard intensity, primary site stimulation was dropped by 10% of the standard on each test day until two "no afterdischarge" days had occurred in a row. If shortened afterdischarge had not been found, the threshold area was explored further.

Histological Technique After the final day of stimulation, subjects were deeply anesthetized with ether or sodium pentobarbital and perfused through the heart with physiological saline followed by a formal saline solution. Sites of stimulation were marked by the use of the Prussian Blue test for inorganic iron as described by Marshall (1940). After perfusion, the brains were removed from the skulls and soaked for at least three days in formal saline. Frozen sections were cut at 50μ, every fourth slice around the electrode tip being kept and mounted on gelatin-coated glass microscope slides. After drying, the slices were stained with thionin according to the progressive method outlined by Davenport (1960), and covered with Permount and cover glasses. A microscopic examination of each slice was made, and the locus of the electrode tip was recorded on diagrams taken from A Stereotaxic Atlas of the Rat Brain (Pellegrino and Cushman, 1967).

RESULTS AND DISCUSSION

Histological Findings

Figure 1 illustrates the electrode placements used in the present study, as verified by histological examination of the brains. Amygdaloid placements, in general, were in or near the baso-lateral septal nucleus. Hippocampal placements were scattered between the hippocampus proper and the fascia dentata. Cortical placements were in the cortical areas designated by Krieg (1946) as 6 and 10. Recent physiological work has indicated that in the rat these areas are part of M I, the primary neocortical motor area (Woolsey, 1958).

Each site in Figure 1 is numbered for reference. Primary and secondary sites for each subject are indicated in Table 2.

Stimulation of the Primary Site

Primary Site Afterdischarge Typical afterdischarge patterns for the five primary sites are illustrated in Figure 2. Previous investigators have sometimes distinguished local afterdischarge types on the basis of site-typical spike rates (e.g. Delgado and Sevillano, 1961; see Kreindler, 1965, for summaries). Such easily distinguishable local rates were not seen in this study. Spike rate was found to vary from point

to point within a single afterdischarge (see, for instance, the traces in Figure 10), and also from stage to stage of discharge development (compare early and late traces in Figure 5 or Figure 6). Perhaps site-typical discharge rhythms are better seen in acute preparations.

Several investigators have commented on the striking increases in afterdischarge duration which result from repeated low level electric stimulation (Delgado and Sevillano, 1961; Racine, 1969; Goddard as reported by Morrell, 1969). Morrell, discussing some of Goddard's data, has even described such growth as a "learning curve for epilepsy". Figures 3, 5, 6, 7 and 8 illustrate the development (if any) of afterdischarge with repeated stimulation in the five primary sites studied here. Table 3 presents group averages for neocortical and subcortical subjects on four crucial test days: the first preseizure afterdischarge; the last preseizure afterdischarge; the first seizure afterdischarge; the last seizure afterdischarge. (Detailed analyses of primary afterdischarge and seizure growth were done on <u>all</u> cortical subjects and on <u>samples of ten</u> subcortical subjects drawn randomly from each group.)

No significant growth was seen in neocortical afterdischarges. The discharges evoked on the last day of stimulation

looked much like those evoked on the first (Figure 3), and average durations did not differ significantly on the two days (Table 3A; $t = 2.1$, $df = 4$, $p > 0.05$). Growth "curves" plotted for individual subjects tended to resemble straight lines parallel to the x - axis (Figure 4).

In the subcortical groups, on the other hand, dramatic discharge growth was seen (Figures 5, 6, 7, 8). Average durations tripled or quadrupled in every group during the course of stimulation (Table 3B), and an analysis of variance for all subjects showed this tendency to be highly significant ($F = 61.0$, $df = 1$ and 36, $p < 0.01$). Further analysis showed that the greater part of the growth took place before the onset of motor seizures: there were significant increases between the first and last preseizure afterdischarges ($t = 4.3$, $df = 108$, $p < 0.005$), and between the last preseizure and first seizure afterdischarges ($t = 6.6$, $df = 108$, $p < 0.005$), but not between the first and last seizure afterdischarges ($t = 0.7$, $df = 108$, $p > 0.05$). There were no significant differences between the subcortical groups at any stage in testing ($F = 2.8$, $df = 3$ and 36, $p > 0.05$). The dorsal hippocampal group showed some tendency to lag behind the others, but the resulting interaction effect was not significant ($F = 2.2$, $df = 3$ and 36, $p > 0.05$).

These changes in subcortical afterdischarge duration were often accompanied by changes in several other discharge characteristics. As previously noted by Racine (1969), later and longer discharges tended to be marked by a higher frequency and amplitude of spiking and by more complex spike forms (see Figures 5-8). They were also more likely to be followed by post-ictal disturbances in the records: post-ictal depression, spiking and the secondary afterdischarge episodes which were originally typical only of hippocampal discharge, (see Figures 5-8). As Racine has previously reported, post-ictal spiking in the amygdala was sometimes seen to develop into a constant inter-ictal pattern.

Growth curves plotted for individual subjects revealed a further aspect of subcortical discharge development. At least in the amygdaloid and septal subjects, growth in afterdischarge duration occurred not gradually, but in a few sudden, large increments. Curves plotted for these subjects resembled a series of "steps" or "plateaus" (Figure 9 A-D). A rough similarity could be seen in the "plateaus" displayed by different subjects: there was sometimes a "plateau" around 10 seconds; usually a "plateau" around 20 seconds; usually a "plateau" around 40 seconds, and so forth (see Figure 9 A-D).

When E.E.G. records were examined at the points where

sudden increments occurred, the added segments of discharge were often found to have their own patterns, distinguishable from the original segments on the basis of amplitude, frequency or polarity (Figure 10). These added patterns sometimes resembled patterns more typically found at other stimulation sites (Figure 10; compare with Figure 2). Long discharges, (the result of two or three sudden increments) often consisted of several such distinguishable patterns (Figure 10C, SD 18). Onsets of post-ictal spiking and of subsequent afterdischarge episodes were also often seen to occur at the time of a sudden increase in afterdischarge duration (Figure 5, SD 8).

A somewhat different pattern of afterdischarge growth was seen in the dorsal and some of the ventral hippocampal subjects. In the hippocampus, active discharge is typically followed by a temporary depression of electrographic activity, the so-called "silent period" (Figure 2C and D; see also Figure 11), which may reflect the inhibitory influence of certain midbrain structures (Lissák and Endrócz, 1968). The silent period apparently inhibited the growth of active spiking in hippocampal subjects, for only small increases were seen in the pattern of large, site-typical spikes that

immediately followed stimulation (Figures 7 and 8). Propagated activity in secondary sites, however, showed a normal pattern of growth, and soon began to outlast the primary site discharge (Figures 7 and 8). After the growth of such secondary discharge, low amplitude waves or blunt spikes began to be seen in the hippocampal records during the silent period (Figure 11; Figures 7 and 8). It was the progressive development of these small waves which caused the growth of hippocampal discharges (Figure 11) and which gave them a gradual character very different from the incremental growth seen at the other subcortical sites, (Figure 9 E and F; a few ventral hippocampal subjects failed to show marked silent periods and also tended to show the incremental pattern of discharge growth normally seen in the amygdala and the septal area). It is interesting to note that similar low-amplitude waves or blunt spikes were also sometimes seen in the records of amygdaloid and septal subjects, occurring <u>just before</u> a sudden increment in discharge duration (Figure 12; see also Figure 10 A and B).

Growth curves plotted for individual subjects sometimes revealed large decreases as well as increases in discharge duration (see Figure 9). These sudden decreases usually involved the temporary disappearance of <u>all</u> of one or more of

the later discharge increments (Figure 10 C), and a return to a length characteristic of an earlier stage of testing (see Figure 9). They were usually associated with a pronounced decrease in propagation (Figure 10 C) and often with a failure of seizure activity (see Figures 7 and 8).

Discharge Propagated from Primary to Secondary Sites

At the outset, the secondary sites differed considerably in their degree of response to primary site discharge. In some secondary sites no driving at all was seen at first (Figure 13 A, ADl), in others small projected spikes occurred (Figure 13 B), and sometimes even the large, site-typical spikes which indicate reactive discharge were found (Figure 13 C). Table 4 indicates the percentage of subjects in each secondary group that showed an immediate response of any type to the first primary site discharge. Such immediate propagation was quite widespread, being found to a certain extent in every group. The amygdala appeared to be a particularly good "receiver", although not a particularly good "sender". The ventral hippocampus seemed to be somewhat better than the dorsal hippocampus both at "sending" and "receiving". Table 5 indicates the percentage of subjects in each secondary group that showed immediate reactive discharge. At this stage in

testing, reactive discharge was seen only between the septal area and hippocampus (it occurred in both directions) and from the ventral hippocampus to the amygdala.

With repetition, propagation of discharge into secondary sites tended to increase: non-responding sites developed projected spiking, and projected spikes grew gradually in amplitude until suddenly large site-typical reactive spikes appeared (Figure 13 A illustrates the whole sequence as it occurred in a single subject; see also Figures 5, 6, 7 and 8). Reactive discharge became more and more common (Table 6 indicates the average number of primary discharges necessary to cause reactive discharge in the various secondary sites), and was widespread by the time of seizure onset (Table 7), and almost universal by the end of the series of primary site stimulations (Table 8). Exceptions were seen only in two hippocampal subjects, #16 and #28, being driven by the amygdala, and in the amygdaloid subjects that were being driven by the anterior neocortex. These subjects showed only projected discharge even on the last day of testing (Figure 13 D). It is interesting to note that the sites which were quickest to show projected discharge were not always the quickest to develop reactive discharge. The amygdala, for instance, showed immediate projected response to septal and dorsal

hippocampal discharge (Table 5), but developed reactive propagation only fairly slowly when these sites were stimulated (Table 6). Averages for the total amount of reactive discharge seen in the various secondary sites during the course of testing are indicated in Table 9.

Primary Site Motor Seizures

1) Rate of Onset Goddard et al. (1969) reported that different amounts of stimulation were required at different forebrain sites to elicit motor seizures. Racine (1969) suggested that instead of measuring the number of stimulations to seizure onset, it would be better to measure the number of afterdischarges, since stimulation which does not cause afterdischarge apparently does not promote seizure development. Table 10 indicates the average number of afterdischarges which were required at the various sites studied in this experiment to elicit the first motor seizure.

A striking difference was seen between the number of afterdischarges necessary to cause seizures in cortical and subcortical subjects. As Racine (1969) had previously reported, seizure onset was found to be immediate in the anterior cortical subjects, the first afterdischarge causing the first seizure (Table 10 A). In all of the subcortical animals, on the other

hand, at least six afterdischarges were required to cause the first seizure (Table 10 B). There was no overlap between the two groups.

The subcortical groups differed significantly from each other as well as from the cortical animals ($F = 40.4$, $df = 72$, $p < 0.01$; see Table 10 B). The shortest average seizure onset was found in the amygdaloid group (10.6 afterdischarges) and the longest average rate in the dorsal hippocampal group (37.3 afterdischarges). The ventral hippocampus and the septal area had intermediate rates (20.6 and 17.4 afterdischarges, respectively). Comparison of the groups two at a time using the Scheffé method (Winer, 1962) revealed significant differences between all of them except the septal area and the ventral hippocampus (Table 10). It is interesting to note that the two hippocampal groups were significantly different from each other.

A further interesting observation was made with regard to the hippocampal subjects. Both in the dorsal and ventral groups there tended to be a bimodal distribution of scores within the group. It seemed quite possible that these differences in rate might reflect the anatomical difference between the hippocampus proper and the fascia dentata. Unfortunately,

many of the electrode tips were close to or in both substructures, but a few clear-cut placements were found. Observations on these few subjects were suggestive. In the dorsal hippocampus, two hippocampus proper subjects (#55 and #57) had rates of 25 and 27 afterdischarges to seizure onset, while two fascia dentata subjects (#62 and #63) both had rates of 43. In the ventral hippocampus, five hippocampus proper subjects (#66, #67, #70, #74 and #76) averaged 15.2 afterdischarges to seizure onset, while one fascia dentata subject (#75) had a rate of 27. In the other primary sites studied, placements were predominantly in one nucleus or complex and scores appeared to be distributed normally.

2) Seizure Types Two basic seizure types have been previously described by Racine (1969) and Goddard et al. (1969), "cortical" (triggered from the anterior neocortex) and "subcortical" (triggered from the various limbic and rhinencephalic structures). Both types were seen in the present experiment approximately as described in previous reports:

a) Cortical The motor seizures elicited by neocortical stimulation involved clonic movements of the mouth, head and forelimbs which were small though intense. The subject was

crouched or prone and seldom reared fully upright. The seizures began as soon as stimulation started, and lasted about 10 seconds (see Tables 11 A and 12 A).

b) Subcortical In the motor seizures elicited by subcortical stimulation clonic movements of the mouth, head and forelimbs were generally large and violent. The subject usually reared up onto its hindlimbs during the seizure, and often fell over. There was generally at least a short delay between the end of stimulation and the start of the seizure (Table 11 B). In well developed seizures, duration was seldom less than 20 seconds (Table 12 B).

A certain amount of variability was seen within the seizures of a given type. In subcortical seizures, for instance, subjects occasionally reared only very late in the seizure, or fell before they had fully reared. These variant seizures did not seem to represent real subtypes, however, since they were occasionally elicited from all the stimulation sites, and often alternated with more typical seizures in the records of individual animals. Basically, as Racine (1969) has suggested, the same seizure seems to be triggered from all the different subcortical sites.

Although the seizures evoked from different subcortical

sites were all similar in type, it seemed possible that they might differ in latency of onset or in duration. Table 11 B presents averages for latencies of subcortical seizures, and Table 12 B presents average durations. No significant differences could be found in the latencies of seizures evoked from different sites (Table 11 B) although there did appear to be a trend towards unusually short latencies in the amygdala during the latter stages of testing. A significant overall difference was found in the durations of the seizures evoked from different sites ($F = 3.7$, $df = 3$ and 36, $p < 0.025$; see Table 12 B). The major contributor to this overall difference seemed to be the dorsal hippocampal group, whose average seizure length was shorter than that found in any of the other groups. (Dorsal hippocampal seizures were significantly shorter than those evoked from the amygdala but not than those evoked from the septal area or ventral hippocampus. See Table 12 B.) Amygdaloid, ventral hippocampal and septal seizures did not differ significantly among themselves (Table 12B).

3) Seizure Development Little growth or development was seen in cortical seizures. These were identical in latency and duration to the afterdischarges which caused them and, like cortical afterdischarges, did not change significantly either

in latency or duration as they were repeated (Table 11 A, 12 A; Figures 14 and 15). Racine (1969) has reported the development of tonic extensions in later cortical seizures. Such tonic extensions were only rarely seen in the present experiments. This is not surprising, however, since the average onset of the tonic extensions reported by Racine did not occur until the sixteenth seizure and only ten seizures were given in the present experiment.

Growth and development did take place in subcortical seizures. This development really began well before seizure onset with the development of motor arrest and various localized seizure signs (eye blinks, mouth jerks, etc.). The progressive development of these partial seizures has already been thoroughly described by several previous investigators (Delgado and Sevillano, 1961; Goddard et al., 1969; Racine, 1969) and will not be re-examined here.

Progressive behavioral development did not stop with the appearance of the first generalized subcortical seizure. As subcortical seizures were repeated, they tended to occur with decreasing latencies and increasing durations. (Tables 11 B and 12 B indicate average latencies and durations of the first and last seizures in each subcortical group. For latency:

$F = 36.6$; df = 1 and 36; $p < 0.005$. For duration: $F = 14.5$; df = 1 and 36; $p < 0.005$, see also Figures 5 - 8.) Graphs of average latency (Figure 14) and duration (Figure 15) for each group suggest that the greatest part of these changes took place between the first and the fifth seizures.

Later seizures also tended to be stronger and better developed. In all the groups, subjects were significantly more likely to have Stage 5 seizures during their last two seizure days than during their first two (See Table 13. The two day measurement interval was used because of the variability of the response. Even long-stimulated and strongly convulsing subjects sometimes alternated Stage 4 seizures with their Stage 5 seizures.)

Individual seizure growth curves plotted for subcortical subjects generally showed the pattern of progressive growth which would be expected from the group averages (Figure 16 A-D). A good deal of random variation appeared (perhaps due to the random variation in discharge duration seen after seizure onset),

but basically, the pattern of growth seemed to be a gradual one, unlike the step-like increases seen in afterdischarge duration. Decrease in seizure latency also seemed to progress gradually (Figure 16 A - D).

A few subjects in each group showed quite a different pattern. They produced long seizures from onset, often with short latencies and Stage 5 development (Figure 16 E and F; see also Tables 11 B, 12 B and 13). In such cases there was often no further growth. Seizure durations tended to vary randomly (Figure 16 E), and very long early seizures even tended to decrease toward the group mean as testing progressed (Figure 16 F).

In both sorts of subjects, a slight decrease in seizure duration was often seen toward the end of the test series (Figure 16), perhaps due to the build-up of some sort of fatigue or inhibition.

4) Electrographic Correlates of Subcortical Seizure Onset Racine (1969) reported a dramatic increase in subcortical afterdischarge duration which occurred a few days before the occurrence of Stage 5 seizures. A similar dramatic increase was often seen in this experiment. Due to the different seizure criterion employed, it could be located more specifically

as occurring just at the onset of generalized seizure activity. In individual records, these changes at seizure onset appeared as typical examples of the sudden increments in duration already discussed (Figure 9 A and C). Sudden increments were even seen in hippocampal records at this time (Figure 9 E and F). Taken all together, these increments produced the significant difference between the average durations of the last preseizure and the first seizure discharges seen in Table 3.

Racine was puzzled by the fact that such increases failed to occur in some of his animals. A few subjects in each of the present groups also failed to show the expected increases. In some of these cases increments were poorly correlated with seizure onset (Figure 9 C and D) and others never occurred at all (Figure 9 E and F). Careful examination of individual records revealed that most of these failures occurred in subjects where medium (around 40 second) or long (over 60 second) discharges had already developed <u>before</u> seizure onset. Medium afterdischarges only occasionally showed an increase at onset, and long afterdischarges never did. Subjects with short (under 40 second) afterdischarges, however, almost invariably showed an increase in duration at seizure onset.

Racine also noted sudden and dramatic growth in the

amplitude of contralateral propagated discharge a few days before Stage 5 seizure onset. Presumably this sudden growth represented the onset of reactive propagation (he notes that it brought the amplitude of the secondary pattern up to or beyond the level of the primary pattern), and very probably it took place around the time of the onset of generalized seizure activity (which usually occurs a few days before the Stage 5 seizure). Table 14 indicates the relation of the onset of ipsilateral secondary reactive discharge in the structures studied in this experiment to primary seizure onset. (Simultaneous onset is scored as "0". Secondary reactive discharge which started before seizure onset is given a "plus" score and secondary reactive discharge which started after seizure onset is given a "minus" score.) In general, the relationship did not appear to be a very close one. In most of the groups, the onset of secondary discharge ranged rather widely about seizure onset, taking place on the average somewhat sooner. Only one secondary structure, the septal area, always showed reactive discharge by seizure onset.

Discussion: Stimulation of the Primary Site Observations made in the present study serve to confirm, to quantify and to extend the reports of previous investigators on the brain's

progressive development of epileptic responsiveness to repeated electrical stimulation.

At the site of stimulation, increasing responsiveness was seen in the growth of afterdischarge amplitude, complexity and duration. The growth in duration was particularly striking, as group averages tripled or quadrupled during the course of stimulation. Such growth was seen, however, only in subcortical structures.

These findings offer confirmation and statistical support for several previous reports of afterdischarge growth in limbic structures (Delgado and Sevillano, 1961; Racine, 1969; Goddard as reported by Morrell, 1969), and extend them by showing that such growth follows a very similar course at different sites (no significant inter-group differences were found at any stage of testing). It was also possible to confirm Racine's previous observation that the bulk of afterdischarge growth takes place by the time of seizure onset. It was not possible to confirm Racine's report of growth in cortical afterdischarge, but, since the growth which Racine observed was very slight and took place over a long period of stimulation, it might well have been missed in the present experiment. Perhaps the important thing to note is that while cortical discharges may show some slight

growth, the growth is very small compared to that seen in limbic structures.

Studies of limbic discharge growth in individual records indicated that in many subjects it took place in large increments (as duration jumped suddenly from one "plateau" to another) and that the added segments of discharge often displayed a pattern of their own quite different from the original discharge. Sudden decreases were also sometimes seen, as whole segments disappeared for a day or two. These sudden changes in primary site afterdischarge duration were quite possibly caused by the onset (and failure) of reactive discharge in secondary sites. When two or more independent discharges exist in related structures, they are known to influence each other's activity by means of the volleys they send (Penfield and Jasper, 1954). It would not be surprising then in this richly interconnected part of the brain to find a "feedback" modification of the primary pattern by volleys from secondary structures, and the onset of a secondary discharge which outlasted the primary pattern might well cause a lengthening of the primary discharge. (Sharpless, 1969, has commented that in the cat's cortex, where growth in after-discharge duration apparently does occur, such growth is seen only when active discharge spreads to other areas.)

Evidence that such a mechanism actually functioned in the present study comes from the observations on discharge growth in the hippocampal subjects where primary site discharge was limited by the silent period. In these subjects, primary discharge was seen to grow only after the onset of reactive discharge in secondary sites, and the added primary segments showed a pattern which clearly resembled "projected" propagation. The observation of similar low-amplitude disturbances at other sites just before a sudden increase in afterdischarge duration suggests that such feedback may have been the cause of discharge growth in all the subcortical sites though its influence was seen clearly only in the hippocampus where the silent period prevented active response. Accepting this hypothesis, the similarity of discharge "plateaus" in subjects with different limbic placements seems to suggest that a few large secondary structures dominated the whole system during discharge. The cortex presumably did not show much discharge growth because it failed to propagate active discharge into the subcortical structures (see Table 9) and therefore did not receive subcortical feedback. (At a later stage in testing, however, the cortex did sometimes propagate active discharge into subcortical structures, and then dramatic cortical discharge growth was

seen. See below.)

At secondary sites, the increasing epileptic responsiveness of the brain was seen in the form of increasing discharge propagation. Reactive discharge, originally fairly rare, became increasingly widespread, and, by the end of testing, was seen in almost every secondary site. Exceptions were seen only between the cortex and the amygdala, and occasionally between the amygdala and the hippocampus. Even in these cases, growth in projected discharge was seen and it seems possible that reactive discharge might have resulted from prolonged stimulation.

These findings are in agreement with the reports of a number of previous investigators and do not require a great deal of discussion. Discharge has long been known to propagate widely throughout the limbic system (for reviews of this extensive literature, see Kreindler, 1965; Racine, 1969) and Delgado and Sevillano (1961) and Racine (1969) have previously reported the progressive development of propagation in much the same preparation. A recent publication by Gersh and Goddard (1970) has employed a sophisticated statistical analysis to demonstrate the eventual independence of the secondary discharges which develop.

Progressive development in the behavioral response to electrical stimulation was seen in the present study only when subcortical sites were stimulated. Cortical afterdischarge caused immediate seizure activity (as previously reported by Racine), but this was not seen to change during the course of stimulation. (Stimulation was apparently not continued long enough to elicit the tonic extensions which Racine found in the later stages of cortical seizure development.) Subcortical afterdischarge had little immediate effect, but with repetition was seen to cause the progressive development of behavioral arrest, partial seizure signs and finally generalized convulsions which has been described by previous investigators (Delgado and Sevillano, 1961; Goddard et al., 1969; Racine, 1969).

Goddard et al. (1969) have suggested that the rate of subcortical seizure onset is related to the site of stimulation. The present study was able to offer statistical support for this suggestion, and, in general, the rank order of the subcortical sites tested in the present study was much like that previously reported by Goddard et al., even though afterdischarges were counted rather than stimulations. The actual rates, however, were all somewhat shorter than those previously

reported by Goddard et al., which suggests that Goddard et al.'s kindling rates probably include both supra- and subthreshold stimulations. An interesting observation was that the ventral part of the hippocampus causes quicker seizure onset than the dorsal part. There may also be a similar difference between the hippocampus proper and the fascia dentata, but only limited data are so far available and further study will be necessary to establish this.

Previous investigators (Goddard et al., 1969; Racine, 1969) have reported that subcortical seizures continue to develop for some time after seizure onset. In the present study it was possible to confirm these reports by showing statistical differences between early and late seizures in latency, duration, and stage of development. This development appeared to take place gradually, resembling in this respect the development of projected driving. Goddard et al. (1969) have suggested that seizure development comes to an end after about ten seizures, but group records in the present study seemed to indicate an earlier end to seizure development. It may be, however, that such group records are misleading because they contain some subjects (previously noted by Racine) that produce full-blown seizures from the start, and who often

show shorter rather than longer seizures during subsequent testing. Individual records sometimes did show seizure development up to the ninth or tenth seizure as Goddard et al. had suggested.

Even at full "maturity," subcortical seizures seldom reflected the primary discharge in the perfect way that cortical seizures did, usually having a definite, if small, latency and a duration somewhat shorter than the duration of the primary site discharge. Particularly poor correlation was seen in the hippocampal subjects, where seizure activity often occurred during the silent period (see also Racine, 1969). The approximate nature of this relationship suggests that it was not primary site discharge which eventually came to drive motor seizures, but the active discharge propagated into secondary (and tertiary, etc.) sites. This possibility is supported by the findings of Delgado and Sevillano, who report that seizure activity never began in their subjects until active discharge had spread out of the primary site. These investigators were even able to correlate the onset of certain partial seizure signs with the onset of reactive propagation in certain secondary sites (Delgado and Sevillano, 1961).

The fact that it is active secondary discharge which drives

seizures explains not only the poor correlation between primary site discharge and seizure activity, but also the somewhat casual relationship which was seen between primary site afterdischarge growth and seizure onset. Seizure onset presumably results not from a change in primary site activity, but from the onset of reactive discharge in some secondary (or tertiary, etc.) structure. Primary seizure growth presumably just reflects the feedback from this event, and it will be seen only if too much feedback from other structures is not already present.

In summary, then, the brain's increasing epileptic responsiveness to repeated electrical stimulation is seen in the growth of primary discharge, in the increase of propagation to secondary sites, and in the onset and development of motor seizures. It seems likely that it is the development of reactive discharge in secondary sites that plays the crucial role not only in driving seizures but also in causing the growth of primary discharge. Primary site discharge plays its role by causing the gradual development of generalized secondary discharge. (See Gastaut and Fischer-Williams, 1959, for a similar suggestion regarding the development of clinical epilepsies.)

Whether the development of active secondary discharge causes seizure onset by activating some particular pathway or structure is still a matter for speculation. Goddard et al.'s proposal that the rate of kindling for different sites is related to their anatomical closeness to the amygdala would seem to suggest a crucial role for that structure. It should be noted, however, that in the present study, reactive discharge was not always seen in the amygdala at the time of seizure onset. An alternate possibility is that rate of seizure onset is related to how widely a structure broadcasts discharge throughout the limbic system. The amygdala is known to have a particularly broad projection system (Gloor, 1955; Goddard, 1964) and the ventral hippocampus is reported to propagate discharge more widely in the limbic system than the dorsal hippocampus (Elul, 1964b). Racine's finding of a good correlation between seizure onset and the sudden growth of contralateral propagation (Racine, 1969) seems to suggest that the onset of widespread <u>bilateral</u> reactive discharge may be a crucial factor in the appearance of generalized seizures. If so, this would explain why full-scale seizures always were bilateral even though stimulation and the early seizure signs were unilateral.

Stimulation of the Secondary Site

Rates of Secondary Seizure Onset The transfer effect described by Racine (1969) and Goddard et al. (1969) consists of an accelerated rate of seizure onset in secondary sites. Column 2 of Table 15 presents the average rates of seizure onset found at the secondary sites studied in the present experiment. Column 1 of the same table presents the primary rates previously found at similar sites, and Column 3 indicates the significance of the differences between the secondary site rates and the normal primary site rates.

Significant acceleration of seizure onset (transfer) was found at all of the secondary limbic sites following primary limbic stimulation. It was not found in the secondary amygdala group which had had the anterior cortex as a primary site. (Even in this group, however, the average for secondary seizure onset was somewhat shorter than normal.)

The largest reductions in secondary rate were seen between the hippocampus and the septal area (both ways) and in the amygdala after primary development in any other limbic site. In all these instances, reductions in secondary rate were well over 50% (Table 15, Column 4), and in most of them a number of instances of immediate secondary seizure onset

were seen (Table 15, Column 5). Smaller reductions were found when the amygdala served as the primary site and the other structures served as secondary sites, the weakest effects of all being seen in the secondary hippocampal groups. The reductions in secondary hippocampal rates were less than 50% and instances of immediate seizure onset were rare.

These secondary hippocampal scores were of interest, not only because they showed the least transfer, but also because they were the only secondary scores which showed increased rather than decreased variability (see Table 15). It seemed possible that differences between the fascia dentata and the hippocampus proper might once again be implicated. As in the primary hippocampal groups, only a small number of unambiguous placements could be found, but these provided some suggestive and unexpected results. In the dorsal hippocampal group after primary amygdaloid stimulation, for instance, three clear-cut hippocampus proper subjects (#17, #20 and #21) averaged 26.7 secondary afterdischarges to seizure onset, while three fascia dentata subjects (#18, #19 and #22) averaged 11.3. In the ventral hippocampus, six hippocampus proper placements (#24, #25, #26, #27, #28 and #29) averaged 12.1 afterdischarges while the single fascia dentata subject (#30)

took only two. In both cases, the fascia dentata placements appeared to show a good transfer effect, while hippocampal proper placements showed very little. (Similar observations were made when the septal area served as the primary site.)

Afterdischarge at Secondary Sites Secondary discharges generally resembled the primary discharges normally elicited from the same sites (Figure 17 A-D; for comparison see Figure 2). There was considerable variation in their duration at onset (Figure 17 E and F), but, at least in the groups that showed significant transfer, they tended to be of medium length or long from the start. A significant overall difference was found between the onset duration of secondary afterdischarges and the shorter onset durations of the discharges which had been produced by primary stimulation ($F = 22.6$, $df = 1$ and 94, $p < 0.01$; see Table 16B). This effect was not seen equally in all the secondary groups, however. The longer secondary onset averages tended to be found in the secondary amygdaloid and septal groups (which also generally showed the quickest secondary seizure onsets), and shorter ones were seen in the secondary hippocampal groups (which tended to show slower rates of secondary seizure onset). Secondary dorsal hippocampal discharges were particularly brief and a significant difference was found between these

durations and the durations of the secondary amygdaloid and septal discharges at onset (see Table 16B for the significant interaction and the comparison of means two at a time). The average for secondary discharge durations at onset in the one group which did not show significant transfer (secondary amygdala after primary cortical stimulation) was found to be exactly equal to the normal primary average (Table 16A).

Afterdischarge growth profiles plotted for individual subjects in the secondary groups that showed transfer (Figure 18) tended to resemble the latter parts of profiles plotted for primary subjects at the same sites (see Figure 9). Discharges which were long from the start (usually accompanied by immediate seizures) tended to show only random variation in length as stimulation was continued (Figure 18 B and D). Short or medium length discharges tended to grow in sudden increments, one of which usually occurred at seizure onset (Figure 18 A, C, E - H).

The length of secondary discharges at seizure onset was not significantly different from that of primary discharges at the same time (see Table 17; for subjects which did not show significant transfer, $t = 1.6$, $p > .10$; for subjects that did show significant transfer, $F = 3.4$, $df = 1$ and 94, $p > .05$).

Discharge Propagated from Secondary to Primary Sites The present experiment provided data on only one particular type of secondary site propagation, propagation back to the original stimulation site. These data do not offer a safe basis for generalization about secondary propagation as a whole since the "target" sites were hardly normal. Nevertheless, they are of some interest with regard to the possible mechanisms underlying transfer.

Table 18 indicates the percentage of subjects in each group that showed immediate propagation (of any sort) to the primary sites during the first secondary site discharge. Table 19 indicates the percentages of subjects that showed immediate reactive discharge in the primary sites. Comparison of these tables with Tables 4 and 5 (propagation between the same sites at the start of primary stimulation) reveals an interesting picture. In general, more immediate propagation was seen during secondary stimulation than had been seen during primary stimulation (compare Table 18 to Table 4). When the secondary amygdala or septal area was stimulated, more immediate reactive discharge was also seen (compare Table 19 to Table 5). Secondary stimulation of the dorsal or ventral hippocampus, however, tended to produce less

immediate reactive discharge than primary stimulation had (compare Table 19 to Table 5). Much the same thing was seen when rates of development of reactive discharge were considered. Secondary amygdaloid and septal stimulation caused reactive discharge to develop sooner than primary stimulation had, but secondary hippocampal stimulation generally caused slower development (compare Table 20 to Table 6).

During stimulation of the primary sites, no very close relationship had been seen between seizure onset and the beginning of reactive discharge in ipsilateral driven sites (Table 14). A far closer relationship was seen during the stimulation of secondary sites (see Table 21). This did not seem to indicate, however, that the secondary sites caused seizures by activating their primaries. Not only were secondary sites sometimes seen to trigger seizures before they drove their primaries to active discharge (Table 21; Figure 19A), they were also sometimes seen to drive their primaries to active discharge <u>before</u> seizure onset (Table 21; Figure 19 B-D). Primary discharge in the latter cases was usually only of moderate length, but was nevertheless well-developed and convincing (Figure 19 B-D).

Motor Seizures Produced by Secondary Stimulation Like secondary afterdischarges, the seizures produced by secondary stimulation tended to be of the same type as those normally produced by primary stimulation, but (at least in the groups which showed transfer) unusually well-developed at onset. Tables 22, 23 and 24 compare primary and secondary seizures at onset for latency, duration, and "stage." As compared to primary seizures, secondary seizures in the groups which showed a significant transfer effect were both significantly shorter in latency ($F = 4.7$, $df = 1$ and 94, $p < 0.05$; see Table 22B), and longer in duration ($F = 8.6$, $df = 1$ and 94, $p < 0.005$; see Table 23B). All of the groups that showed transfer also produced more early Stage 5 seizures than the groups receiving primary stimulation had produced. (This effect was significant for the amygdaloid, septal and dorsal hippocampal subjects, but not for the ventral hippocampal subjects. See Table 24B.) It is interesting to note that the tendency toward "early maturity" was much clearer in the case of seizure duration than it was in the case of seizure latencies. Most of the seizures produced by secondary stimulation had durations at onset which were roughly equivalent to those found in fully-developed primary seizures (see Table 12).

This was true whether seizures occurred soon after the start of secondary stimulation (as with most of the amygdaloid subjects) or only after a long period (as in the case of most of the dorsal hippocampal subjects). The latencies of secondary seizures at onset, however, were not so different from the onset latencies of primary seizures, and most of the difference that did exist was contributed by the groups which showed the fastest rates of secondary seizure onset (amygdaloid and septal). Even in these groups, latencies were not as short as the latencies of mature primary seizures (see Table 11).

Early seizures in the secondary group that did not show transfer resembled the early seizures produced by normal primary stimulation both in duration (Table 23A) and seizure stage (Table 24"). Curiously, however, they showed a significantly shorter average latency (Table 22A).

The Relation of Transfer to Previous Reactive Discharge

Racine has suggested that each propagated reactive discharge works like an electrically evoked discharge to promote secondary seizure development and to reduce by one the number of electrical stimulations eventually necessary to trigger seizures from that site. Column 6 of Table 15 indicates the average number of reactive discharges which had occurred in each of the secondary

groups before the start of secondary stimulation (the data are re-presented from Table 9). These data seem to offer a good deal of support for Racine's hypothesis. Transfer was found in all the secondary groups where there had been previous reactive discharge, and was absent in the single group of subjects where reactive discharge had failed to develop. (Transfer also appeared to be absent in the two hippocampal subjects which had failed to develop reactive discharge during primary amygdaloid stimulation. Each of these had a secondary rate of seizure onset which was the slowest in its group, and which was quite within the range of normal primary subjects at that site.)

Among the groups that did show significant evidence of transfer, the amount of secondary acceleration seemed to be roughly related to the amount of previous reactive discharge. In groups where the average number of previous reactive discharges was equal to or greater than the number of primary discharges which normally occurred before seizure onset, secondary seizure onset was rapid (Table 15, Column 2), and immediate transfer was common (Table 15, Column 5; these groups are marked with an asterisk in Column 6 of Table 15). Comparison of seizure onset rates in these groups with rates

in the other groups showed them to be significantly shorter (Mann-Whitney U = 0; N_1 = 5, N_2 = 6; $p < 0.004$, two-tailed). In the other groups, the sum of the previous reactive discharges plus the number of secondary discharges required to elicit seizures often roughly approximated the number of primary discharges normally necessary to cause seizure onset.

Discussion: Stimulation of the Secondary Site A significantly accelerated rate of seizure onset was found at every secondary site in the present experiment except the amygdala after primary cortical seizures. These data confirm Goddard et al.'s (1969) previous report of ipsilateral transfer between the amygdala and septal area, and extend it by demonstrating ipsilateral transfer from the septal area back to the amygdala, and both ways between the amygdala and septal area and both parts of the hippocampus. Taken together with Racine's and Goddard et al.'s previous data on contralateral transfer, these data show the phenomenon to be very widespread in the limbic system, occurring both between ipsilateral and contralateral homologous and non-homologous structures, between structures with and without direct anatomical connection, and between "old" cortical and subcortical structures.

At present, there is only one reported failure of limbic-limbic transfer: Racine's (1969) report of no acceleration in the rate of secondary contralateral hippocampal seizure development after primary seizure development in the amygdala. This instance bears re-examination in the light of the present finding of ipsilateral transfer between the amygdala and both the dorsal and ventral hippocampus. Racine's sample was relatively small and it seems possible that more extensive testing might reveal contralateral amygdaloid-hippocampal transfer.

The failure of neocortical-amygdaloid transfer in the present study seems particularly striking in view of the widespread occurrence of limbic-limbic transfer. It would be premature, however, to draw any general conclusions from these data. Motor seizures occurred immediately when the cortex was stimulated, and therefore the number of after-discharges generated in the cortex was never more than ten, considerably less than that generated in the other primary sites. Even this relatively small number of discharges apparently had some effect, since secondary amygdaloid seizures after primary cortical stimulation did have an unusually short latency at onset (even if onset itself was not significantly

accelerated). The problem of cortical-subcortical transfer (like the problem of contralateral amygdaloid-hippocampal transfer) needs further investigation.

Two different explanations have been proposed for the transfer phenomenon:

1) that secondary sites, activated by reactive propagation from the primary sites, go through independent seizure development just as if they were being subjected to direct electrical stimulation (Racine, 1969);

2) that secondary sites simply "tie into" response circuits previously established by primary site activity (Goddard et al., 1969).

The present study provides some support for both points of view. Relative to the idea that transfer results from the activation of secondary sites by propagated discharge, it was found that transfer occurred only at the secondary sites which had previously developed reactive propagation, and that the amount of transfer was roughly proportional to the amount of previous reactive propagation that had occurred. (As noted in the Methods Section, gross recording only allows an estimate of reactive propagation. Still, the fact that such good correspondence was found even with a crude technique is very suggestive.) Moreover, discharges tended to be long from onset in sites that showed transfer and propagation

tended to be well-developed (i.e., "transfer" sites resembled normal sites that have experienced repeated discharge). This electrographic maturity was most pronounced in the sites where the strongest transfer was seen. (The very small increase in the duration of secondary discharge in the dorsal hippocampal group is quite consistent with the very gradual growth of preseizure discharge observed in these and in some ventral hippocampal subjects. See Figure 9 E and F. The actual decrease in secondary propagated reactive discharge from both parts of the hippocampus, despite the increase in projected propagation, is harder to explain, and seems to suggest some sort of inhibitory or fatigue process.) Actually, it would be surprising if the occurrence of active discharge in secondary sites did not initiate a secondary process of seizure development since Racine has shown that it is discharge per se rather than stimulation which causes the process.

On the other hand, the "maturity" of secondary seizures at onset is rather hard to explain on the basis of the "independent development" approach. If the "seizure circuits" from the secondary sites were entirely independent, secondary seizures ought to have shown the same sort of gradual development that primary seizures did. Instead, they were long and fully developed from onset, and this was true whether secondary onset was fast or slow. This characteristic of secondary

seizures suggests a "tying in" on pre-organized circuits at some level. (Further evidence that "tying in" of a sort can occur will be presented in the following section of the Results and Discussion.)

There seems, then, to be some support for both hypotheses of transfer. Actually, of course, the two mechanisms are not mutually exclusive, and on the basis of the present data it seems quite possible that both function in the development of secondary seizures: reactive discharge in secondary sites causing a growth of the secondary sites' ability to activate some "downstream" structure which actually drives the motor neurons; the "downstream" structure producing a super-normal response due to its previous activation by the first site. The only puzzling point is why "tying in" should not work at higher levels to cause even faster secondary seizure onsets (i.e., by activating any part of the primary site's "upstream" seizure circuitry). One observation from the present experiment offers a possible clue. In several animals the secondary site was seen to cause reactive propagation in the primary site itself without causing seizures. This is rather hard to understand, but it seems to suggest that all after-discharges may not be equivalent, and that those accompanied by direct electrical stimulation may be more effective for triggering seizures.

Resumption of Primary Site Stimulation

Post-Transfer Motor Seizure Suppression Goddard et al. (1969) have reported a temporary suppression of primary site seizures following transfer. This suppression, they suggest, may have resulted from some modification of the primary site's seizure circuits due to their use by the secondary site during transfer testing. Racine (1969) has suggested instead that such post-transfer seizure suppression may result from trans-synaptic elevation of the primary thresholds during transfer stimulation and the subsequent failure of primary afterdischarge when primary stimulation is recommenced.

The primary sites in the present study were all retested after transfer to provide further data on this phenomenon. Table 25 indicates the number of post-transfer stimulations (if any) that were given at each primary site before the recurrence of seizures and also the number of stimulations (if any) which had previously occurred in the same subjects between the ninth and tenth seizures during the original stimulation of the primary site (an indication of the rate of spontaneous seizure failure). Post-transfer seizure suppression was calculated by taking the difference between the two. At this late stage in testing some of the groups had been depleted by illness, but most of them were still comparable in size to those employed by Goddard et al.

As indicated by Table 25, post-transfer seizure suppression was found in the present experiment, but it occurred in significant amounts only in subcortical sites, and only following secondary stimulation of the amygdala. The ventral hippocampus, for instance, averaged 1.8 days of suppression after secondary amygdaloid stimulation, the septal area 1.4 days, and the dorsal hippocampus 1.2 days (the first two values are significant at the 0.05 level, one-tailed; the dorsal hippocampal group fails to reach significance, perhaps because of its higher spontaneous failure rate). The other subcortical combinations all produced smaller (non-significant) suppression scores, noteworthy "trends" being seen only between the dorsal hippocampus and the septal area. The amygdala itself never showed any signs of suppression.

According to Racine's hypothesis, primary site discharge should have been absent during the period of post-transfer seizure suppression. Table 26 indicates the actual percentages of post-transfer, pre-seizure stimulations that were found to be accompanied by discharge in the present experiment. Contrary to Racine's suggestion, primary site afterdischarge was generally found during the post-transfer period, and was actually present on every stimulation in the two groups which showed significant post-transfer seizure suppression

(ventral hippocampus and septal area after secondary stimulation of the amygdala). A survey of afterdischarge durations in these two groups during the period of suppression revealed a wide range of variation (Figure 20), with a mean of 42.6 seconds in the hippocampal group and a mean of 70.7 in the septal group (Table 27). While discharges of this length are not short, they were somewhat shorter than the discharges found in the same subjects just before transfer testing (Table 27 A and B; the difference was significant in the ventral hippocampal group at the 0.05 level, two-tailed, but failed to reach significance in the septal group), and a sudden increase in duration was often seen when seizures reappeared.

Afterdischarge at Lowered Stimulation Intensities

Although afterdischarge was present during seizure suppression, it appeared to be somewhat shortened. To test the possibility that this shortening might be related to elevated thresholds, samples of five subjects were chosen at random from each of the primary subcortical groups, and after primary site seizures had been firmly re-established, stimulation intensity was gradually lowered on succeeding days until afterdischarge threshold was reached. This procedure was designed to show what kind of afterdischarges occurred when stimulating current

was closer to threshold. It seemed possible that discharge duration might decline (and seizures disappear) as stimulation was lowered. Pinsky and Burns (1961) had not found this sort of parametric relationship between afterdischarge duration and stimulus intensity, but their experiments had involved short periods of stimulation in isolated cortical slabs.

Figure 21 illustrates the three different patterns of response that resulted from the lowering of stimulation intensity and Table 28 indicates the numbers of subjects in each group that displayed each pattern. In about half of the subjects in each group, long discharges and seizures continued unchanged until both disappeared at threshold (Table 28; Figure 21A). In most of the remaining subjects, long afterdischarges with seizures continued unchanged until stimulating current was just (5 - 10 μa) above threshold. At that point afterdischarges suddenly became very short and seizures usually disappeared (Table 28; Figure 21B). A more gradual decline occurred in only one ventral hippocampal subject. In this single case discharge dropped to moderate levels as stimulation current was lowered, and seizures occurred only intermittently (Table 28; Figure 21C).

An interesting observation was made in two of the amygdaloid subjects. In these subjects the brief afterdischarges caused by near threshold stimulation caused brief motor

seizures (Figure 22). Motor seizures had never been seen to accompany this sort of afterdischarge in the early stages of testing.

Subcortical "Generalization" of Cortical Seizures An interesting and unexpected phenomenon was observed during the retesting of the primary site in the cortical-amygdaloid group. Little or no tendency toward post-transfer seizure suppression was seen in these subjects and post-transfer stimulation quickly evoked afterdischarges and seizures. At first typical "cortical" afterdischarges and seizures were seen (Figure 23 C, SD 25). As stimulation continued, however, several of the subjects suddenly began to produce discharges of "subcortical" length (Figure 23 C, SD 26). These new, longer discharges were accompanied by seizures of the "subcortical" type, and sometimes (but not always) by the onset of reactive discharge in the amygdala (see Figures 23F and 23 C, SD 26).

Several observations suggest that this transformation of cortically evoked afterdischarges and seizures was caused not by a change in cortical function itself, but by the propagation of active discharge from the cortex into subcortical structures:

1) The lengthened seizures sometimes clearly

consisted of two discrete episodes, a short "cortical" episode and a longer "subcortical" episode (see Figure 23 F).

2) The transformation occurred only after subcortical seizures had been developed by independent subcortical stimulation. (The present study unfortunately did not include a group of subjects given only cortical stimulation, but in previous studies by Racine cortical stimulation alone was never seen to cause this sort of afterdischarge or seizure even when administered for as many as 60 sessions. See Racine, 1969.)

3) The later, "subcortical," components of the lengthened discharges and seizures sometimes disappeared spontaneously, and could be suppressed at will by lowering the stimulating current to near threshold levels (Figure 23 E), by raising it to very high levels (Figure 23 E), or by "fatiguing" the subcortical system by triggering a previous subcortical seizure from the amygdala (Figure 23 D). When the later components were suppressed, a normal "cortical" pattern was seen.

Discussion: Resumption of Primary Site Stimulation

Goddard et al.'s report of the post-transfer suppression of primary site seizures was confirmed by the present study and extended by the observation that such suppression appears to

occur only in certain situations. Significant amounts of suppression were found only in subcortical structures and only after secondary stimulation of the amygdala. Small "trends" toward suppression were seen between some of the other subcortical sites (i.e., the hippocampus and the septal area), but in several instances no tendency at all was seen and it must be concluded that suppression is not the invariable concomitant of transfer. Why the amygdala should be a particularly powerful suppressor is not clear from the present data. Presumably some special characteristic of the structure itself is involved since the procedures related to amygdaloid transfer testing were not in any way exceptional (the levels of stimulation involved were neither the highest nor the lowest, the time involved in transfer testing was neither the longest nor the shortest, etc.).

One clear-cut discrepancy exists between the present findings and those previously reported by Goddard et al. Goddard et al. found an average of 1.8 days of suppression in the amygdala after secondary stimulation of the ipsilateral septal area. No amygdaloid suppression was found in the present study after secondary septal stimulation. This discrepancy may be related to one of the several procedural differences between the two studies: Goddard et al. used

a low standard current of 50 μa, stimulated their subjects daily rather than every other day, measured suppression in terms of stimulations instead of afterdischarges, and may have given a smaller number of secondary site seizures (a "few" were given). Further experimental work will be required to settle this point.

The present study was not able to offer much support for Racine's suggestion that seizure suppression results from raised thresholds and inhibited discharge at the primary site. Afterdischarges were seen at primary sites during the period of seizure suppression. It must also be noted that Racine looked for and failed to find trans-synaptic threshold elevation between the amygdala and the septal area, one of the pairs of sites which produced significant suppression in the present study. An attempt to relate the shortening of afterdischarge seen at some sites during the suppression period to changes in threshold also failed. Discharge duration (and seizure occurrence) remained relatively constant over a wide range of intensities as stimulation intensity was lowered towards threshold. Sometimes a sudden drop in duration (with seizure failure) was seen just above threshold, but this phenomenon, though an interesting addition to Pinsky and Burns' previous observations, is probably quite unrelated

to post-transfer seizure suppression since these short discharges occurred only within a very narrow range, and since they were much shorter than the discharges usually seen during the depression period.

The present data suggest that post-transfer seizure suppression results not from a failure in primary site discharge, but from a failure of the primary site to cause active secondary discharge in some "downstream" structure. The cause of such a failure might be either the trans-synaptic threshold elevation suggested by Racine or the modification of circuits postulated by Goddard et al. Perhaps threshold elevation seems more likely in view of Goddard's recent discovery that post-transfer seizure suppression dissipates spontaneously with the passage of time (Goddard, Personal communication). Threshold elevations have been found to be temporary in some cases, but the neural reorganization caused by the repetition of after-discharge appears to be permanent.

Several incidental observations made during the re-testing of the primary site are also of interest. The sudden appearance of extended discharges and "subcortical" seizures in post-transfer cortical subjects was particularly interesting because of the light it throws on several different theoretical points. The sudden extension of

afterdischarge duration seen in these subjects, for instance, could clearly be related to the onset of active discharge in another system because it was accompanied by the onset of the seizure behavior characteristically caused by subcortical activity. It was also clear that the lengthening of local discharge in this case was the result, not the cause of distant activity, because it did not occur when the subcortical system had been fatigued by a previous seizure.

The fact that the "generalization" of cortical discharge did not occur until after subcortical seizure development had taken place is relevant to the problem of transfer. While it does not prove that transfer normally involves "tying in," it is a good demonstration that one system <u>can</u> "tie in" to another after the second has been reorganized by independent stimulation. (It is worth noting, however, that the amygdala itself was not always actively involved in the generalization of cortical seizures. "Tying in" apparently need not involve activation of the original site of stimulation.)

The finding that the "local" and "generalized" parts of lengthened cortical discharges could be dissociated near threshold throws some light on the short afterdischarges found near threshold stimulation in subcortical sites. It

suggests that these too represent a local response, unaugmented by the spread of active discharge into other structures and the subsequent feedback.

A further interesting finding was the observation of occasional seizures associated with some brief near threshold amygdaloid discharges. Since short, low-amplitude discharges had never driven seizures during the early stages of testing, and since propagated reactive discharge was not seen in these cases, these seizures may be an indication of some sort of improved transmission or sensitization that had developed during the course of seizure development.

The various observations discussed above all deserve further experimental analysis. The phenomenon of cortical generalization to subcortical structures in particular might be developed as an experimental model for the generalization of focal epilepsy in humans.

SUMMARY AND CONCLUSIONS

It has recently been suggested that the development of epileptic activity may involve a neural reorganization similar to that normally involved in the process of learning. In the present experiment, low levels of repeated electrical stimulation were applied to sites in the forebrain of the rat, and evolution of afterdischarges and convulsive behavior was studied. Results were as follows:

1) At primary sites, measurements were made of the progressive development of afterdischarges, of afterdischarge propagation, and of convulsive behavior. It was noted that afterdischarge growth often took place not gradually but in sudden large increments. One of these increments often occurred at the onset of generalized seizures.

2) Accelerated rates of secondary seizure onset (Racine's "transfer effect") were found at all secondary limbic sites following primary limbic stimulation, but not in the amygdala following neocortical stimulation. Such accelerated rates were associated with the immediate appearance at secondary sites of the long afterdischarges and enhanced propagation which normally occur only after repeated stimulation. "Transfer" seizures were also found to be unusually well-developed at onset.

3) Retesting of primary sites after transfer stimulation revealed the post-transfer suppression of primary seizures previously reported by Goddard et al., but it was found only in limbic sites, and only after secondary stimulation of the amygdala. It did not seem to depend on the suppression of primary site discharge. Sometimes during post-transfer stimulation, cortical discharge was seen to produce "subcortical" seizures.

It seems likely that both the growth of primary site discharge and the evolution of motor seizures reflect the development of reactive discharge in secondary structures. Reactive discharge also seems to promote independent secondary seizure development and is therefore basic to the "transfer effect." A further investigation ought to be made of the neural changes basic to the development of such independent secondary discharge activity. If (as seems possible) some permanent improvement in neural transmission is involved, the development of epilepsy may well provide an excellent analog for the learning process.

REFERENCES

Cowan, W., Raisman, G., & Powell, T. The connexions of the amygdala. J. Neurol. Neurosurg. Psychiat., 1965, 28, 137 - 151.

Davenport, H. Histological and Histochemical Technics. Philadelphia: W.B. Saunders Company, 1960.

Delgado, J., & Sevillano, M. Evolution of repeated hippocampal seizures in the cat. EEG clin. Neurophysiol., 1961, 13, 722 - 733.

Doty, R., & Giurgea, C. Conditioned reflexes established by coupling electrical excitations of two cortical areas. In Delafresnaye, J. (Ed.), Brain Mechanisms and Learning. Oxford: Blackwell, 1961, 133 - 151.

Elul, R. Regional differences in the hippocampus of the cat. I. Specific discharge patterns of the dorsal and ventral hippocampus and their role in generalized seizures. EEG clin. Neurophysiol., 1964a, 16, 470 - 488.

Elul, R. Regional differences in the hippocampus of the cat. II. Projections of the dorsal and ventral hippocampus. EEG clin. Neurophysiol., 1964b, 16, 489 - 502.

Ferguson, G. Statistical Analysis in Psychology and Education, (3rd Edition). New York: McGraw-Hill Book Company, Inc., 1971.

Forster, F. Conditional Reflexes and sensory-evoked epilepsy: the nature of the therapeutic process. Conditional Reflex, 1969, 4, 103 - 114.

Forster, F., & Chun, R. Behavioral studies in experimental focal seizures. Trans. Amer. Neuro. Assoc., 1962, 87, 199 - 200.

Forster, F., Chun, R., & Forster, M. Conditioned changes in focal epilepsy: I. In animals with intact central nervous system. Archives of Neurology, 1963, 9, 98 - 193.

Gastaut, H., & Fischer-Williams, M. Physiopathology of epileptic seizures. In Field, J., Magoun, H., & Hall, V. (Eds.), Handbook of Physiology, Section I. Neurophysiology, 1959, Vol. I, 329 - 363.

Gersch, W., & Goddard, G. Epileptic focus location: spectral analysis method. Science, 1970, 169, 701 - 702.

Gloor, P. Electrophysiological studies on the connections of the amygdaloid nucleus in the cat. Part I: The neuronal organization of the amygdaloid projection system. EEG clin. Neurophysiol., 1955, 7, 223 - 242.

Goddard, G. Functions of the amygdala. Psychol. Bull., 1964, 62, 89 - 109.

Goddard, G. Development of epileptic seizures through brain stimulation at low intensity. Nature (London), 1967a, 214, 1020 - 1021.

Goddard, G. Electrical induction of experimental epilepsy. Medical News (London), 1967b, Sept.

Goddard, G., McIntyre, D., & Leech, C. A permanent change in brain function resulting from daily electrical stimulation. Exp. Neurol., 1969, 25, 295 - 330.

Guerrero-Figueroa, R., Barros, A., Heath, R., & Gonzalez, G. Experimental subcortical epileptiform focus. Epilepsia, 1964, 5, 112 - 139.

Herberg, L., Tress, K., Blundell, J. Raising the threshold in experimental epilepsy by hypothalamic and septal stimulation and by audiogenic seizures. Brain, 1969, 92, 313 - 328.

Herberg, L., & Watkins, P. Epileptiform seizures induced by hypothalamic stimulation in the rat: resistance to fits following fits. Nature, 1966, 209, 515 - 516.

Hughes, J. Bilateral EEG abnormalities on corresponding areas. Epilepsia, 1966, 7, 44 - 52.

Jasper, H., Ward, A., & Pope, A. (Eds.) Basic Mechanisms of the Epilepsies. Boston: Little, Brown and Company, 1969.

Kreindler, A. Experimental epilepsy: Progress in brain research, Vol. 19. New York: Elsevier, 1965.

Krieg, W. Connections of the cerebral cortex: I. The albino rat. A topography of the cortical areas. J. Comp. Neurol., 1946, 84, 221 - 276.

Lescault, H. Some Neocortico-Amygdaloid Connections in the Cat. Unpublished Doctoral Dissertation, University of Ottawa, Ontario, Canada, 1971.

Lissák, K., & Endróczi, E. Electrical correlates of limbic activity. 24th Int. Cong. Physiological Sci., 1968, 6, 220 - 221.

Marshall, W. An application of the frozen sectioning technic for cutting serial sections thru the brain. Stain Technology, 1940, 15, 133 - 138.

Milner, P. Physiological Psychology. New York: Holt, Rinehart and Winston, Inc., 1970.

Morrell, F. Electrophysiological contributions to the neural basis of learning. Physiol. Rev., 1961a, 41, 493 - 494.

Morrell, F. Lasting changes in synaptic organization produced by continuous neuronal bombardment. In Delafresnaye, J. (Ed.), Brain Mechanisms and Learning. Oxford: Blackwell, 1961b, 375 - 392.

Morrell, F. Physiology and histochemistry of the mirror focus. In Jasper, H., Ward, A., & Pope, A. (Eds.), Basic Mechanisms of the Epilepsies. Boston: Little, Brown and Company, 1969, 357 - 370.

Morrell, F. Secondary epileptogenic lesions. Epilepsia, 1960, 1, 538 - 560.

Morrell, F., & Naquet, R. Conditioning of generalized hypersynchronous discharges in cats with epileptogenic lesions. EEG clin. Neurophysiol., 1956, 8, 728.

Naquet, R., & Morrell, F. Conditioning of hypersynchronous discharges of the myoclonic type produced by cardiozol injection into the cat. EEG clin. Neurophysiol., 1956, 8, 728.

Newman, B., & Feldman, S. Electrophysiological activity accompanying intracranial self-stimulation. J. Comp. and Physiol. Psychol., 1964, 57, No. 2, 244 - 247.

Pellegrino, L., & Cushman, A. A Stereotaxic Atlas of the Rat Brain. New York: Appleton-Century-Crofts, 1967.

Penfield, W. Epileptogenic lesions. Acta Neurol. Psychiat. Belg., 1956, 56, 75 - 88.

Penfield, W., & Jasper, H. Epilepsy and the Functional Anatomy of the Human Brain. Boston: Little, Brown and Company, 1954.

Pinsky, C., & Burns, B. Production of epileptiform afterdischarges in cat's cerebral cortex. J. Neurophysiol., 1961, 25, 359 - 379.

Powell, E. Septal efferents revealed by axonal degeneration in the rat. Experimental Neurology, 1963, 8, 406 - 422.

Proctor, F., Prince, D., & Morrell, F. Primary and secondary foci following depth lesions. Arch. Neurol., 1966, 15, 151 - 162.

Racine, R. The Modification of Afterdischarge and Convulsive Behaviour in the Rat by Electrical Stimulation. Unpublished Doctoral Dissertation, McGill University, Quebec, Canada, 1969.

Raisman, G. The connexions of the septum. Brain, 1966 89, 317 - 348.

Raisman, G., Cowan, W., & Powell, T. The extrinsic, afferent, commissural and association fibres of the hippocampus. Brain, 1965, 88, 963 - 996.

Robb, P. Epilepsy A Review of Basic and Clinical Research. Washington: U.S. Department of Health, Education and Welfare Public Health Service Publication No. 1357, 1965.

Sharpless, S. Isolated and deafferented neurons: disuse supersensitivity. In Jasper, H., Ward, A., & Pope, A. (Eds.), Basic Mechanisms of the Epilepsies. Boston: Little, Brown and Company, 1969, 329 - 348.

Thompson, R. Foundations of Physiological Psychology. New York: Harper & Row, Publishers, Incorporated, 1967.

Ungher, J., & Steriade, M. L'analyse électrographique de l'access épileptique conditionné. Acta Neurol. Psychiat. Belg., 1960, 10, 923 - 933.

Wada, A., & Cornelius, L. Functional alteration of deep structures in cats with chronic focal cortical irritative lesions. Arch. Neurol., 1960, 3, 425 - 447.

Ward, A., Jasper, H., & Pope, A. Clinical and experimental challenges of the epilepsies. In Jasper, H., Ward, A., & Pope, A. (Eds.), Basic Mechanisms of the Epilepsies. Boston: Little, Brown and Company, 1969, 1 - 12.

Winer, B. Statistical Principles in Experimental Design. New York: McGraw-Hill Book Company, Inc., 1962.

Woolsey, C. Organization of somatic sensory and motor areas in the cerebral cortex. In Harlow, H., & Woolsey, C. (Eds.), Biological and Biochemical Bases of Behavior. Madison: University of Wisconsin Press, 1958, 63 - 81.

ABBREVIATIONS FOR TABLES & FIGURES

A or AMYG	= amygdala.
AD	= afterdischarge.
Av.	= average (mean).
C or CORT	= anterior neocortex.
df	= degrees of freedom.
dH or dHPC	= dorsal hippocampus.
F	= variance ratio.
N	= number of subjects or observations.
p	= probability.
S or SEPT	= septal area.
SD	= stimulation day.
S's	= subjects.
(Sec.)	= seconds.
t	= student's "t" statistic.
vH or vHPC	= ventral hippocampus.
$\bar{X}_C$	= Column mean.
$\bar{X}_R$	= Row mean.
μv	= microvolts.

Table 1

Anatomical relationships of the structures used for transfer testing. Column 1 indicates the pairs of structures used for transfer testing (primary site listed first). Column 2 indicates the general nature of each of the structures (e.g. neocortex, "old" cortex). Column 3 indicates whether or not direct connections exist from the primary site to the secondary site. Column 4 lists some relevant anatomical references. (The propagation which was found between these structures at various stages of testing is indicated in Tables 4, 5, 7 and 8.)

(Table 1)

Column One	Column Two	Column Three	Column Four
CORT-AMYG	Neocortex-Subcortex	No direct connections.	Cowan et al., 1965. Lescault, 1971.
AMYG-SEPT	Subcortex-Subcortex	Probably no direct connections to medial or lateral nucleus.	Cowan et al., 1965. Raisman, 1966.
AMYG-dHPC	Subcortex-Archicortex	No direct connections.	Cowan et al., 1965. Raisman et al., 1965.
AMYG-vHPC	Subcortex-Archicortex	No direct connections.	Cowan et al., 1965. Raisman et al., 1965.
SEPT-AMYG	Subcortex-Subcortex	No direct connections.	Cowan et al., 1965. Raisman, 1966.
SEPT-dHPC	Subcortex-Archicortex	Direct connections.	Raisman, 1966. Raisman et al., 1965.
SEPT-vHPC	Subcortex-Archicortex	Direct connections.	Raisman, 1966. Raisman et al., 1965.
dHPC-AMYG	Archicortex-Subcortex	No direct connections.	Cowan et al., 1965.
dHPC-SEPT	Archicortex-Subcortex	Direct connections.	Raisman, 1966.
vHPC-AMYG	Archicortex-Subcortex	No direct connections.	Cowan et al., 1965.
vHPC-SEPT	Archicortex-Subcortex	Direct connections.	Raisman, 1966.

Table 2

Sites of primary and secondary stimulation in each subject as verified by histological examination. Each subject is listed by number (e.g. "#14"), and following each subject number is a designation of the subject's primary (listed first) and secondary (listed second) electrode placement (e.g. "A 12, S 4;" letters and numbers refer to the placements illustrated in Figure 1). Subject numbers are provided for reference purposes only and do not indicate the order of surgery.

(Table 2)

AMYG-CORT

#6: A24,C7
#7: A19,C7*
#8: A25,C7
#9: A19,C4
#10: A13,C6

CORT-AMYG

#1: C6,A22*
#2: C5,A19*
#3: C2,A18*
#4: C1,A11*
#5: C3,A14*

SEPT-AMYG

#31: S16,A 2*
#32: S15,A 4
#33: S17,A23
#34: S 6,A20
#35: S10,A18*

dHPC-AMYG

#52: dH12,A 3
#53: dH15**
#54: dH15,A 5
#55: dH 1,A 7*
#56: dH 4,A21*
#57: dH 2,A16*

vHPC-AMYG

#66: vH 7,A 1*
#67: vH13,A 2*
#68: vH11,A21*
#69: vH 3,A 8*
#70: vH 4,A20*
#71: vH10**
#72: vH12,A12

AMYG-SEPT

#11: A23,S12*
#12: A14,S 2
#13: A16,S 3
#14: A12,S 4*
#15: A23,S12*

dHPC-SEPT

#58: dH 8,S1*
#59: dH 5,S7*
#60: dH12**
#61: dH 6,S4*
#62: dH 4,S5*
#63: dH 6,S9*
#64: dH 8,S5*
#65: dH 4,S6*

vHPC-SEPT

#73: vH 9,S4*
#74: vH 5,S2*
#75: vH11,S5*
#76: vH 2,S1
#77: vH 8,S9*
#78: vH 3,S7*

AMYG-dHPC

#16: A16,dH 9*
#17: A13,dH 3*
#18: A18,dH 7
#19: A20,dH 7
#20: A15,dH 9
#21: A17,dH14
#22: A18,dH10*
#23: A18,dH16

SEPT-dHPC

#36: S 9,dH11*
#37: S13,dH 9
#38: S 1,dH 7*
#39: S 5,dH 2*
#40: S 3,dH 3
#41: S 7,dH 3
#42: S 7,dH 4*
#43: S 2**
#44: S16,dH14

AMYG-vHPC

#24: A23,vH 4*
#25: A 9,vH 2*
#26: A 8,vH 3
#27: A20,vH 3*
#28: A 6,vH 4
#29: A10,vH 4
#30: A16,vH11

SEPT-vHPC

#45: S 5,vH 5*
#46: S 5,vH14*
#47: S11**
#48: S 5,vH 5*
#49: S14,vH 6
#50: S 7,vH 6*
#51: S 4,vH 1

* Records used for detailed analysis of afterdischarge and seizure development.

** Subject lost to illness before testing of the secondary site.

Table 3

Mean durations of primary afterdischarges in (A.) cortical and (B.) subcortical subjects on four crucial test days: the day of the first preseizure afterdischarge; the day of the last preseizure afterdischarge; the day of the first seizure discharge; the day of the last seizure discharge. (Ranges are indicated in parentheses. N = number of subjects.) A statistical analysis of the differences found follows each part of the table. (Two-tailed probabilities are indicated for the individual comparisons.)

(Table 3)

A. Cortical S's

	First Preseiz. AD (Sec.)	Last Preseiz. AD (Sec.)	First Seiz. AD (Sec.)	Last Seiz. AD (Sec.)
CORT N = 5	---*	---*	8.5 (7.0-11.5)	10.8 (8.5-13.0)

* Seizure onset occurred immediately in Cortical S's.
$t = 2.1$, $df = 4$, $p > 0.05$

B. Subcortical S's

	First Preseiz. AD (Sec.)	Last Preseiz. AD (Sec.)	First Seiz. AD (Sec.)	Last Seiz. AD (Sec.)	$\bar{X}_R$
AMYG N = 10	20.1 (5.5-45.0)	41.5 (22.5-70.0)	75.5 (32.5-145.0)	70.0 (49.0-95.0)	51.8
SEPT N = 10	17.3 (3.5-35.0)	47.1 (8.0-95.0)	76.3 (28.5-111.0)	76.0 (44.5-109.0)	54.2
dHPC N = 10	21.1 (15.0-35.0)	35.1 (21.0-53.0)	46.1 (26.0-62.5)	56.1 (23.5-73.0)	39.6
vHPC N = 10	18.8 (4.0-43.0)	34.0 (11.5-49.0)	83.3 (26.0-178.5)	91.4 (41.5-139.0)	56.9
$\bar{X}_C$	19.4	39.4	70.3	73.4	

Analysis of Variance for Table 3B

Source	df	Mean Square	F	p
Rows	3	2321.5	2.8	> 0.05
Columns	3	26755.6	61.0	< 0.01
Interaction	9	978.0	2.2	> 0.05
S's within Rows	36	815.0		
Columns x S's within Rows	108	438.8		

Individual Comparisons

First vs Last Preseizure AD's: $t = 4.28$, $df = 108$, $p < 0.005$
Last Preseizure vs First Seizure AD's: $t = 6.60$, $df = 108$, $p < 0.005$
First Seizure vs Last Seizure AD's: $t = 0.66$, $df = 108$, $p > 0.05$

Table 4

Percentage of subjects in each group that showed propagated discharge (either projected or reactive) in the secondary site during the first discharge in the primary site.
(N = number of subjects.)

(Table 4)

Secondary Site (Driven)

Primary Site (Stimulated)	AMYG % S's with Prop. AD in 2nd Site	SEPT % S's with Prop. AD in 2nd Site	dHPC % S's with Prop. AD in 2nd Site	vHPC % S's with Prop. AD in 2nd Site
CORT	40.0 N = 5			
AMYG		20.0 N = 5	12.5 N = 8	28.6 N = 7
SEPT	100.0 N = 5		37.5 N = 8	100.0 N = 6
dHPC	100.0 N = 5	71.4 N = 7		
vHPC	100.0 N = 6	100.0 N = 6		

Table 5

Percentage of subjects in each group that showed reactive discharge in the secondary site during the first discharge in the primary site. (N = number of subjects.)

(Table 5)

Secondary Site (Driven)

Primary Site (Stimulated)	AMYG % S's with React. AD in 2nd Site	SEPT % S's with React. AD in 2nd Site	dHPC % S's with React. AD in 2nd Site	vHPC % S's with React. AD in 2nd Site
CORT	0.0 N = 5			
AMYG		0.0 N = 5	0.0 N = 8	0.0 N = 7
SEPT	0.0 N = 5		25.0 N = 8	50.0 N = 6
dHPC	0.0 N = 5	57.1 N = 7		
vHPC	50.0 N = 6	50.0 N = 6		

Table 6

Mean number of discharges required at each primary site to cause reactive discharge in each secondary site. (Ranges are indicated in parentheses. N = number of subjects.)

(Table 6)

Secondary Site (Driven)

Primary Site (Stimulated)	AMYG No. Prim. AD's to 2nd Site React. AD Onset	SEPT No. Prim. AD's to 2nd Site React. AD Onset	dHPC No. Prim. AD's to 2nd Site React. AD Onset	vHPC No. Prim. AD's to 2nd Site React. AD Onset
CORT	--* N = 5			
AMYG		6.8 (4 - 9) N = 5	10.0** (5 - 19) N = 8	10.3** (2 - 22) N = 7
SEPT	14.5 (12 - 20) N = 5		8.4 (1 - 28) N = 8	7.2 (1 - 24) N = 6
dHPC	25.4 (24 - 27) N = 5	3.4 (1 - 12) N = 7		
vHPC	6.2 (1 - 17) N = 6	3.5 (1 - 14) N = 6		

* No subject ever developed reactive discharge.

**Includes one subject that never developed reactive discharge (scored as actual number of discharges plus one).

Table 7

Percentage of subjects in each group that showed reactive discharge in the secondary site during the first motor seizure triggered from the primary site.

(Table 7)

Secondary Site (Driven)

Primary Site (Stimulated)	AMYG % S's with React. AD in 2nd Site	SEPT % S's with React. AD in 2nd Site	dHPC % S's with React. AD in 2nd Site	vHPC % S's with React. AD in 2nd Site
CORT	0.0 N = 5			
AMYG		100.0 N = 5	75.0 N = 8	57.1 N = 7
SEPT	100.0 N = 5		62.5 N = 8	83.3 N = 6
dHPC	80.0 N = 5	100.0 N = 7		
vHPC	100.0 N = 6	100.0 N = 6		

Table 8

Percentage of subjects in each group that showed reactive discharge in the secondary site during the last (pre-transfer) motor seizure triggered from the primary site.

(TABLE 8)

Secondary Site (Driven)

Primary Site (Stimulated)	AMYG % S's with React. AD in 2nd Site	SEPT % S's with React. AD in 2nd Site	dHPC % S's with React. AD in 2nd Site	vHPC % S's with React. AD in 2nd Site
CORT	0.0 N = 5			
AMYG		100.0 N = 5	87.5 N = 8	85.7 N = 7
SEPT	100.0 N = 5		100.0 N = 8	100.0 N = 6
dHPC	100.0 N = 5	100.0 N = 7		
vHPC	100.0 N = 6	100.0 N = 6		

Table 9

Mean number of reactive discharges that occurred at each secondary site during the whole course of the pre-transfer stimulation of the primary site. (Ranges are indicated in parentheses. N = number of subjects.)

(Table 9)

Secondary Site (Driven)

Primary Site (Stimulated)	AMYG Av. Total React. AD's	SEPT Av. Total React. AD's	dHPC Av. Total React. AD's	vHPC Av. Total React. AD's
CORT	0.0 (None) N = 5			
AMYG		15.0 (13 - 17) N = 5	11.6 (0 - 19) N = 8	9.4 (0 - 15) N = 7
SEPT	13.6 (11 - 17) N = 5		14.9 (1 - 25) N = 8	17.8 (7 - 25) N = 6
dHPC	9.2 (4 - 12) N = 5	47.6 (33 - 69) N = 7		
vHPC	15.7 (10 - 24) N = 6	29.3 (10 - 42) N = 6		

Table 10

Mean numbers of primary site afterdischarges required at primary sites to cause the first motor seizure in (A.) cortical and (B.) subcortical subjects. (Ranges are indicated in parentheses. N = number of subjects.) There was no overlap between the scores for cortical and subcortical subjects. A statistical analysis of the differences found among the subcortical subjects follows Part B. (Two-tailed probabilities are indicated for the individual comparisons.)

A. Cortical S's

	No. AD's to Seizure
CORT N = 5	0.0 (None)

B. Subcortical S's

	No. AD's to Seizure
AMYG N = 25	10.6 (6-19)
SEPT N = 21	17.4 (7-29)
dHPC N = 14	37.3 (25-60)
vHPC N = 13	20.6 (9-28)

Analysis of Variance for Table 10B

Source	df	Mean Square	F	p
Between Groups	3	1981.4	40.4	< 0.01
Within Groups	69	49.0		

Individual Comparisons

AMYG vs SEPT: $t = 3.6$, $df = 69$, $p < 0.01$
AMYG vs dHPC: $t = 11.0$, $df = 69$, $p < 0.005$
AMYG vs vHPC: $t = 3.4$, $df = 69$, $p < 0.05$
SEPT vs dHPC: $t = 7.5$, $df = 69$, $p < 0.005$
SEPT vs vHPC: $t = 0.3$, $df = 69$, $p > 0.05$
dHPC vs vHPC: $t = 6.6$, $df = 69$, $p < 0.005$

Table 11

Mean latencies of first and last motor seizures evoked in (A.) cortical and (B.) subcortical subjects during primary site stimulation. (Ranges are indicated in parentheses. N = number of subjects.) A statistical analysis of the differences found among the subcortical subjects follows Part B.

A. Cortical S's

	Average Latency of First Seizure (Sec.)	Average Latency of Last Seizure (Sec.)
CORT N = 5	0.0 (None)	0.0 (None)

B. Subcortical S's

	Average Latency of First Seizure (Sec.)	Average Latency of Last Seizure (Sec.)	$\bar{X}_R$
AMYG N = 10	30.5 (0.5 - 64.5)	4.9 (0.0 - 16.0)	17.7
SEPT N = 10	43.2 (4.0 - 86.5)	12.4 (0.0 - 37.5)	27.8
dHPC N = 10	30.5 (15.0 - 42.0)	18.5 (11.0 - 30.0)	24.5
vHPC N = 10	37.5 (0.5 - 87.5)	18.1 (1.0 - 49.0)	27.8
$\bar{X}_C$	35.4	13.4	

Analysis of Variance for Table 11B

Source	df	Mean Square	F	p
Rows	3	455.6	1.3	> 0.05
Columns	1	9636.0	36.6	< 0.005
Interaction	3	332.8	1.3	> 0.05
S's within Rows	36	351.7		
Columns x S's within Rows	36	263.3		

Table 12

Mean durations of the first and last motor seizures evoked in (A.) cortical and (B.) subcortical subjects during primary site stimulation. (Ranges are indicated in parentheses. N = number of subjects.) Statistical analyses of the differences found follow each part of the table. (Two-tailed probabilities are indicated for the individual comparisons.)

A. Cortical S's

	Average Duration of First Seizure (Sec.)	Average Duration of Last Seizure (Sec.)
CORT N = 5	8.5 (7.0 - 11.5)	10.8 (8.5 - 13.0)

$t = 2.1$, $df = 4$, $p > 0.05$

B. Subcortical S's

	Average Duration of First Seizure (Sec.)	Average Duration of Last Seizure (Sec.)	$\bar{X}_R$
AMYG N = 10	39.5 (5.0 - 90.5)	49.7 (25.0 - 72.5)	44.6
SEPT N = 10	23.3 (3.0 - 67.0)	41.5 (35.0 - 58.0)	32.4
dHPC N = 10	17.8 (9.0 - 33.0)	34.0 (17.5 - 49.0)	26.0
vHPC N = 10	29.3 (6.5 - 91.0)	51.8 (24.5 - 80.5)	40.6
$\bar{X}_C$	27.5	44.3	

Analysis of Variance for Table 12B

Source	df	Mean Square	F	p
Rows	3	1387.9	3.7	< 0.025
Columns	1	5619.6	14.5	< 0.005
Interaction	3	128.3	0.3	> 0.05
S's within Rows	36	351.7		
Columns x S's within Rows	36	263.3		

Individual Comparisons

AMYG vs SEPT: $t = 2.00$, $df = 36$, $p > 0.05$
AMYG vs dHPC: $t = 3.06$, $df = 36$, $p < 0.05$
AMYG vs vHPC: $t = 0.66$, $df = 36$, $p > 0.05$
SEPT vs dHPC: $t = 1.06$, $df = 36$, $p > 0.05$
SEPT vs vHPC: $t = 1.34$, $df = 36$, $p > 0.05$
dHPC vs vHPC: $t = 2.40$, $df = 36$, $p > 0.05$

Table 13

Number of subjects in each subcortical group that displayed at least one Stage 5 seizure during their first two and during their last two seizure days. A statistical analysis of the differences between "early" and "late" seizures is presented to the right of each section of the table. (The chi square test was used to calculate the probabilities.)

(Table 13)

First 2 Seizure Days

Last 2 Seizure Days

	No. S's with no Stage 5 Seizures	No. S's with at least one Stage 5 Seizure		
AMYG				
No. S's with at least one Stage 5 Seizure	0	2	2	$X^2 = 6.0$
No. S's with no Stage 5 Seizures	2	6	8	df = 1
	2	8		$p < 0.02$
SEPT				
No. S's with at least one Stage 5 Seizure	0	2	2	$X^2 = 5.0$
No. S's with no Stage 5 Seizures	3	5	8	df = 1
	3	7		$p < 0.05$
dHPC				
No. S's with at least one Stage 5 Seizure	0	1	1	$X^2 = 8.0$
No. S's with no Stage 5 Seizures	1	8	9	df = 1
	1	9		$p < 0.01$
vHPC				
No. S's with at least one Stage 5 Seizure	0	4	4	$X^2 = 5.0$
No. S's with no Stage 5 Seizures	1	5	6	df = 1
	1	9		$p < 0.05$

Table 14

Mean numbers of primary afterdischarges evoked between the onset of secondary reactive discharge and the onset of primary site motor seizures. (Ranges are indicated in parentheses. N = number of subjects.) Simultaneous onset was scored as "0." When secondary reactive discharge started before seizure onset, a "plus" score was given and when it started after seizure onset, a "minus" score was given.

(Table 14)

Secondary Site (Driven)

Primary Site (Stimulated)	AMYG No. AD's between 1st React. AD & 1st Seizure	SEPT No. AD's between 1st React. AD & 1st Seizure	dHPC No. AD's between 1st React. AD & 1st Seizure	vHPC No. AD's between 1st React. AD & 1st Seizure
CORT	--* N = 5			
AMYG		+4.0 (+6 to +1) N = 5	+0.9** (+8 to -10) N = 8	-0.7** (+4 to -10) N = 7
SEPT	+4.6 (+8 to 0) N = 5		+4.0 (+12 to -7) N = 8	+13.7 (+28 to -2) N = 6
dHPC	+3.8 (+19 to -2) N = 5	+42.0 (+59 to +29) N = 7		
vHPC	+11.2 (+18 to +5) N = 6	+19.0 (+26 to 0) N = 6		

* No subject ever developed reactive discharge. Score would be over 10 in a negative direction.

**Contains one subject which never developed reactive discharge (scored as "-10").

Table 15

Measurements related to the transfer effect.

Column 1 Mean numbers of afterdischarges required at the subcortical sites to cause the first seizure during primary stimulation. (The data are re-presented from Table 10. Ranges are indicated in parentheses. N = number of subjects.)

Column 2 Mean number of afterdischarges required at the same sites to cause the first seizure during secondary stimulation. (Ranges are indicated in parentheses. N = number of subjects.)

Column 3 Probabilities associated with the differences between the scores in Columns 1 and 2 as calculated by the Mann-Whitney U Test. (Probabilities are one-tailed.)

Column 4 Percent decrease in the number of seizures required to cause seizures during secondary stimulation.

Column 5 Percent of subjects in each secondary group that had a seizure during the first secondary afterdischarge.

Column 6 Average number of reactive discharges which had occurred in each of the secondary sites during the previous stimulation of the primary sites. (These data are re-presented from Table 9.) Groups in which the mean number of discharges during primary site stimulation was equal to or greater than the mean number of primary discharges normally necessary to cause seizures are marked with an asterisk.

(Table 15)

	1 Primary AD's to 1st Seiz.	2 Secondary AD's to 1st Seiz.	3 p	4 % Dec. in Sec. Rate	5 % Imm. Sec. Seiz.	6 Prev. Sec. React. AD's
AMYG	10.6 (6-19) N = 25	After 7.6 CORT (5-9) N = 5	= 0.095	28.3	0.0	0.0
		After 2.0 SEPT (1-3) N = 5	= 0.0006	81.1	40.0	*13.6
		After 1.8 dHPC (1-3) N = 5	= 0.0006	83.0	40.0	* 9.2
		After 1.5 vHPC (1-3) N = 6	= 0.0002	85.8	66.7	*15.7
SEPT	17.4 (7-29) N = 21	After 8.2 AMYG (5-13) N = 5	= 0.009	52.9	0.0	15.0
		After 2.4 dHPC (1-6) N = 7	= 0.0001	86.2	57.1	*47.6
		After 2.0 vHPC (1-3) N = 6	< 0.0003	88.5	33.3	*29.3
dHPC	37.3 (25-60) N = 14	After 24.0 AMYG (4-50) N = 8	= 0.05	35.7	0.0	11.6
		After 14.5 SEPT (7-32) N = 8	= 0.002	61.1	0.0	14.9
vHPC	20.6 (9-28) N = 13	After 10.7 AMYG (1-26) N = 7	= 0.02	48.1	14.3	9.4
		After 5.2 SEPT (2-9) N = 6	< 0.002	74.8	0.0	17.8

Table 16

Mean durations of first afterdischarges in primary subcortical subjects (data re-presented from Table 3), and in secondary subcortical subjects (A.) that did not show transfer, and (B.) that did show transfer. (Ranges are indicated in parentheses. N = number of subjects.) A statistical analysis of the differences found in the case of the subjects that did show transfer follows Part B. (Two-tailed probabilities are given for the individual comparisons.)

A. Comparison for S's that Did Not Show Transfer

	Primary AD's (Sec.)	Secondary AD's (Sec.)
AMYG	20.1 (5.5 - 45.0) N = 10	20.1 (11.5 - 30.0) N = 5

B. Comparison for S's that Did Show Transfer

	Primary AD's (Sec.)	Secondary AD's (Sec.)	$\bar{X}_R$
AMYG	20.1 (5.5 - 45.0) N = 10	54.7 (8.0 - 87.0) N = 16	37.4
SEPT	17.4 (3.5 - 35.0) N = 10	55.3 (7.5 - 96.0) N = 18	36.3
dHPC	21.2 (15.0 - 35.0) N = 10	23.5 (14.0 - 40.0) N = 16	22.3
vHPC	18.7 (4.0 - 43.0) N = 10	35.8 (11.0 - 71.0) N = 12	27.2
$\bar{X}_C$	19.3	42.3	

Analysis of Variance for Table 16B*

Source	df	Mean Square	F	p
Rows	3	1278.5	2.3	> 0.05
Columns	1	12752.6	22.6	< 0.01
Interaction	3	1643.6	2.9	< 0.05
Within Cells	94	564.2		

Individual Comparisons (Secondary Groups)

AMYG vs SEPT: $t = 0.07$, $p > 0.05$
AMYG vs dHPC: $t = 3.71$, $p < 0.005$
AMYG vs vHPC: $t = 2.06$, $p > 0.05$
SEPT vs dHPC: $t = 3.90$, $p < 0.005$
SEPT vs vHPC: $t = 2.21$, $p > 0.05$
dHPC vs vHPC: $t = 1.34$, $p > 0.05$

* Unweighted-Means Solution

Table 17

Mean durations of afterdischarges at seizure onset in primary subcortical subjects (data re-presented from Table 3) and in secondary subcortical subjects (A.) that did not show transfer and (B.) that did show transfer. (Ranges are indicated in parentheses. N = number of subjects.) A statistical analysis follows both parts of the table. (Two-tailed probabilities are given for individual comparisons.)

A. Comparison for S's that Did Not Show Transfer

	Primary AD's (Sec.)	Secondary AD's (Sec.)
AMYG	75.5 (32.5 - 145.0) N = 10	45.8 (28.5 - 87.0) N = 5

$t = 1.6$, $df = 13$, $p > 0.10$

B. Comparison for S's that Did Show Transfer

	Primary AD's (Sec.)	Secondary AD's (Sec.)	$\bar{X}_R$
AMYG	75.5 (32.5 - 145.0) N = 10	76.9 (22.5 - 126.5) N = 16	76.2
SEPT	76.3 (28.5 - 111.0) N = 10	87.4 (34.5 - 170.0) N = 18	81.8
dHPC	46.1 (26.0 - 62.5) N = 10	82.4 (22.0 - 128.0) N = 16	64.3
vHPC	83.3 (26.0 - 178.5) N = 10	89.4 (15.0 - 226.5) N = 12	86.4
$\bar{X}_C$	70.3	84.0	

Analysis of Variance for Table 17B*

Source	df	Mean Square	F	p
Rows	3	2203.2	1.6	> 0.05
Columns	1	4537.2	3.4	> 0.05
Interaction	3	1451.5	1.1	> 0.05
Within Cells	94	1339.3		

* Unweighted-Means Solution

Table 18

Percentage of subjects in each group that showed propagated discharge (either projected or reactive) in the primary site during the first (electrically evoked) discharge in the secondary site. (N = number of subjects.)

(Table 18)

Primary Site (Driven)

Secondary Site (Stimulated)	CORT % S's with Prop. AD in 1st Site	AMYG % S's with Prop. AD in 1st Site	SEPT % S's with Prop. AD in 1st Site	dHPC % S's with Prop. AD in 1st Site	vHPC % S's with Prop. AD in 1st Site
AMYG	100.0 N = 5		100.0 N = 5	50.0* N = 4	100.0 N = 6
SEPT		100.0 N = 5		85.7 N = 7	100.0 N = 6
dHPC		100.0 N = 8	100.0 N = 8		
vHPC		100.0 N = 7	100.0 N = 6		

* Day's records lost for one subject.

Table 19

Percentage of subjects in each group that showed reactive discharge in the primary site during the first (electrically evoked) discharge in the secondary site. (N = number of subjects.)

(Table 19)

Primary Site (Driven)

Secondary Site (Stimulated)	CORT % S's with React. AD in 1st Site	AMYG % S's with React. AD in 1st Site	SEPT % S's with React. AD in 1st Site	dHPC % S's with React. AD in 1st Site	vHPC % S's with React. AD in 1st Site
AMYG	0.0 N = 5		40.0 N = 5	0.0* N = 4	83.3 N = 6
SEPT		0.0 N = 5		71.4 N = 7	83.3 N = 6
dHPC		0.0 N = 8	12.5 N = 8		
vHPC		0.0 N = 7	33.3 N = 6		

* Day's records lost for one subject.

Table 20

Mean number of (electrically evoked) discharges required at each secondary site to cause reactive discharge in each primary site. (Ranges are indicated in parentheses. N = number of subjects.)

(Table 20)

Primary Site (Driven)

Secondary Site (Stimulated)	CORT No. Sec. AD's to 1st Site React. AD Onset	AMYG No. Sec. AD's to 1st Site React. AD Onset	SEPT No. Sec. AD's to 1st Site React. AD Onset	dHPC No. Sec. AD's to 1st Site React. AD Onset	vHPC No. Sec. AD's to 1st Site React. AD Onset
AMYG	9.0 (5-12) N = 5		2.2 (1-4) N = 5	3.0 (2-5) N = 4*	1.7 (1-5) N = 6
SEPT		7.8 (3-13) N = 5		1.9 (1-5) N = 7	1.2 (1-2) N = 6
dHPC		24.1 (4-50) N = 8	10.9 (1-29) N = 8		
vHPC		10.5 (2-17) N = 6*	4.5 (1-9) N = 6		

* One subject omitted due to incompleteness of electrographic records.

Table 21

Mean numbers of secondary afterdischarges evoked between the onset of primary reactive discharge and the onset of secondary site motor seizures. (Ranges are indicated in parentheses. N = number of subjects.) Simultaneous onset was scored as "0." When primary reactive discharge started before seizure onset, a "plus" score was given and when it started after seizure onset, a "minus" score was given.

(Table 21)

Primary Site (Driven)

Secondary Site (Stimulated)	CORT No. AD's between 1st React. AD & 1st Seizure	AMYG No. AD's between 1st React. AD & 1st Seizure	SEPT No. AD's between 1st React. AD & 1st Seizure	dHPC No. AD's between 1st React. AD & 1st Seizure	vHPC No. AD's between 1st React. AD & 1st Seizure
AMYG	-1.6 (0 to -4) N = 5		0.0 (None) N = 5	-1.3 (-1 to -2) N = 3*	-0.2 (+1 to -2) N = 6
SEPT		+0.4 (+2 to 0) N = 5		-0.3 (0 to -2) N = 7	+0.8 (+2 to 0) N = 6
dHPC		0.0 (None) N = 8	+3.6 (+26 to -6) N = 8		
vHPC		+1.7 (+10 to 0) N = 6**	+0.7 (+3 to 0) N = 6		

* Two subjects omitted due to incompleteness of electrographic records.

** One subject omitted due to incompleteness of electrographic records.

Table 22

Mean latencies of the first seizures produced by primary subcortical subjects (data re-presented from Table 11), and by secondary subcortical subjects (A.) that did not show transfer and (B.) that did show transfer. (Ranges are indicated in parentheses. N = number of subjects.) Statistical analyses follow each part of the table. (Two-tailed probability is indicated for the t test.)

A. Comparison for S's that Did Not Show Transfer

	Average Primary Seizure Latency (Sec.)	Average Secondary Seizure Latency (Sec.)
AMYG	30.5 (0.5 - 64.5) N = 10	6.8 (1.0 - 16.5) N = 5

$t = 2.2$, $df = 13$, $p < 0.05$

B. Comparison for S's that Did Show Transfer

	Average Primary Seizure Latency (Sec.)	Average Secondary Seizure Latency (Sec.)	$\bar{X}_R$
AMYG	30.5 (0.5 - 64.5) N = 10	23.0 (0.5 - 47.0) N = 16	26.8
SEPT	43.2 (4.0 - 86.5) N = 10	19.0 (2.5 - 45.0) N = 18	31.1
dHPC	30.5 (15.0 - 42.0) N = 10	30.0 (14.0 - 50.5) N = 16	30.2
vHPC	37.5 (0.5 - 87.5) N = 10	37.5 (3.0 - 76.0) N = 12	37.5
$\bar{X}_C$	35.4	27.4	

Analysis of Variance for Table 22B*

Source	df	Mean Square	F	p
Rows	3	486.0	1.5	> 0.05
Columns	1	1549.3	4.7	< 0.05
Interaction	3	772.9	2.3	> 0.05
Within Cells	94	331.4		

* Unweighted-Means Solution

Table 23

Mean durations of the first seizures produced by primary subcortical subjects (data re-presented from Table 12), and by secondary subcortical subjects (A.) that did not show transfer and (B.) that did show transfer. (Ranges are indicated in parentheses. N = number of subjects.) Statistical analyses follow each part of the table. (Two-tailed probability is indicated for the t test.)

A. Comparison for S's that Did Not Show Transfer

	Average Primary Seizure Duration (Sec.)	Average Secondary Seizure Duration (Sec.)
AMYG	39.5 (5.0 - 90.5) N = 10	34.6 (9.0 - 78.0) N = 5

$t = 0.3$, $df = 13$, $p > 0.20$

B. Comparison for S's that Did Show Transfer

	Average Primary Seizure Duration (Sec.)	Average Secondary Seizure Duration (Sec.)	$\bar{X}_R$
AMYG	39.5 (5.0 - 90.5) N = 10	45.6 (1.0 - 81.5)	42.5
SEPT	23.4 (3.0 - 67.0) N = 10	47.3 (6.0 - 111.5) N = 18	35.3
dHPC	17.9 (9.0 - 33.0) N = 10	42.9 (5.0 - 81.5) N = 16	30.4
vHPC	29.4 (6.5 - 91.0) N = 10	30.5 (5.5 - 67.0) N = 12	29.9
$\bar{X}_C$	27.5	41.6	

Analysis of Variance for Table 23B*

Source	df	Mean Square	F	p
Rows	3	829.5	1.5	> 0.05
Columns	1	4756.3	8.6	< 0.005
Interaction	3	899.8	1.6	> 0.05
Within Cells	94	553.7		

* Unweighted-Means Solution

Table 24

Number of subjects that displayed at least one Stage 5 seizure during their first two seizure days in primary subcortical subjects (data re-presented from Table 13), and in secondary subcortical subjects (A.) that did not show transfer and (B.) that did show transfer. A statistical analysis of the differences between "early" seizures in primary and secondary subjects is presented to the right of each section of the table. (The chi square test was used to calculate probabilities.)

(Table 24)

A. AMYG

	First 2 Primary Seizures	First 2 Secondary Seizures		
No. S's with at least one Stage 5 Seizure	2	0	2	$\chi^2 = 0.6$
No. S's with no Stage 5 Seizures	8	5	13	df = 1
	10	5		$p > 0.30$

B. AMYG

No. S's with at least one Stage 5 Seizure	2	13	15	$\chi^2 = 7.3$
No. S's with no Stage 5 Seizures	8	3	11	df = 1
	10	16		$p < 0.01$

SEPT

No. S's with at least one Stage 5 Seizure	2	13	15	$\chi^2 = 5.1$
No. S's with no Stage 5 Seizures	8	5	13	df = 1
	10	18		$p < 0.05$

dHPC

No. S's with at least one Stage 5 Seizure	1	11	12	$\chi^2 = 6.3$
No. S's with no Stage 5 Seizures	9	5	14	df = 1
	10	16		$p < 0.02$

vHPC

No. S's with at least one Stage 5 Seizure	4	8	12	$\chi^2 = 0.8$
No. S's with no Stage 5 Seizures	6	4	10	df = 1
	10	12		$p > 0.30$

Table 25

Post-transfer seizure suppression seen in primary sites after five secondary seizures. Each cell indicates the mean number of post-transfer primary site stimulations given in that group before the recurrence of primary site seizures; the mean number of stimulations which had been previously given to the same subjects between the ninth and tenth pre-transfer seizures; and the difference between the two, i.e. the mean "suppression" score. (N = number of subjects.) The significances of the differences are also indicated. (One-tailed probabilities are given, calculated by Wilcoxon's matched-pairs signed-ranks test. See Ferguson, 1971.)

(Table 25)

Secondary Site (Site of Previous Transfer Stimulation)

Primary Site (Site of Stimulation)		AMYG	SEPT	dHPC	vHPC
CORT	Stims. Post	0.2			
	Stims. Pre.	-0.0			
	Suppression	0.2			
		p > 0.05			
		N = 5			
AMYG	Stims. Post		0.0	0.0	0.0
	Stims. Pre.		-0.0	-0.0	-0.0
	Suppression		0.0	0.0	0.0
			p > 0.05	p > 0.05	p > 0.05
			N = 5	N = 7*	N = 4**
SEPT	Stims. Post	1.5		0.9	0.3
	Stims. Pre.	-0.2		-0.0	-0.0
	Suppression	1.3		0.9	0.3
		p < 0.05		p > 0.05	p > 0.05
		N = 6		N = 7*	N = 6
dHPC	Stims. Post	1.6	1.0		
	Stims. Pre.	-0.4	-0.0		
	Suppression	1.2	1.0		
		p > 0.05	p > 0.05		
		N = 5	N = 6*		
vHPC	Stims. Post	2.0	0.4		
	Stims. Pre.	-0.2	-0.4		
	Suppression	1.8	0.0		
		p < 0.02	p > 0.05		
		N = 6	N = 5*		

* One subject lost to illness.

** Three subjects lost to illness.

Table 26

Percentages of post-transfer, pre-seizure primary site stimulations that were found to be accompanied by after-discharge. (N = number of stimulations.)

(Table 26)

Secondary Site (Site of Previous Transfer Stimulation)

Primary Site (Site of Stimulation)	AMYG	SEPT	dHPC	vHPC
CORT % Stims. with AD	0.0 N = 1			
AMYG % Stims. with AD		--**	--**	--**
SEPT % Stims. with AD	100.0* N = 9		83.3 N = 6	100.0 N = 2
dHPC % Stims. with AD	50.0 N = 8	0.0 N = 8		
vHPC % Stims. with AD	100.0* N = 12	50.0 N = 2		

* Group showed significant evidence of post-transfer seizure suppression.

** Resumption of primary site stimulation caused immediate seizures in every subject.

Table 27

Mean durations of primary afterdischarges during the last pre-transfer seizures and during the period of post-transfer seizure suppression following secondary stimulation of the amygdala in (A.) septal and (B.) ventral hippocampal subjects. (Ranges are indicated in parentheses. N = number of subjects. Mean pre- and post-transfer duration scores were first calculated for each subject by averaging all of the discharge durations during suppression and during a similar number of pre-transfer seizures. Group means were then calculated from these scores.) A statistical analysis of the differences between pre- and post-transfer durations is presented to the right of each part of the table. (Two-tailed probabilities are indicated.)

(Table 27)

Average AD Duration (Sec.)

Primary Site

A. SEPT
(N = 5)

During Last Pre-Transfer Seizures	During Post-Transfer Seizure Suppression	t	p
95.3 (80.5 - 103.5)	70.7 (15.0 - 118.0)	1.2	> 0.05

B. vHPC
(N = 6)

During Last Pre-Transfer Seizures	During Post-Transfer Seizure Suppression	t	p
99.9 (42.5 - 159.8)	42.6 (38.2 - 47.5)	3.2	< 0.05

Table 28

Numbers of subjects in each primary group that showed each of the patterns of response to decreasing stimulation illustrated in Figure 21. Indicated at the bottom of each column are the total number of subjects and the percentage of subjects which displayed each pattern.

(Table 28)

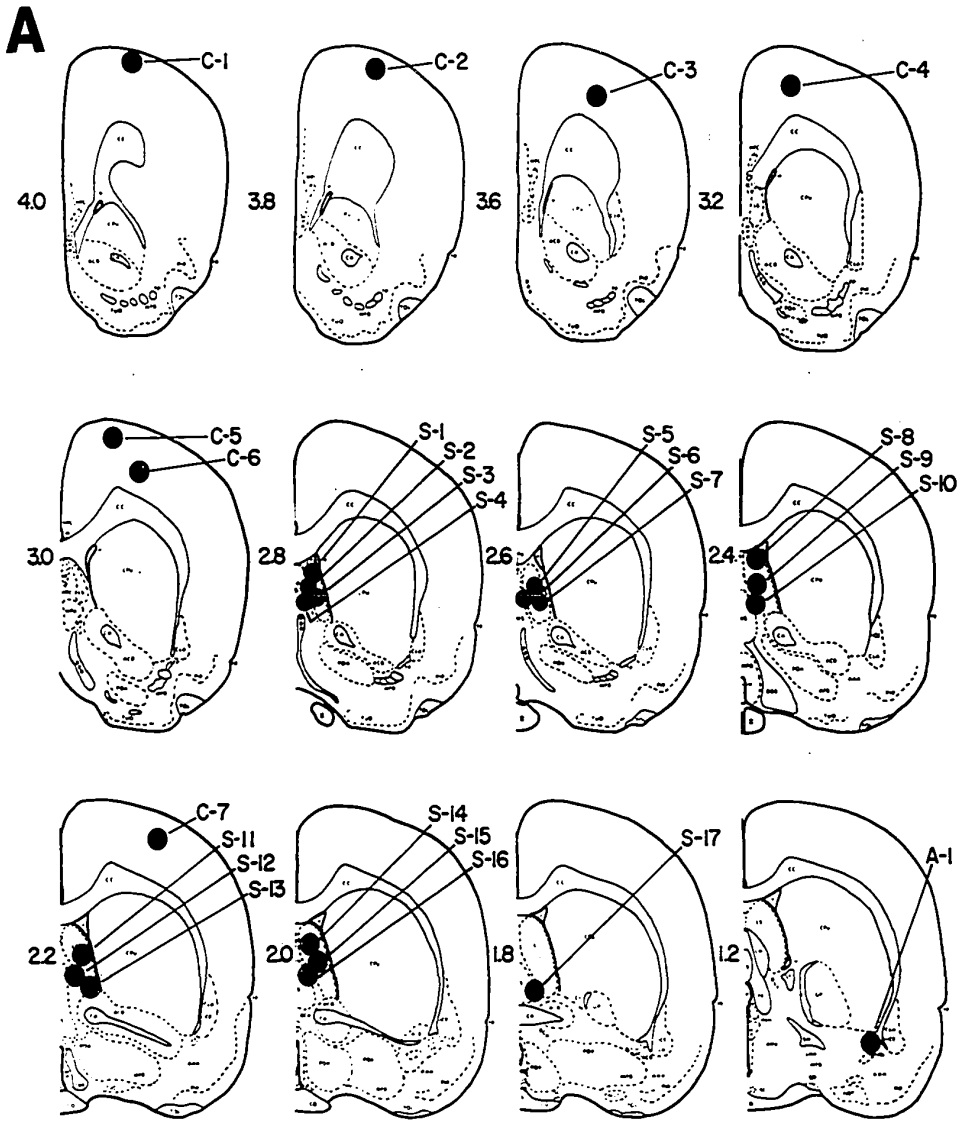
Pattern of Response

Site	Pattern A (No. of S's)	Pattern B (No. of S's)	Pattern C (No. of S's)
AMYG	2	3	0
SEPT	3	2	0
dHPC	3	2	0
vHPC	2	2	1
Total Subjects	10	9	1
% of Subjects	50	45	5

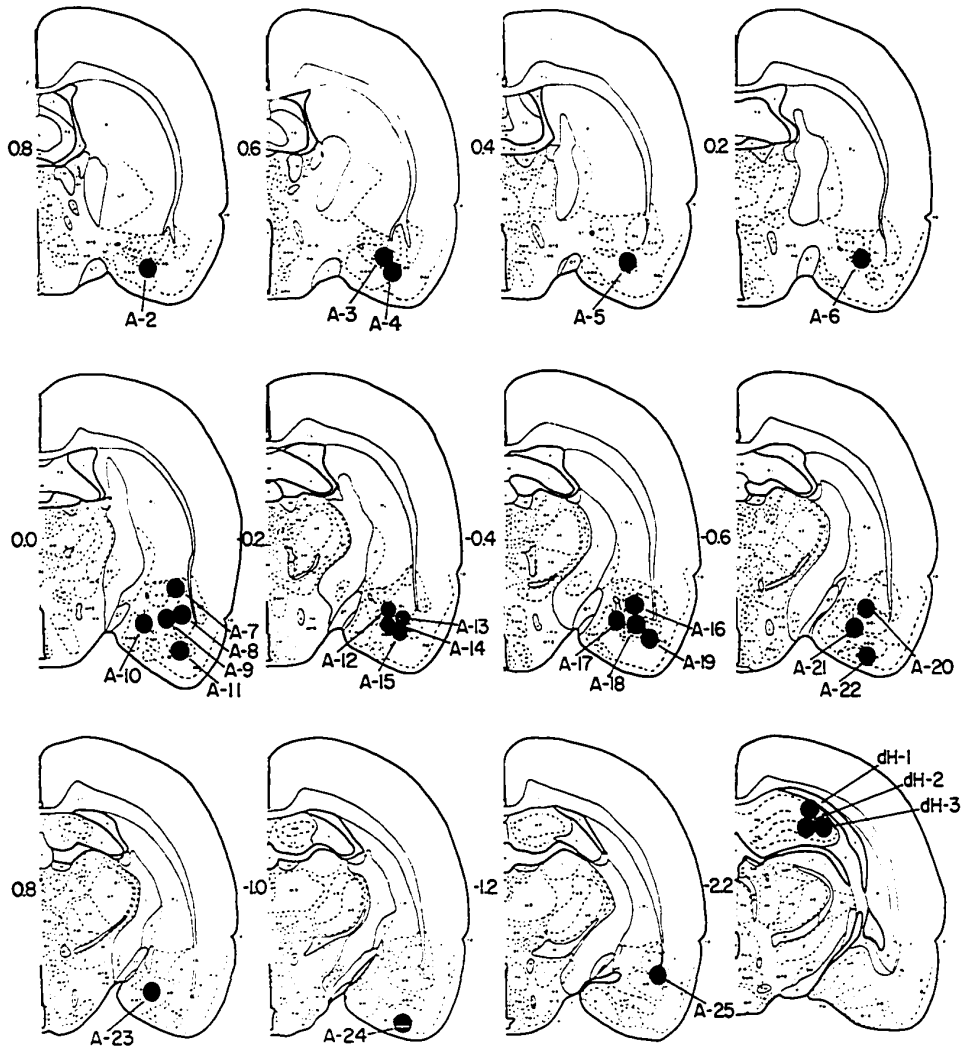
Figure 1

Electrode placements as verified by histological examination. A. All placements, plotted on frontal sections reproduced from A Stereotaxic Atlas of the Rat Brain (Pellegrino and Cushman, 1967) and numbered for reference (see Table 2; C = anterior neocortex; A = amygdala; S = septal area; dH = dorsal hippocampus; vH = ventral hippocampus). The anterior-posterior co-ordinates relative to bregma (millimeters) are indicated to the left of each section. B. Neocortical placements plotted on a parcellation of the cortical areas (modified from Krieg, 1946).

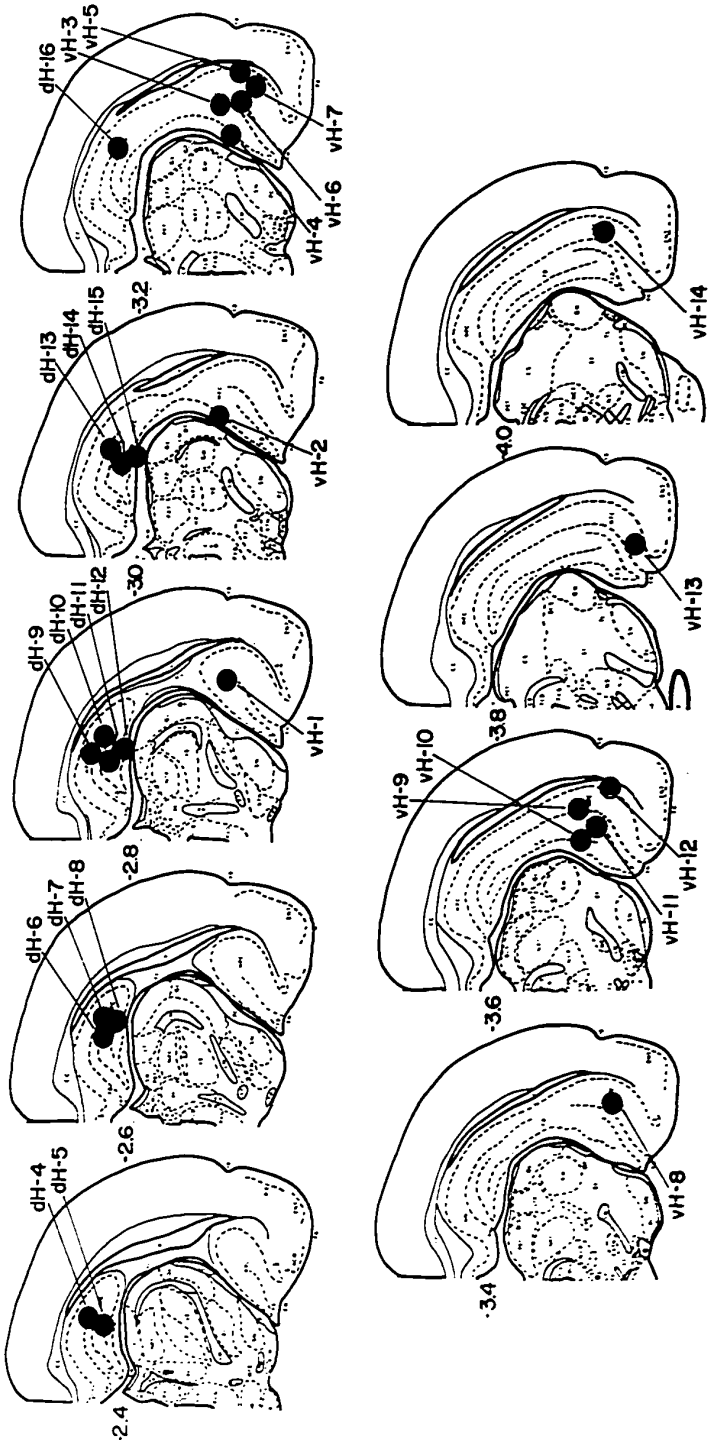
(Figure 1)


A
C-1
C-2
C-3
C-4
4.0
3.8
3.6
3.2
C-5
C-6
S-1
S-2
S-3
S-4
S-5
S-6
S-7
S-8
S-9
S-10
3.0
2.8
2.6
2.4
C-7
S-11
S-12
S-13
S-14
S-15
S-16
S-17
A-1
2.2
2.0
1.8
1.2

(Figure 1)


0.8
A-2
0.6
A-3
A-4
0.4
A-5
0.2
A-6
0.0
A-7
A-8
A-9
A-10
A-11
-0.2
A-12
A-13
A-14
A-15
-0.4
A-16
A-17
A-18
A-19
-0.6
A-20
A-21
A-22
-0.8
A-23
-1.0
A-24
-1.2
A-25
-2.2
dH-1
dH-2
dH-3

(Figure 1)


dH-16
vH-3
vH-5
vH-7
vH-6
vH-4
-3.2
dH-13
dH-14
dH-15
vH-2
-3.0
dH-9
dH-10
dH-11
dH-12
vH-1
-2.8
dH-6
dH-7
dH-8
-2.6
dH-4
dH-5
-2.4
vH-14
-4.0
vH-13
-3.8
vH-9
vH-10
vH-12
vH-11
-3.6
vH-8
-3.4

(Figure 1)

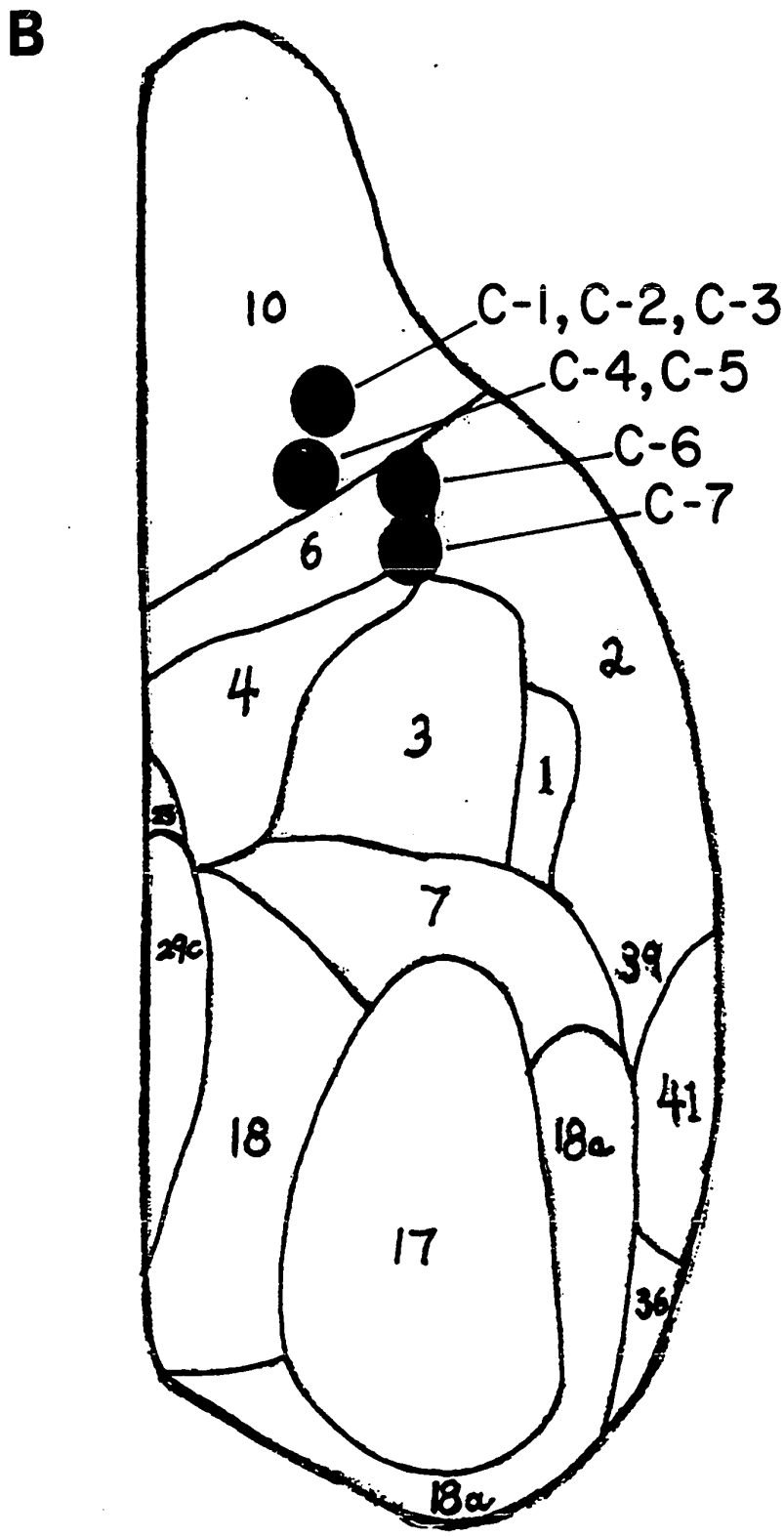


Figure 2

Typical afterdischarge patterns produced by primary stimulation. (Vertical arrows indicate the period of stimulation. Heavy horizontal line indicates seizure activity.) A. Anterior neocortical. Note: brief duration; seizure. B. Amygdaloid. C. Dorsal Hippocampal. Note: reversal in polarity; post-ictal depression; subsequent afterdischarge episode. D. Ventral Hippocampal. Note: pattern is sometimes like dorsal hippocampal; sometimes more like amygdaloid pattern. E. Septal. (All traces taken a few days after the start of stimulation.)

(Figure 2)

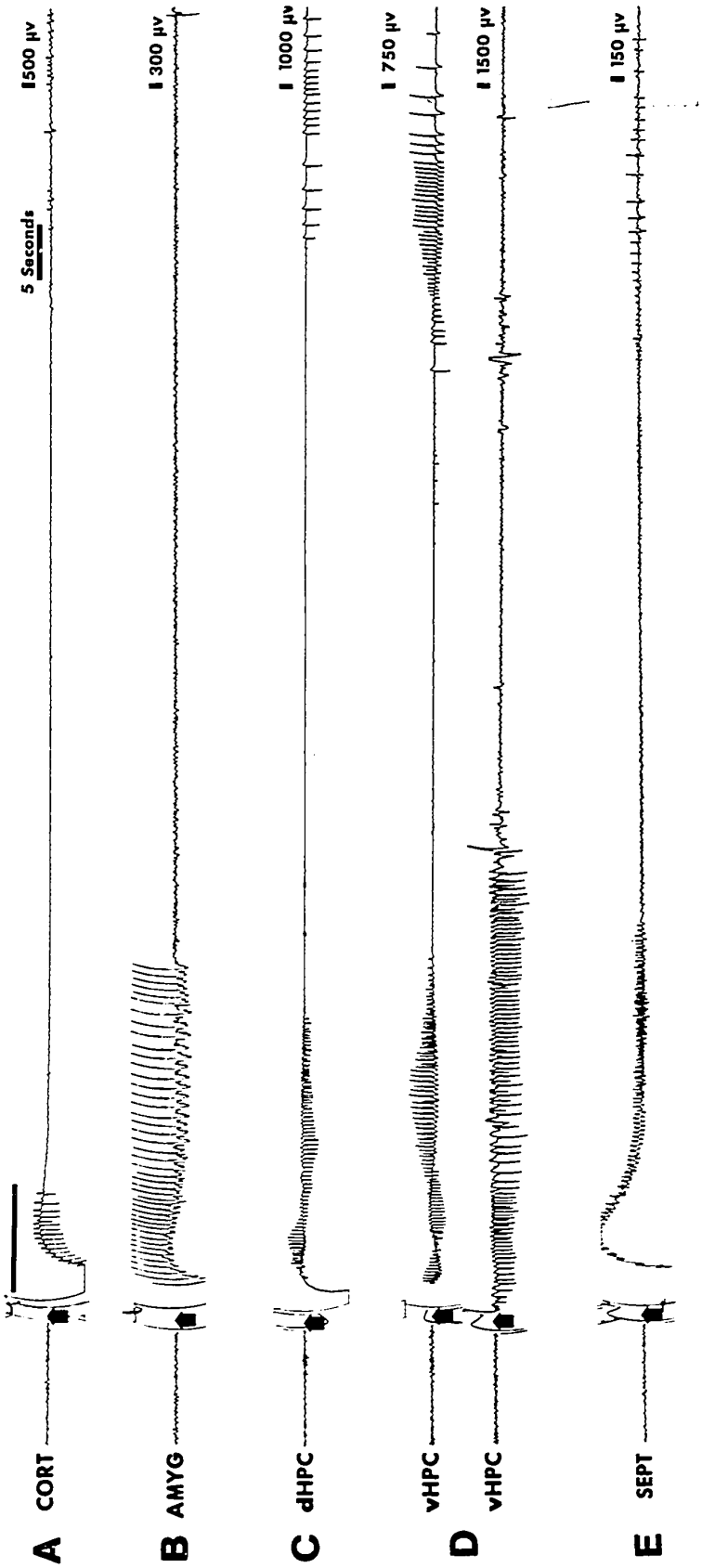

A
CORT
1500 µv
5 Seconds
B
AMYG
300 µv
C
dHPC
1000 µv
D
vHPC
750 µv
vHPC
1500 µv
E
SEPT
150 µv

Figure 3

Patterns of afterdischarge during repeated primary stimulation of the anterior neocortex. (Vertical arrows indicate the period of stimulation. Heavy horizontal lines indicate seizure activity.) A. First afterdischarge. Note immediate seizure onset. B. Fifth afterdischarge. C. Tenth afterdischarge. Note lack of change in afterdischarges or seizures. (The "growth curve" for this subject is presented in Figure 4.)

(Figure 3)

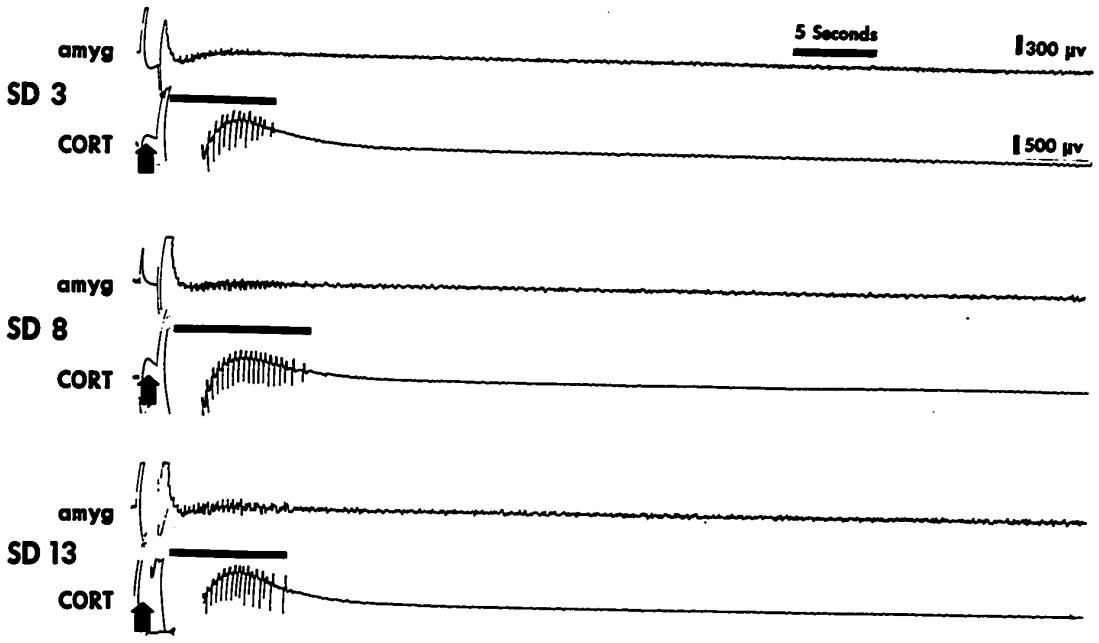

amyg
SD 3
CORT
5 Seconds
300 µv
500 µv
amyg
SD 8
CORT
amyg
SD 13
CORT

Figure 4

A growth "curve" for afterdischarge duration in a neocortical subject during repeated primary stimulation ("Open" circles indicate afterdischarges accompanied by seizures.) No growth is seen. (Records for this subject are illustrated in Figure 3. Arrows indicate the days illustrated.)

(Figure 4)

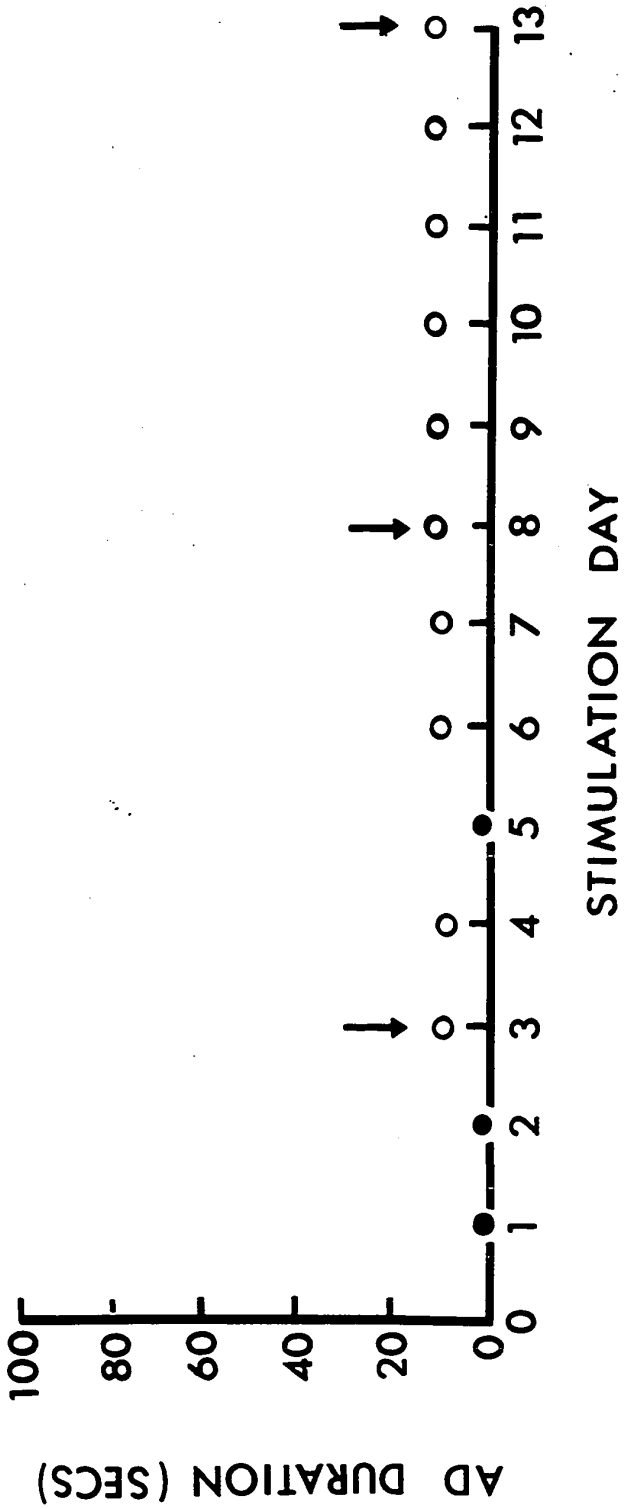
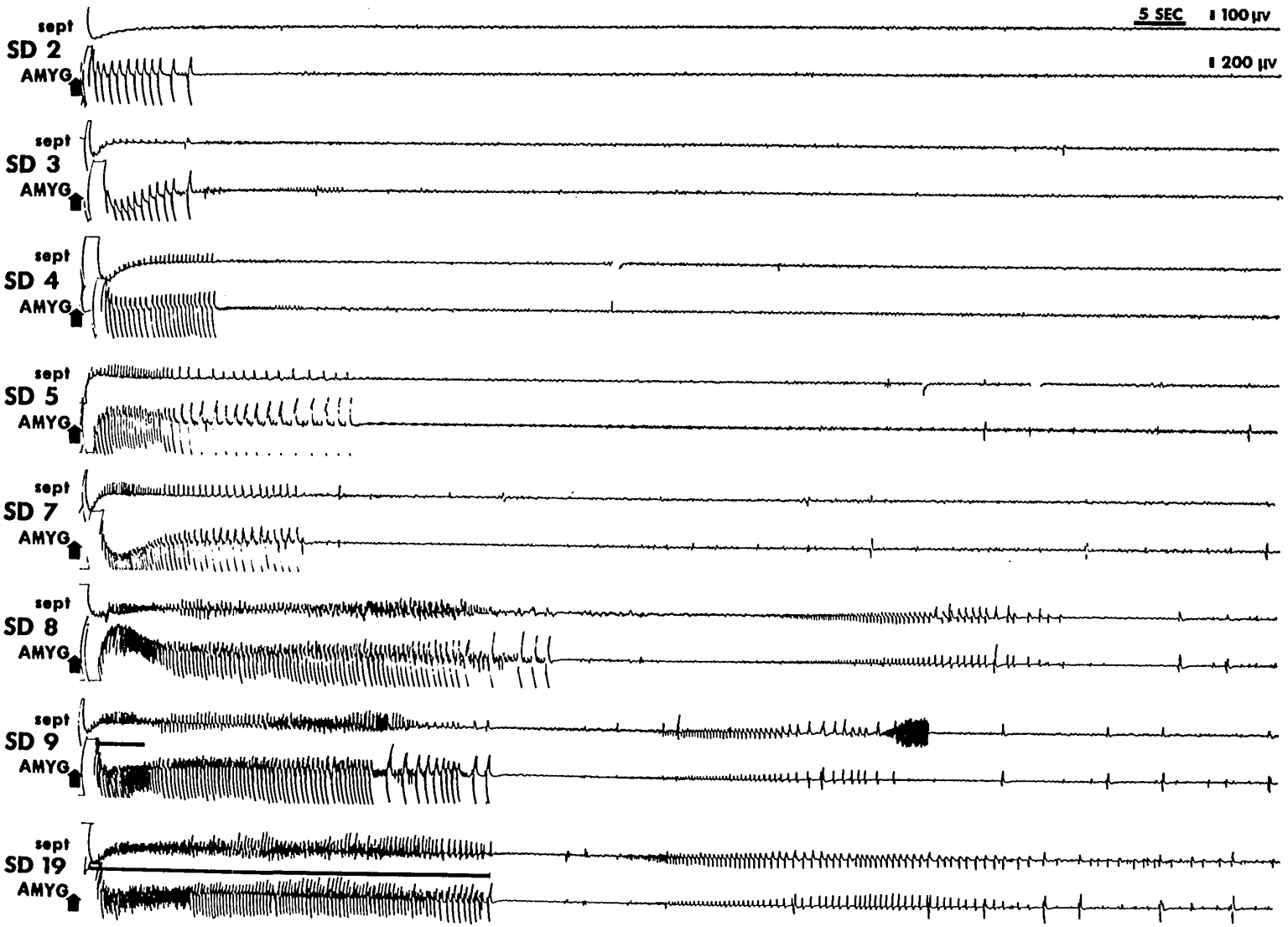

AD DURATION (SECS)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13
STIMULATION DAY

Figure 5

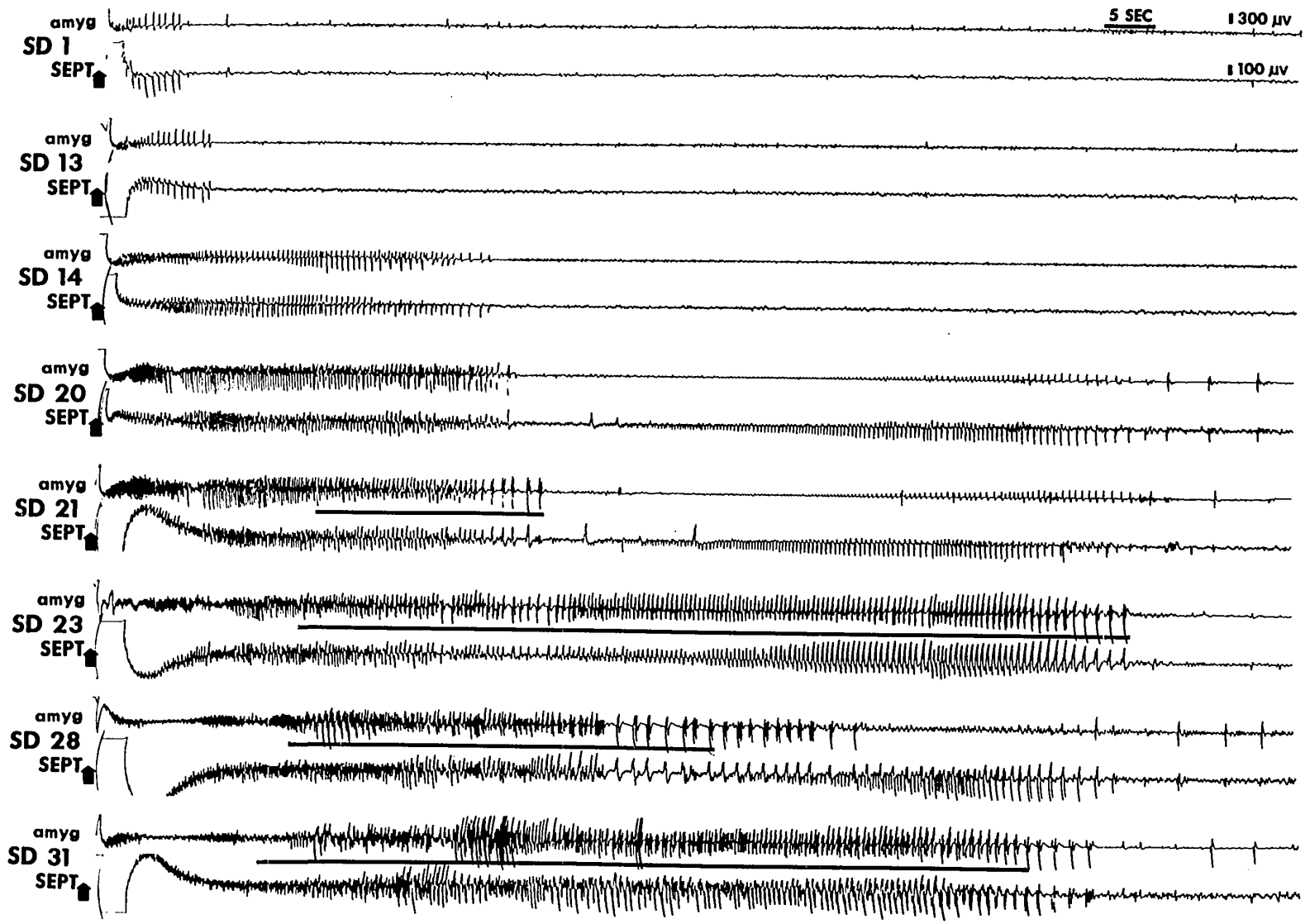
Patterns of afterdischarge during repeated primary stimulation of the amygdala. (Vertical arrows indicate the period of stimulation. Heavy horizontal lines indicate seizure activity.) SD 2 - 4. Typical short afterdischarges at the start of stimulation. SD 5, 7. A sudden increment in duration occurs and duration jumps to a new "plateau." SD 8. A further increment. A secondary episode of afterdischarge appears in the record. SD 9. Seizure onset. Note brevity of seizure. SD 19. Last day of primary site stimulation (tenth seizure). Note the growth in seizure duration which has occurred. (The growth curve for this subject is presented in Figure 9 B.)


5 SEC
100 µv
200 µv
sept
SD 2
AMYG
sept
SD 3
AMYG
sept
SD 4
AMYG
sept
SD 5
AMYG
sept
SD 7
AMYG
sept
SD 8
AMYG
sept
SD 9
AMYG
sept
SD 19
AMYG

(Figure 5)

Figure 6

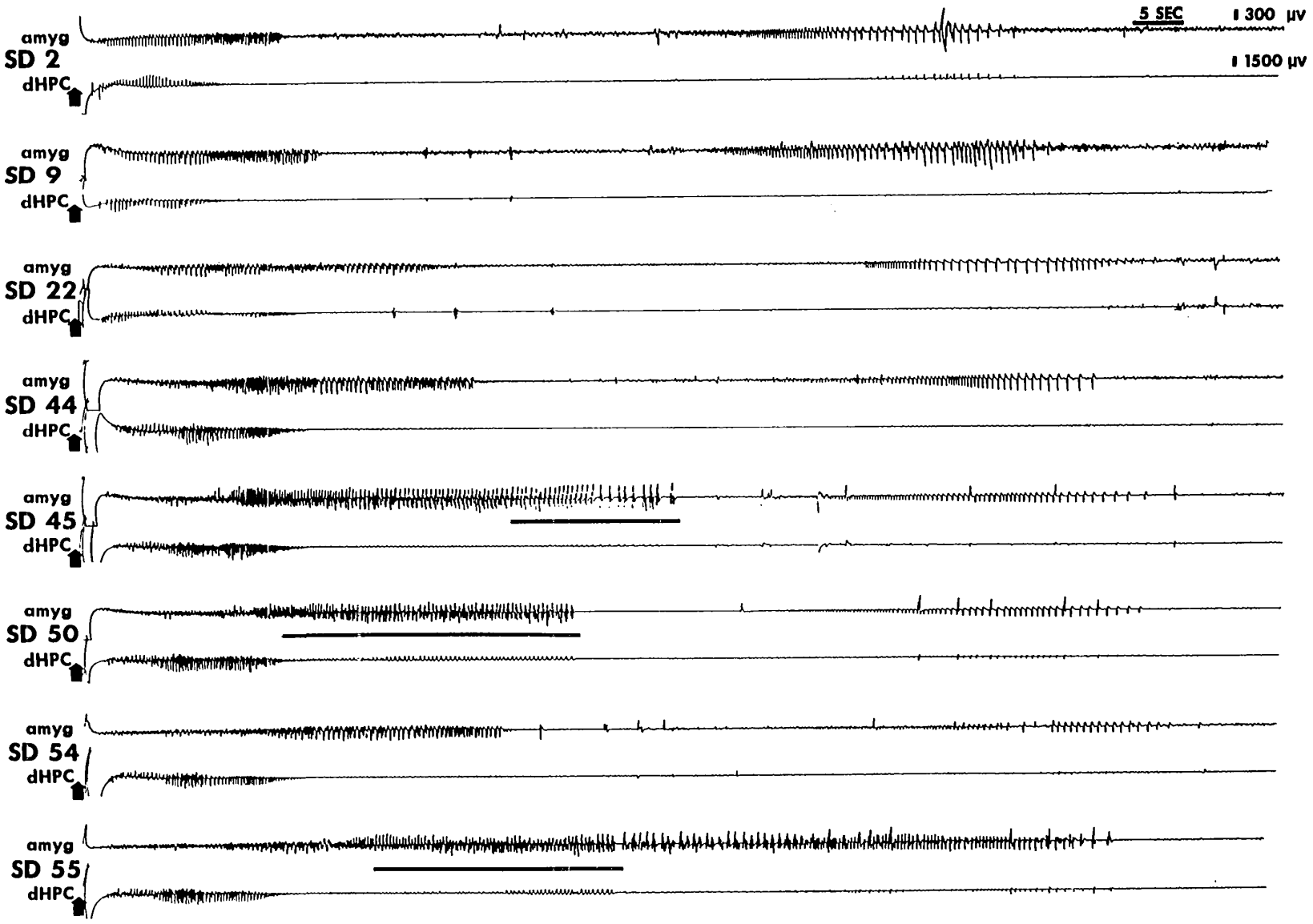
Patterns of afterdischarge during repeated primary stimulation of the septal area. (Vertical arrows indicate the period of stimulation. Heavy horizontal lines indicate seizure activity.) SD 1. First afterdischarge. SD 13. Duration has shown little growth. SD 14. A sudden increment. SD 20. Duration stays on the new "plateau". SD 21. Seizure onset without further growth in afterdischarge. SD 23. A further increment. Note longer seizure. SD 28. Afterdischarge and seizure duration drop back temporarily to an earlier level. SD 31. Last day of primary site stimulation (10th seizure). Note lack of further growth in seizure duration. (The growth curve for this subject is presented in Figure 9 - D.)


amyg
SD 1
SEPT
5 SEC
300 µv
100 µv
amyg
SD 13
SEPT
amyg
SD 14
SEPT
amyg
SD 20
SEPT
amyg
SD 21
SEPT
amyg
SD 23
SEPT
amyg
SD 28
SEPT
amyg
SD 31
SEPT

(Figure 6)

Figure 7

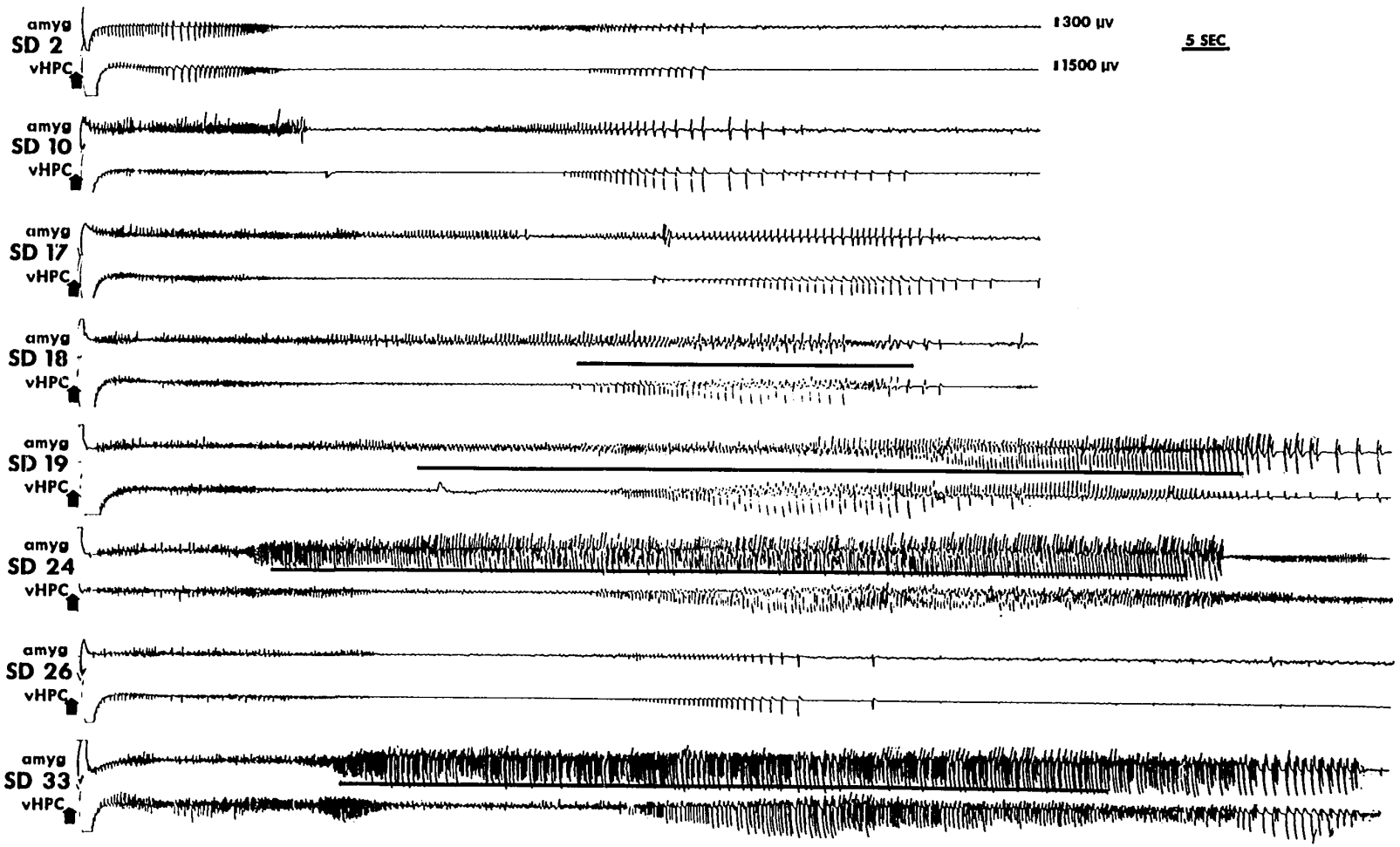
Patterns of afterdischarge during repeated primary stimulation of the dorsal hippocampus. (Vertical arrows indicate the period of stimulation. Heavy horizontal lines indicate seizure activity.) SD 2. First afterdischarge. Propagated discharge appears to outlast primary discharge even on the first day. SD 9-44. Propagated activity extends farther and farther beyond primary discharge. Primary record begins to show small "projected" spikes which extend its duration (see Figure 11 for detail). SD 45. Seizure onset and an increment in propagated discharge. Primary discharge also reflects this growth. SD 50. Sixth seizure. Note seizure growth. SD 54. Failure of seizure activity. Shortening of discharge. SD 55. Last day of primary site stimulation (tenth seizure). Note lack of further seizure growth. (The growth curve for this subject is presented in Figure 9 E.)


5 SEC
300 µv
1500 µv
amyg
SD 2
dHPC
amyg
SD 9
dHPC
amyg
SD 22
dHPC
amyg
SD 44
dHPC
amyg
SD 45
dHPC
amyg
SD 50
dHPC
amyg
SD 54
dHPC
amyg
SD 55
dHPC

(Figure 7)

Figure 8

Patterns of afterdischarge during repeated primary stimulation of the ventral hippocampus. (Vertical arrows indicate the period of stimulation. Heavy horizontal lines indicate seizure activity.) SD 2. First afterdischarge. SD 10-17. Propagated discharge grows and begins to outlast the primary pattern. Low "projected" spikes begin to extend the primary pattern. SD 18. Seizure onset and an increment in propagated discharge which is reflected in the hippocampal record. SD 19 and 24. Second and fifth seizures. Further growth in seizure duration and in amplitude of hippocampal "projected" pattern. SD 26. Seizure failure. Afterdischarge resembles earlier patterns. SD 33. Last day of primary site stimulation (tenth seizure). Note lack of further seizure growth. (The growth curve for this subject is presented in Figure 9 F).

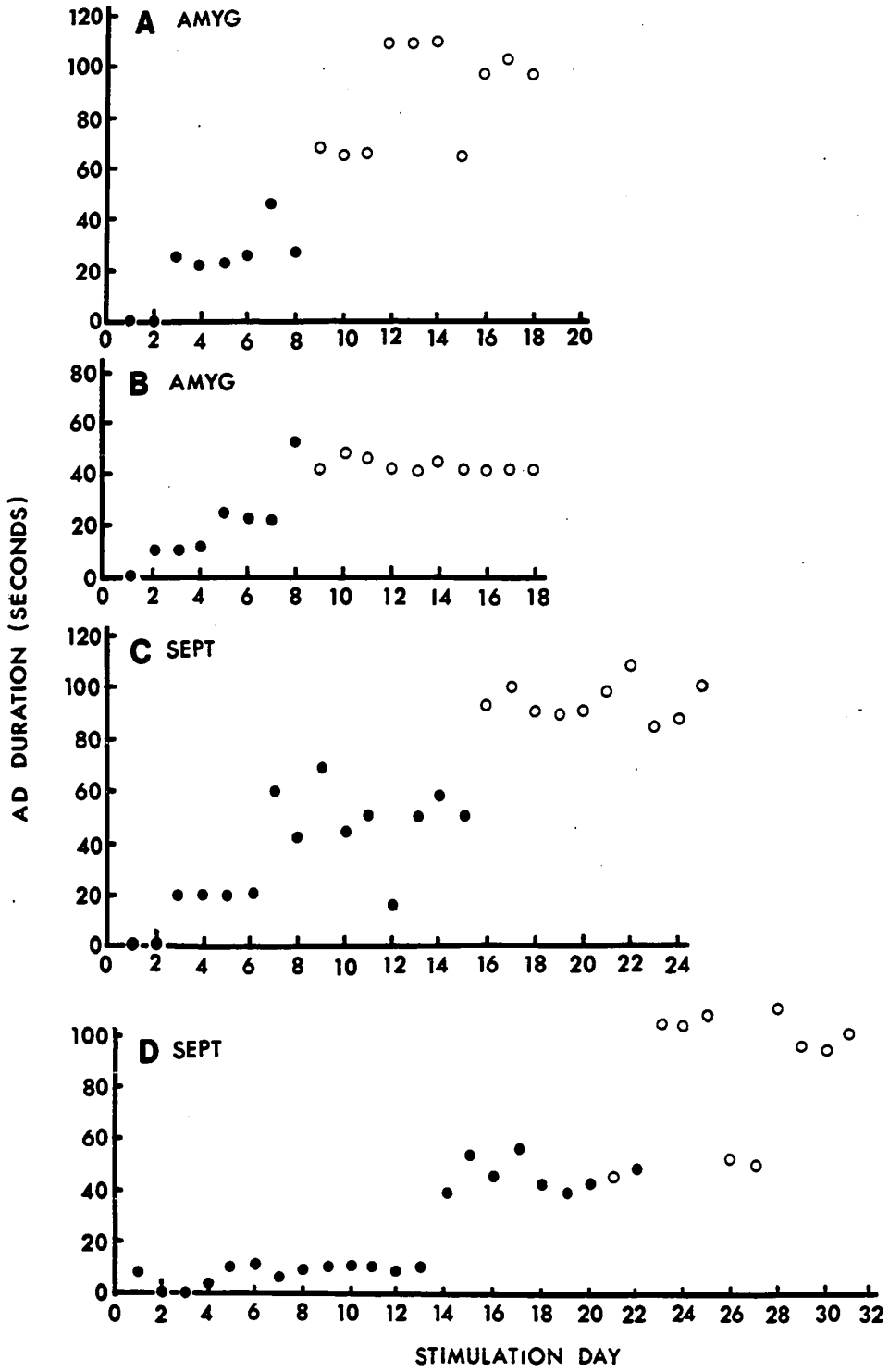

amyg
SD 2
vHPC
300 µv
1500 µv
5 SEC
amyg
SD 10
vHPC
amyg
SD 17
vHPC
amyg
SD 18
vHPC
amyg
SD 19
vHPC
amyg
SD 24
vHPC
amyg
SD 26
vHPC
amyg
SD 33
vHPC

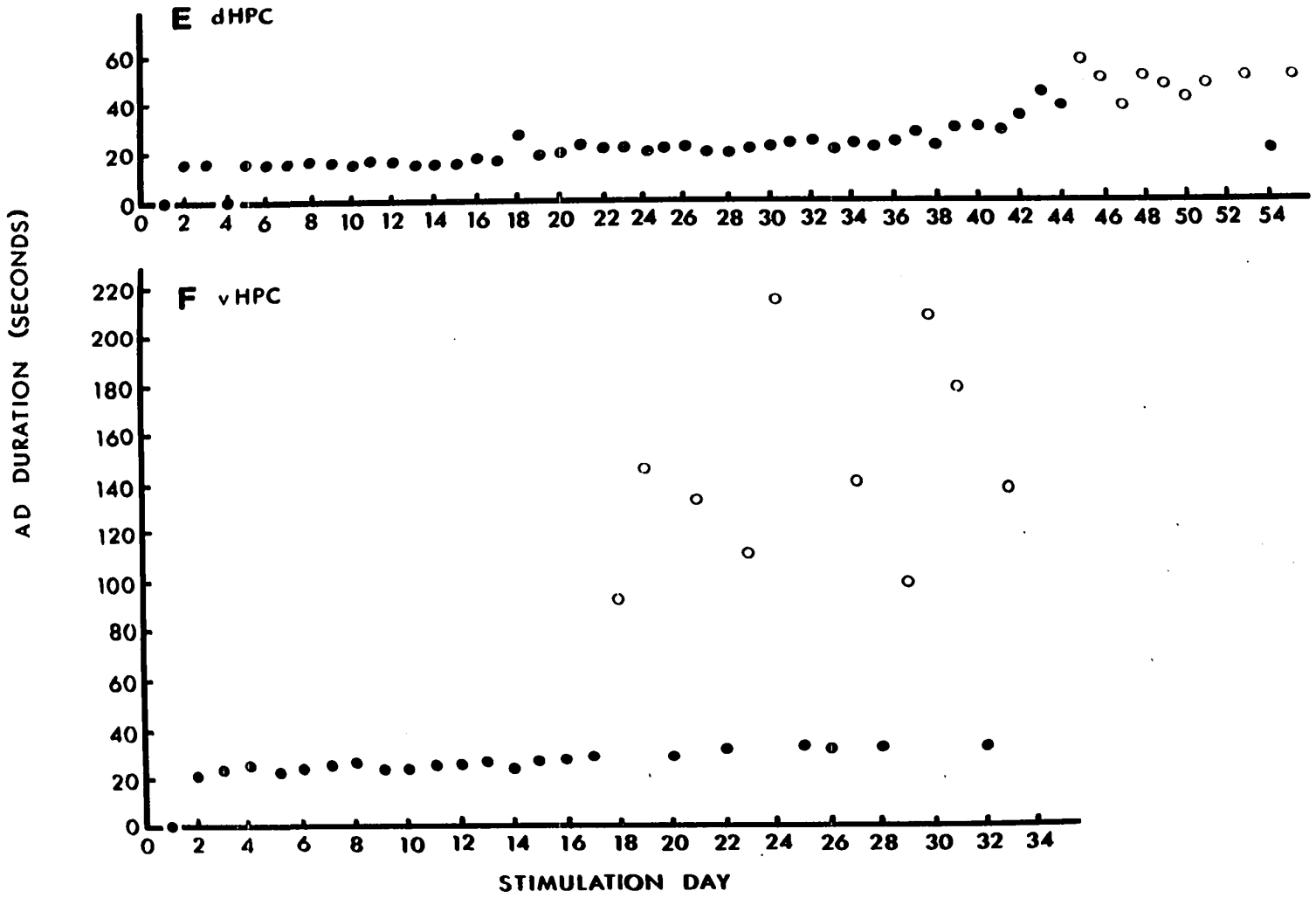
(Figure 8)

Figure 9

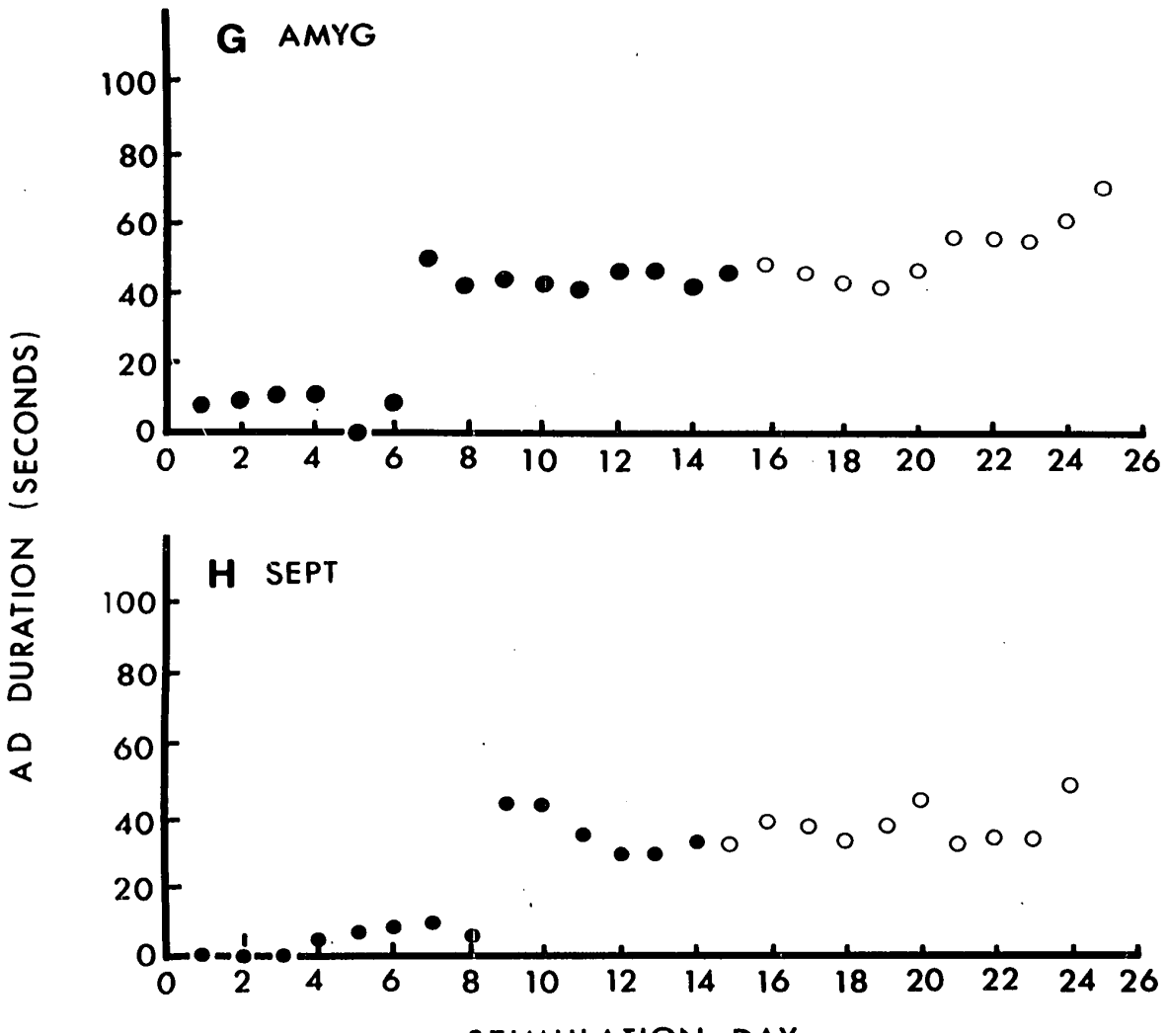
Growth curves plotted for afterdischarge duration in subcortical subjects during repeated primary stimulation. ("Filled in" circles indicate afterdischarge without seizures. "Open" circles indicate afterdischarge with seizures.) A. & B. Amygdaloid subjects. C. & D. Septal subjects. In the amygdaloid and septal subjects growth occurs in sudden increments. Sudden temporary decreases are also seen. The same discharge levels or "plateaus" tend to occur in different subjects. Seizure onset is often associated with a sudden increment in length. E. & F. Dorsal and ventral hippocampal subjects. In hippocampal subjects, gradual growth tends to be seen, although an increment may be seen at seizure onset. G. & H. No sign of growth at seizure onset in two subjects with medium length afterdischarges.

(Figure 9)


A AMYG
B AMYG
C SEPT
D SEPT
AD DURATION (SECONDS)
STIMULATION DAY



(Figure 9)

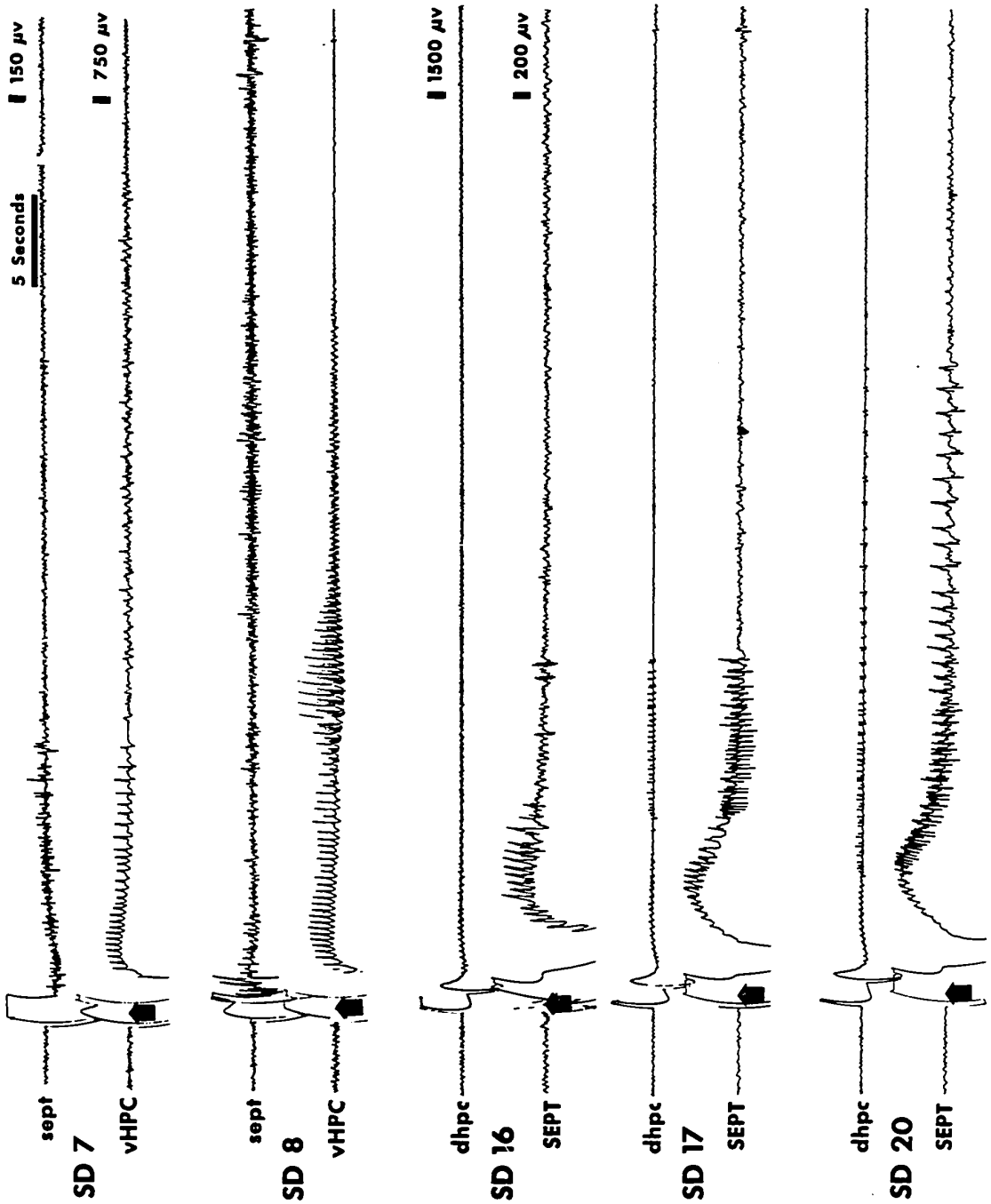

G AMYG
H SEPT
AD DURATION (SECONDS)
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26

(Figure 9)

Figure 10

Sudden increments and decreases in afterdischarge duration. (Vertical arrows indicate the site and time of stimulation.) A. A sudden increment in a ventral hippocampal subject. Note the hint of spiking in the primary record just before the sudden increment (SD 7), and the distinctive pattern of the new segment (SD 8). B. A sudden increment in a septal subject. Note the hint of spiking in the primary record just before the increment (SD 16), and the distinctive pattern of the new segment (SD 17). A few days later another segment appeared (SD 20). C. A sudden decrease in duration in a septal subject (SD 17 ; note the reduction in propagation), followed by a sudden increase (SD 18). Note the distinctive patterns in different parts of the long discharge (SD 18).

(Figure 10)


A
SD 7
sept
vHPC
5 Seconds
150 µv
750 µv
SD 8
sept
vHPC
B
SD 16
dhpc
SEPT
1500 µv
200 µv
SD 17
dhpc
SEPT
SD 20
dhpc
SEPT

(Figure 10)

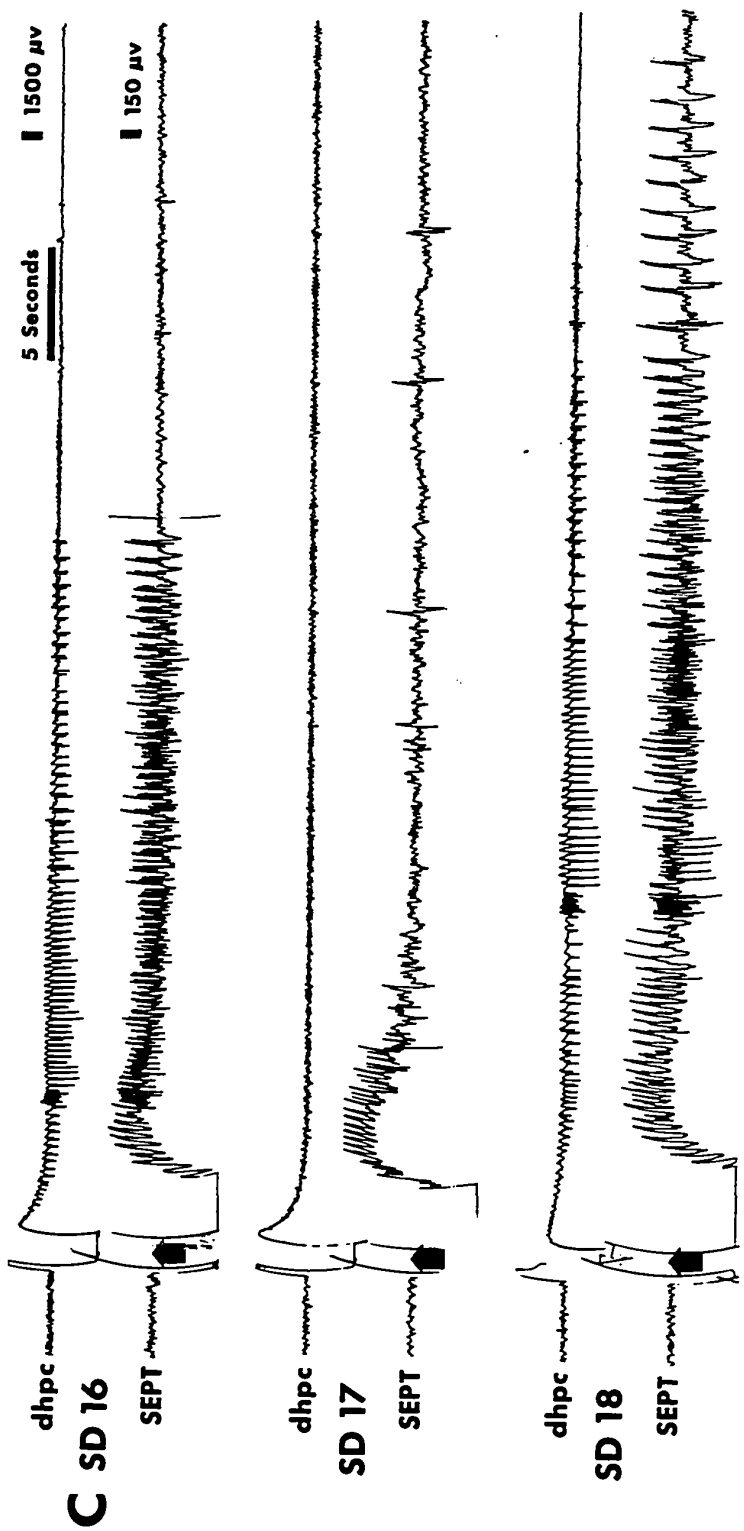
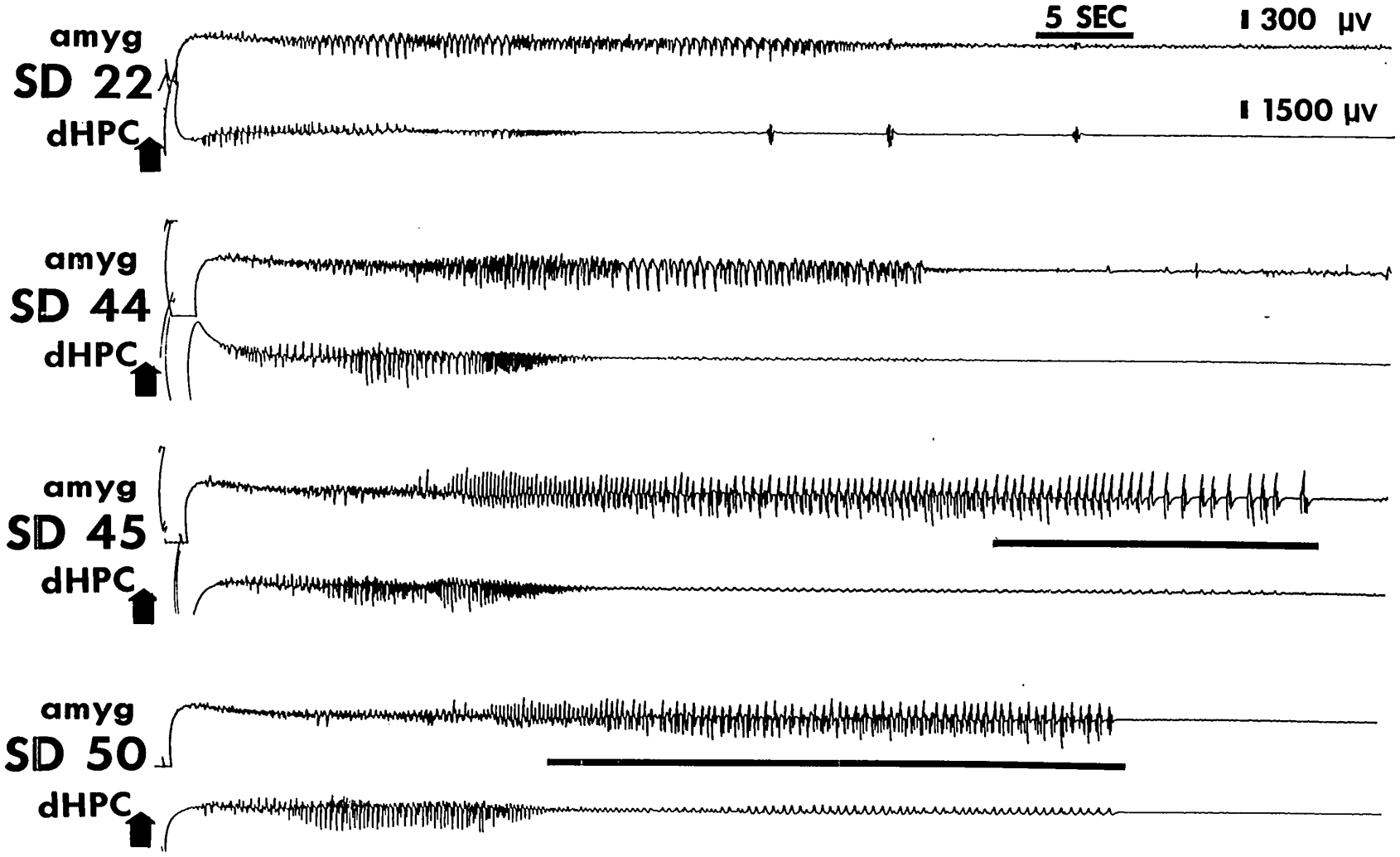

1500 µv
150 µv
5 Seconds
dhpc
SEPT
C SD 16
dhpc
SEPT
SD 17
dhpc
SEPT
SD 18

Figure 11

Growth of low-amplitude waves during the hippocampal "silent period." (Detail from Figure 7. Vertical arrows indicate the site and time of stimulation. Heavy horizontal lines indicate seizure activity.) SD 22 - SD 50. After secondary propagated discharge had begun to outlast the primary pattern, low-amplitude spikes appeared during the silent period and gradually grew in amplitude. These tended to resemble the spikes seen in cases of projected propagation (see Figure 13 A).


5 SEC
300 µv
1500 µv
amyg
SD 22
dHPC
amyg
SD 44
dHPC
amyg
SD 45
dHPC
amyg
SD 50
dHPC

(Figure 11)

(Figure 11)

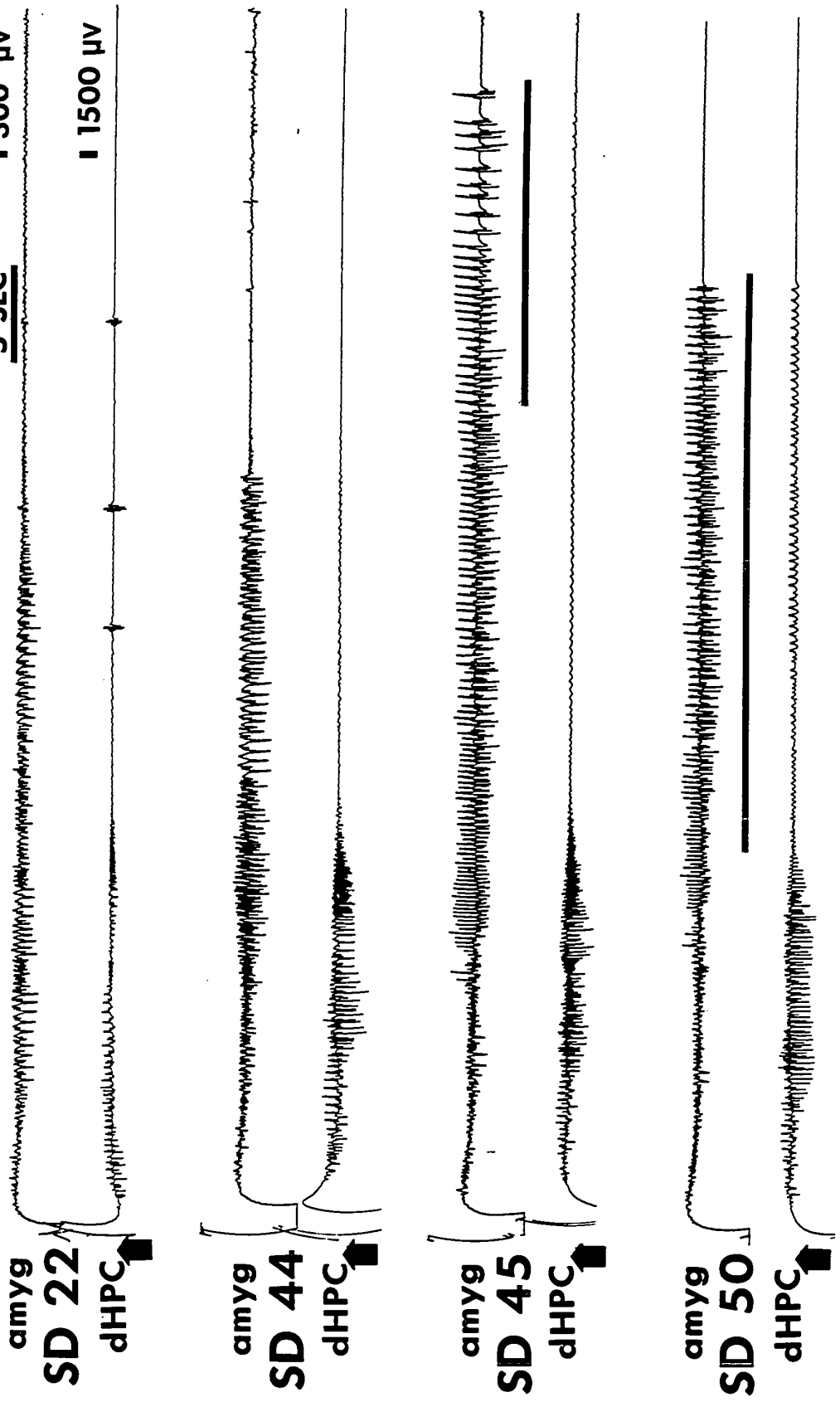

5 SEC
300 µV
1500 µV
amyg
SD 22
dHPC
amyg
SD 44
dHPC
amyg
SD 45
dHPC
amyg
SD 50
dHPC

Figure 12

Occurrence of low-amplitude spikes just before a sudden increment in afterdischarge duration. (Detail of Figure 5. Vertical arrows indicate the site and time of stimulation.) Note the low amplitude "blunt" spikes that follow the major discharge on SD 3 and SD 4. On SD 5, full scale spiking appeared at this point in the record.

(Figure 12)

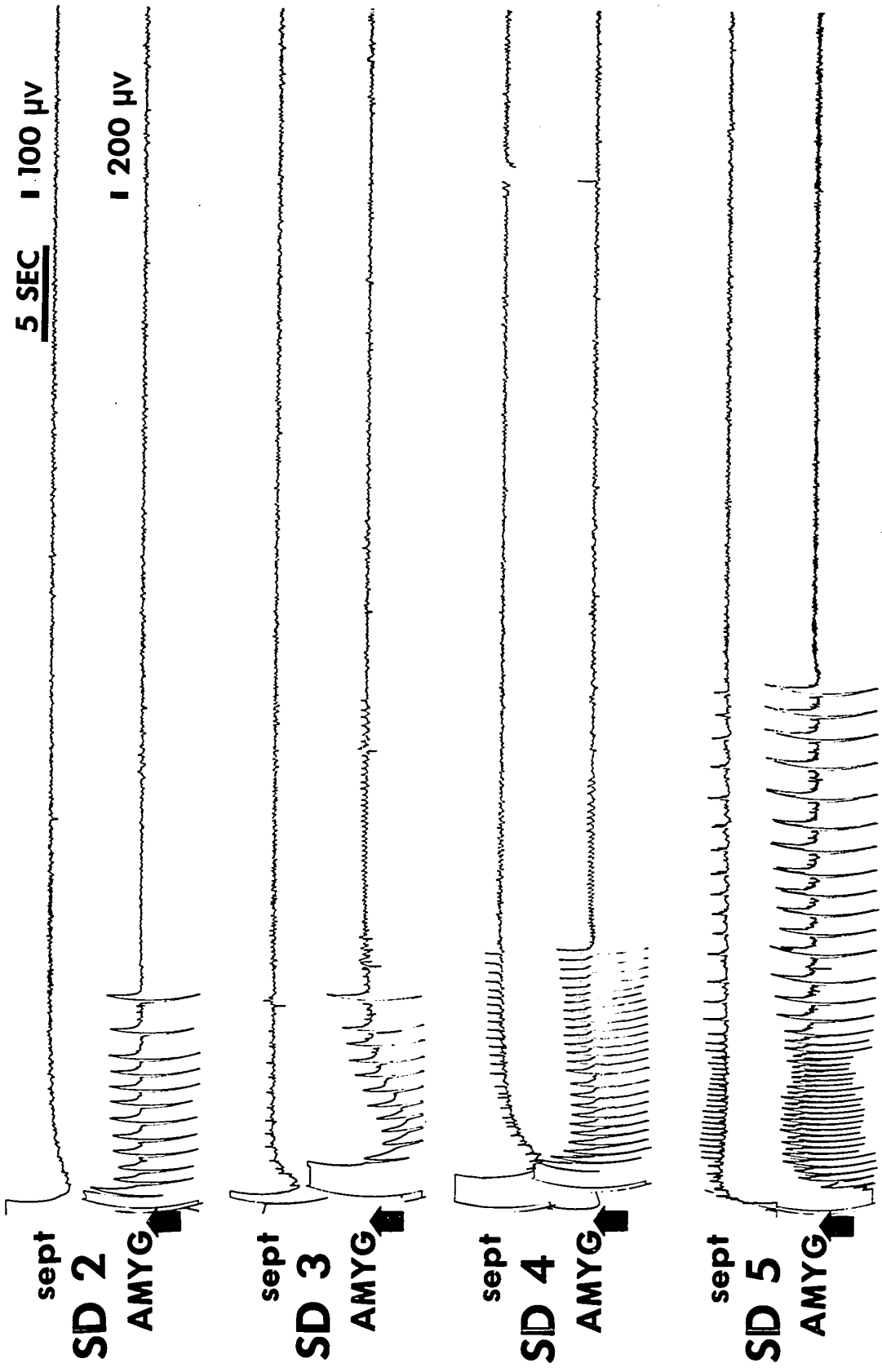
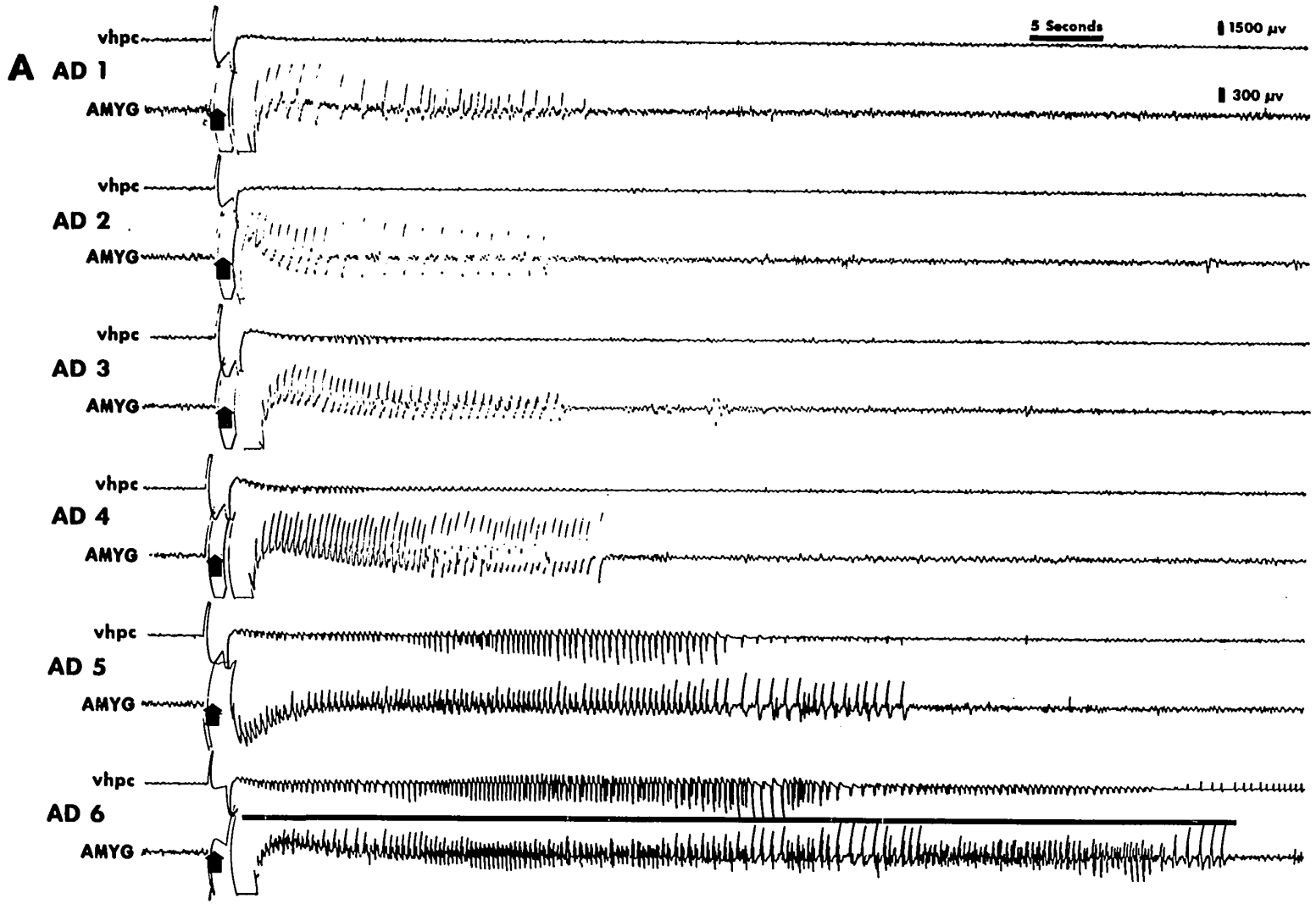
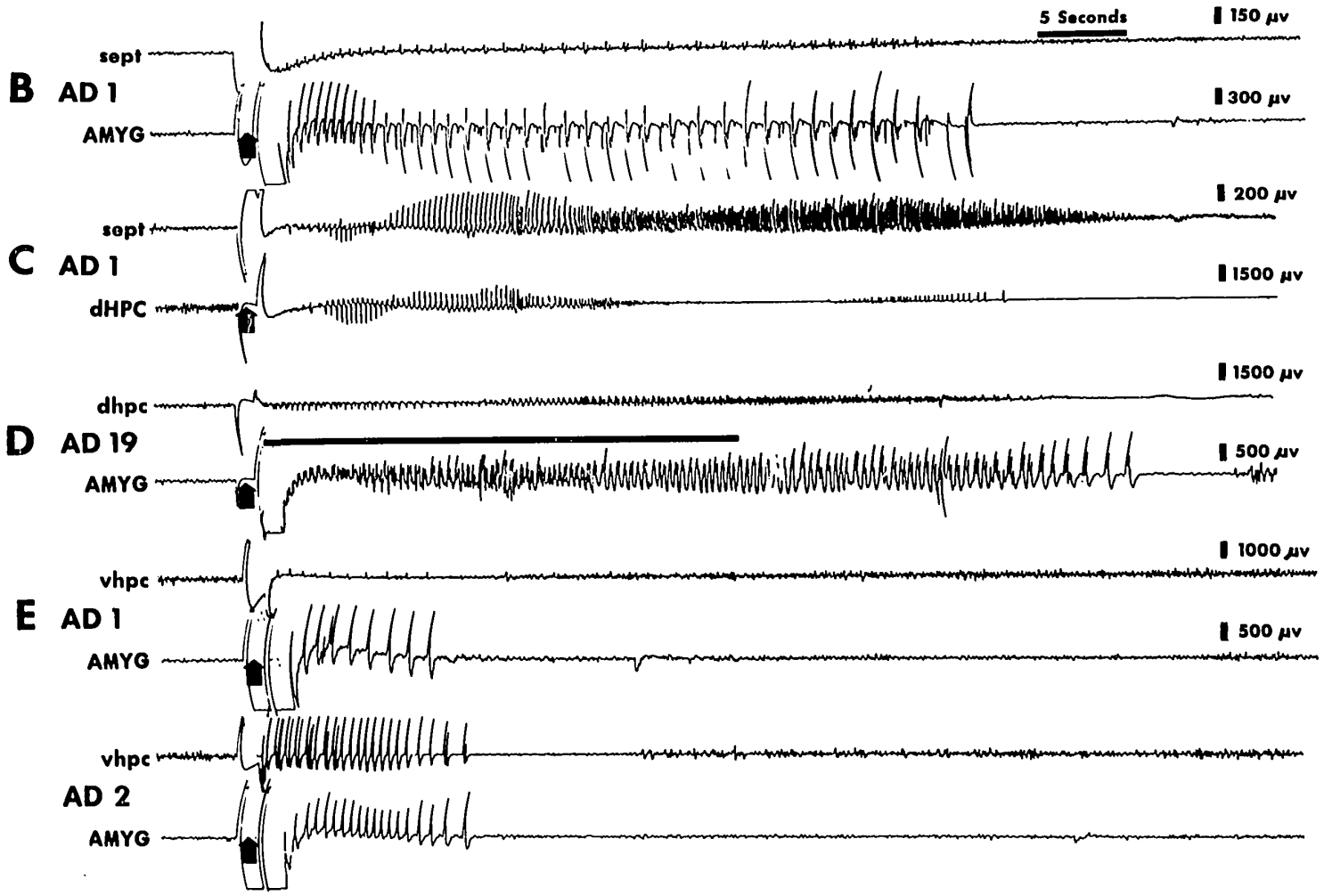

5 SEC
100 µv
200 µv
sept
SD 2
AMYG
sept
SD 3
AMYG
sept
SD 4
AMYG
sept
SD 5
AMYG

Figure 13

Discharge propagated from primary to secondary sites. (Vertical arrows indicate site and time of stimulation. Heavy horizontal lines indicate seizure activity.) A. The progressive development of propagation illustrated in a single subject. Note the gradual growth of projected discharge (AD 1 to AD 4) and the onset of reactive discharge (AD 5). B. Projected discharge during an initial primary discharge. C. Reactive discharge during an initial primary discharge. D. Projected discharge during a final primary seizure (reactive discharge had failed to develop). E. Onset of reactive discharge.


A
vhpc
AD 1
AMYG
5 Seconds
1500 µv
300 µv
vhpc
AD 2
AMYG
vhpc
AD 3
AMYG
vhpc
AD 4
AMYG
vhpc
AD 5
AMYG
vhpc
AD 6
AMYG

(Figure 13)


5 Seconds
150 µv
sept
B AD 1
AMYG
300 µv
200 µv
sept
C AD 1
dHPC
1500 µv
1500 µv
dhpc
D AD 19
AMYG
500 µv
1000 µv
vhpc
E AD 1
AMYG
500 µv
vhpc
AD 2
AMYG

(Figure 13)

Figure 14

Changes in the mean latencies of seizures evoked by repeated primary site stimulation.

(Figure 14)

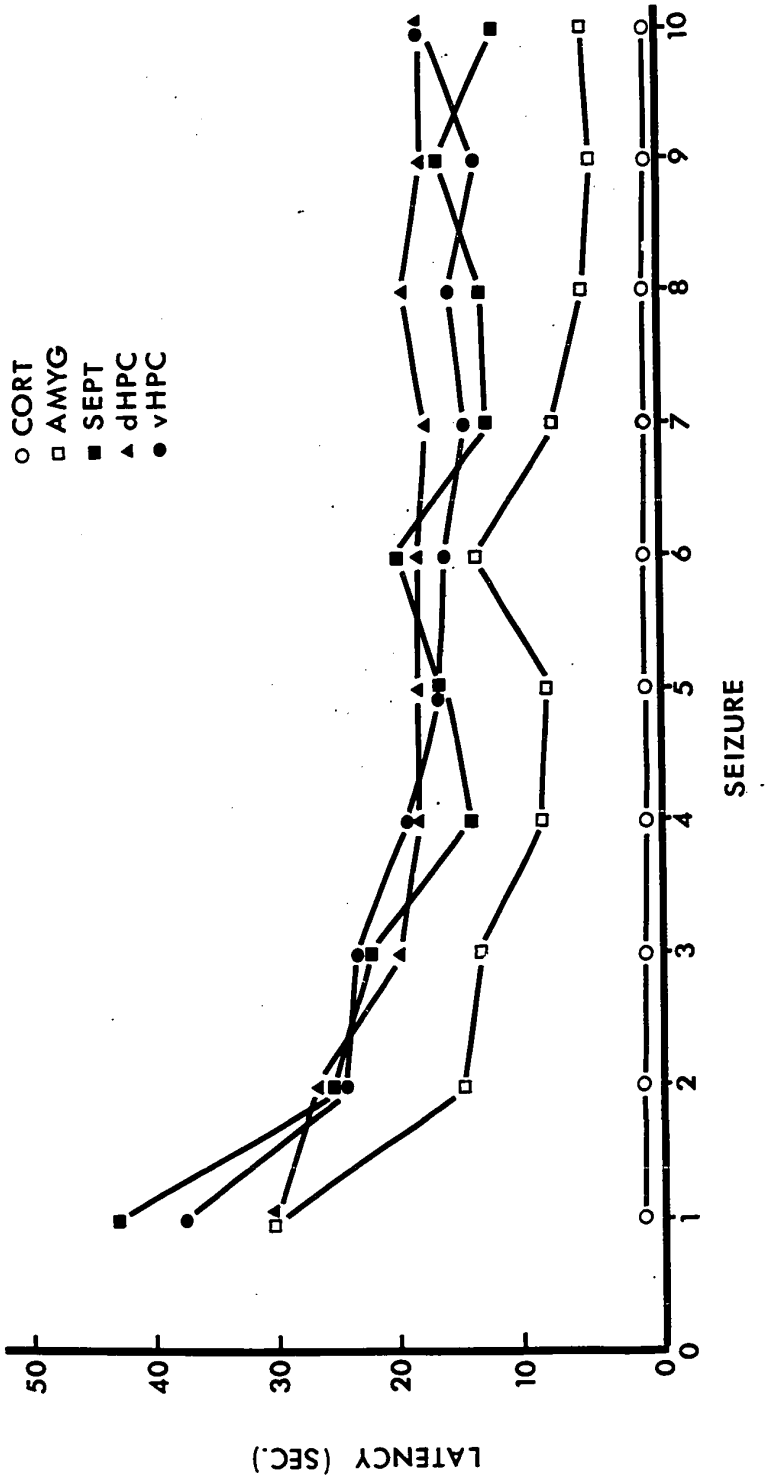

CORT
AMYG
SEPT
dHPC
vHPC
LATENCY (SEC.)
SEIZURE
0
10
20
30
40
50
1
2
3
4
5
6
7
8
9
10

Figure 15

Changes in the mean durations of seizures evoked by repeated primary site stimulation.

(Figure 15)

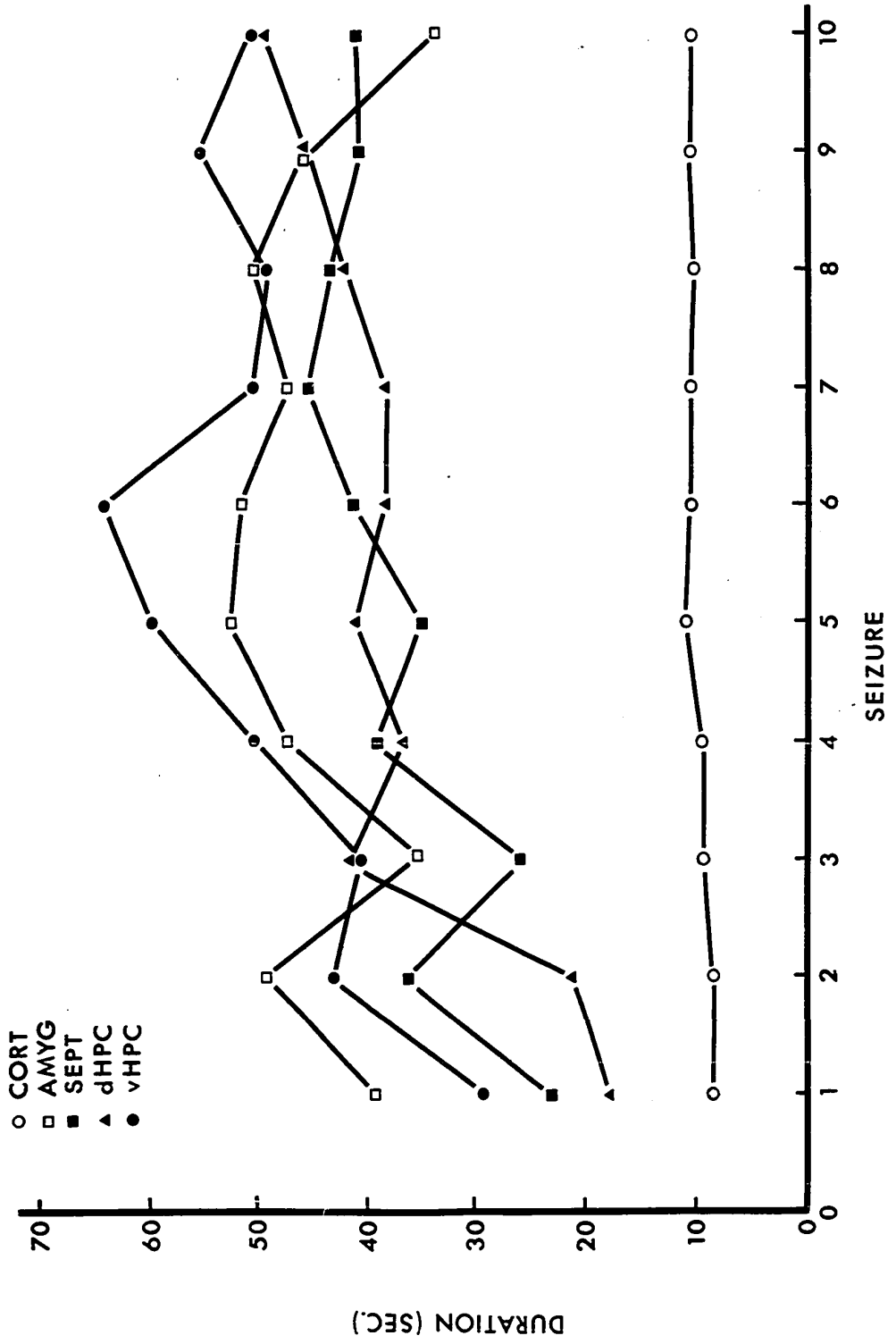
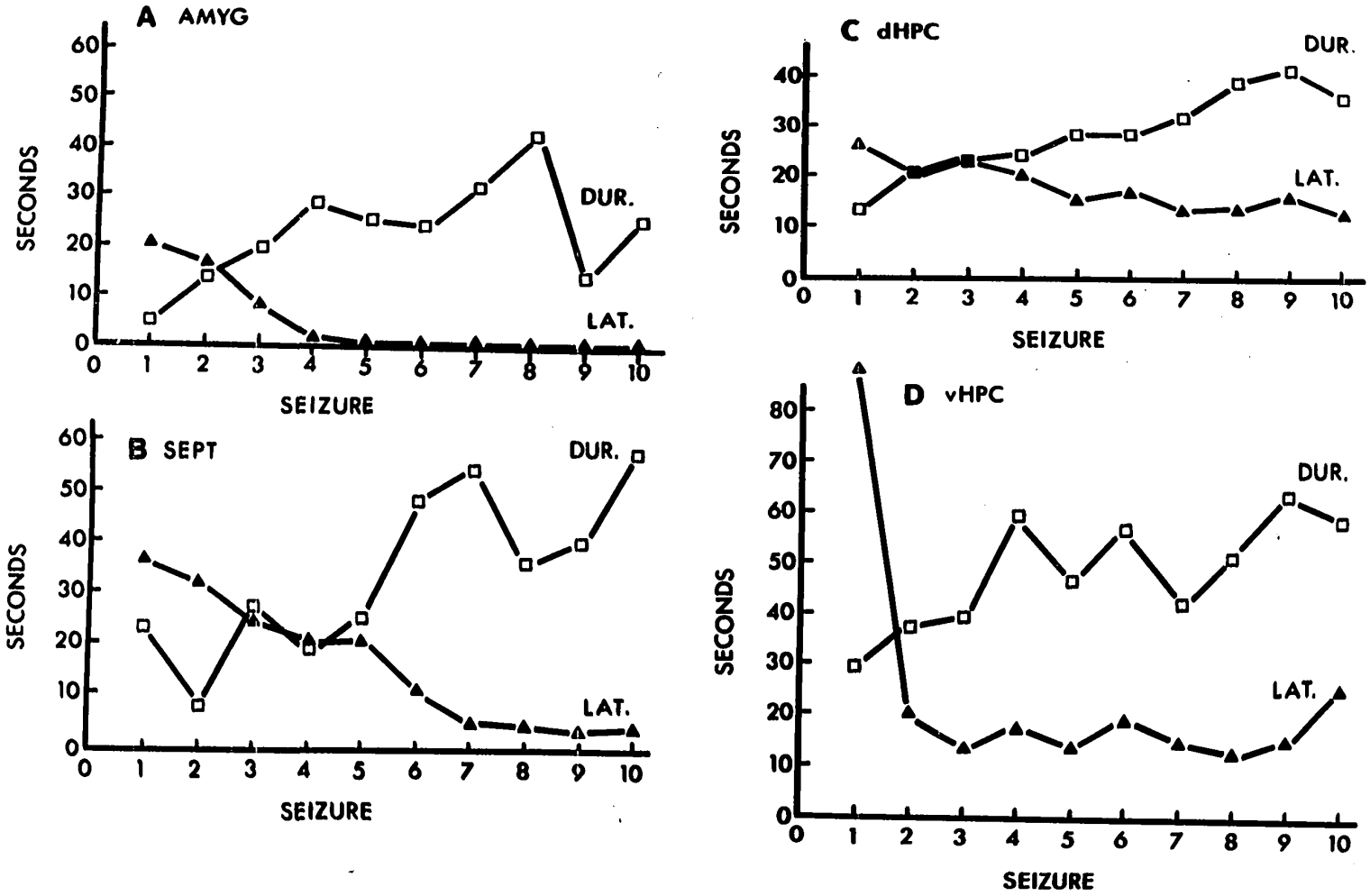
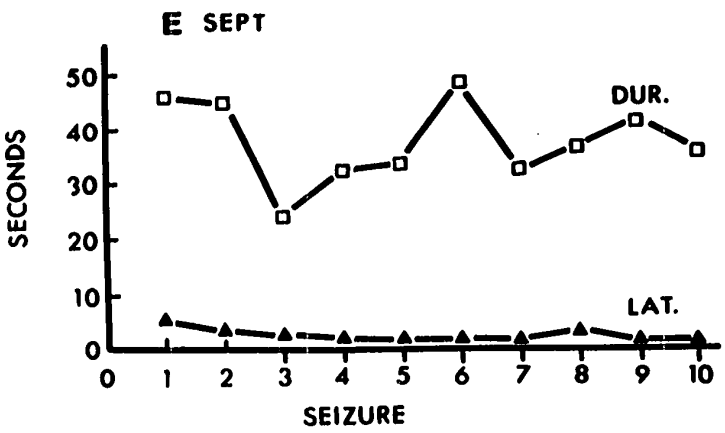

CORT
AMYG
SEPT
dHPC
vHPC
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
SEIZURE
DURATION (SEC.)

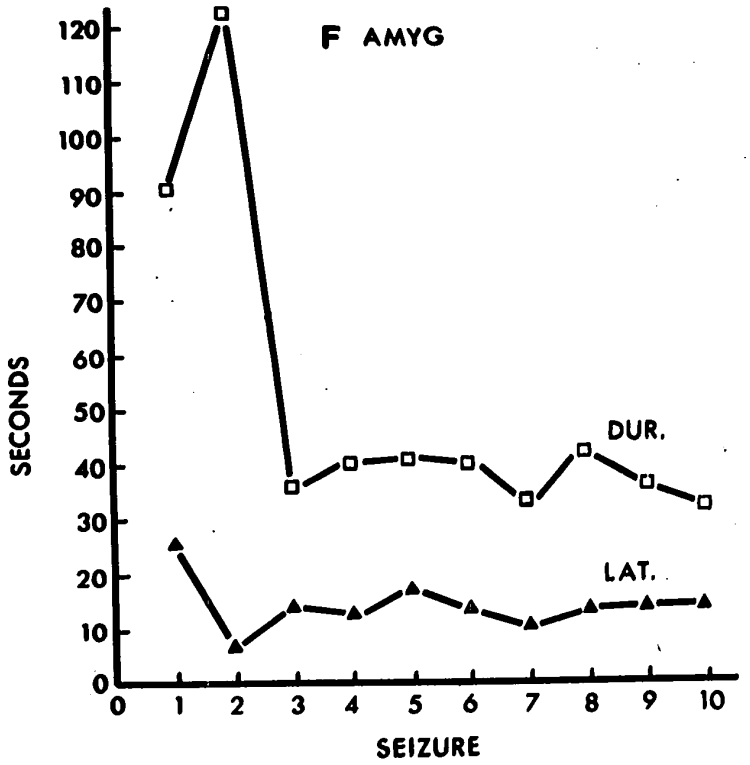
Figure 16

Growth curves for seizure latency and duration in subcortical subjects during primary site stimulation. A.- D. Subjects showing progressive decreases in latency and growth in duration. E. and F. Subjects that produced fully developed seizures from onset.



(Figure 16)

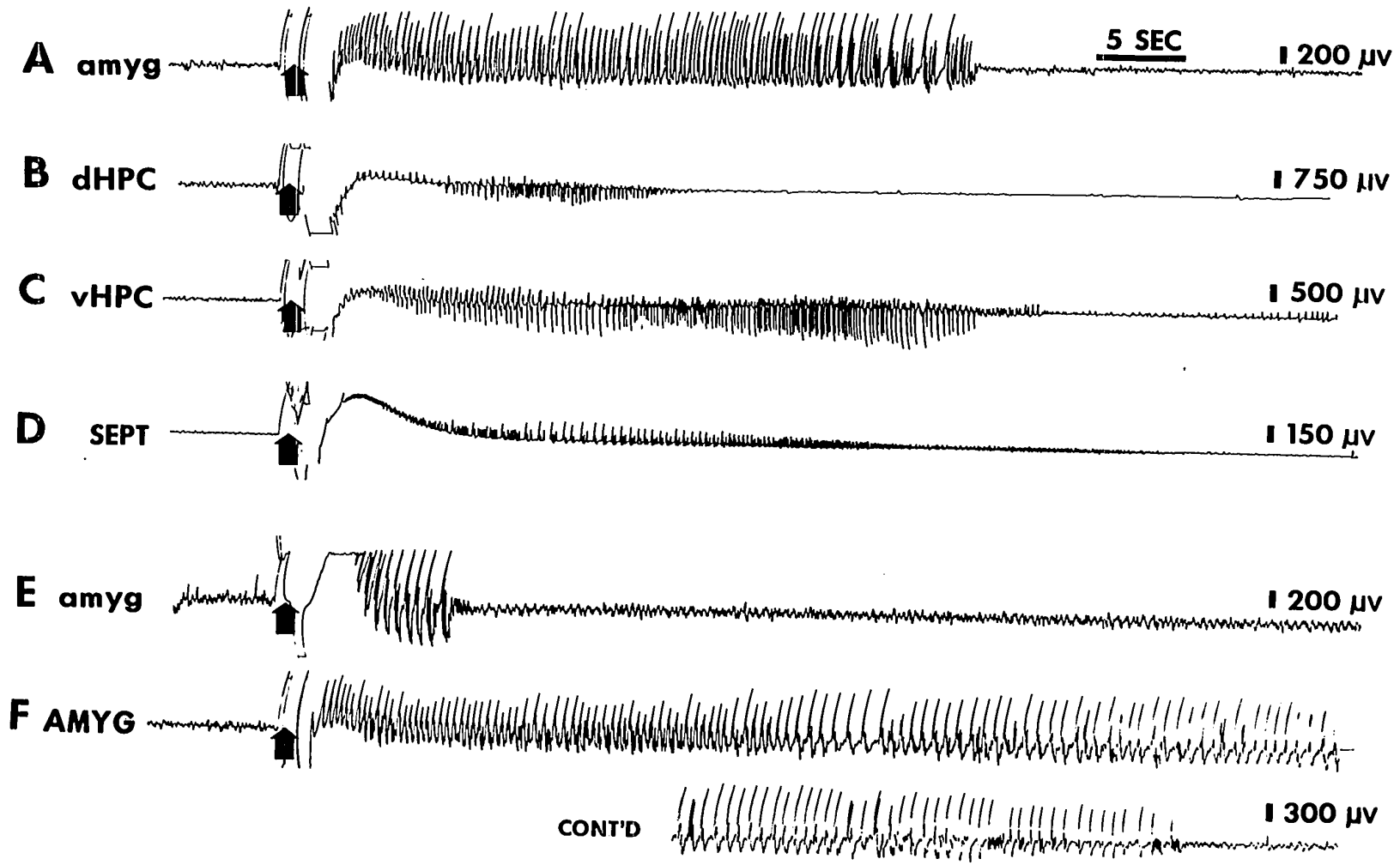

E SEPT
SECONDS
50
40
30
20
10
0
DUR.
LAT.
0 1 2 3 4 5 6 7 8 9 10
SEIZURE


F AMYG
SECONDS
120
110
100
90
80
70
60
50
40
30
20
10
0
DUR.
LAT.
0 1 2 3 4 5 6 7 8 9 10
SEIZURE

(Figure 16)

Figure 17

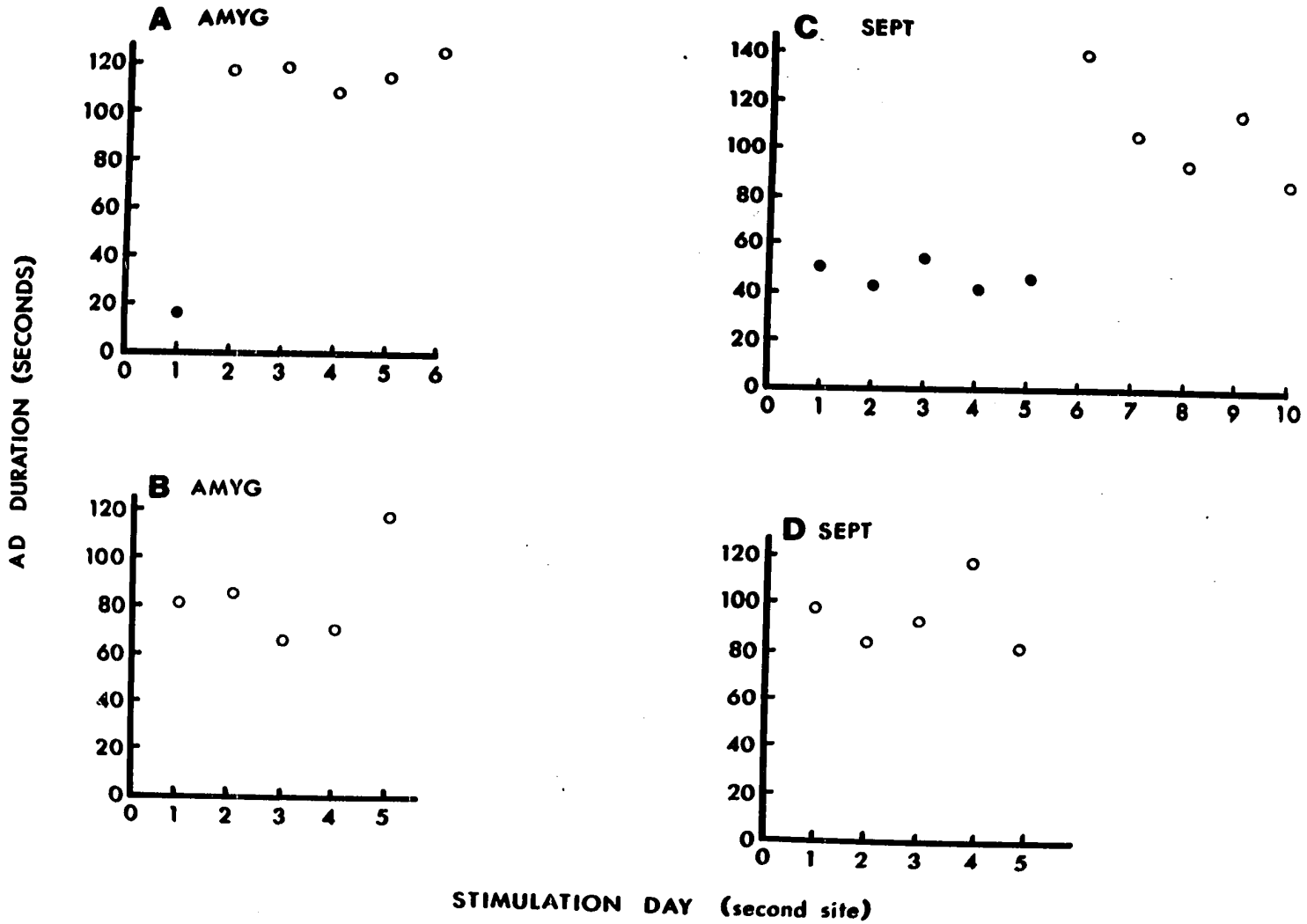
Typical afterdischarge patterns produced by secondary stimulation. (Vertical arrows indicate time of stimulation.) A. Amygdala. B. Dorsal Hippocampal. C. Ventral Hippocampal. D. Septal. Note the similarity of these traces to the traces illustrated in Figure 2. E. and F. illustrate the extreme range of duration seen at onset in secondary afterdischarges.


A amyg
5 SEC
200 µv
B dHPC
750 µv
C vHPC
500 µv
D SEPT
150 µv
E amyg
200 µv
F AMYG
CONT'D
300 µv

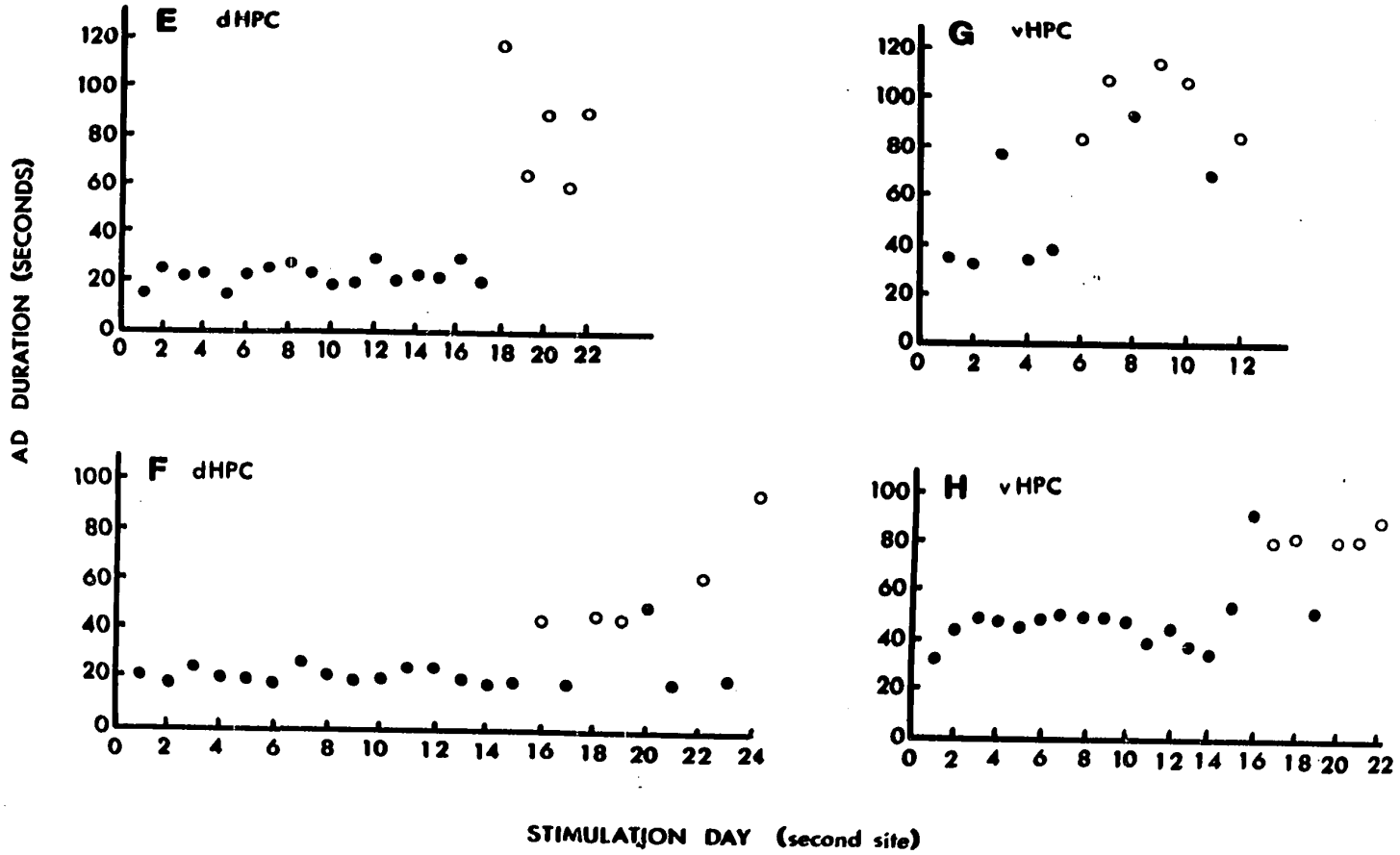
(Figure 17)

Figure 18

Growth curves for afterdischarge duration during secondary stimulation in subcortical subjects that showed transfer. ("Filled in" circles indicate afterdischarges without seizures. "Open" circles indicate afterdischarges accompanied by seizures.) A. and B. Amygdaloid subjects. C. and D. Septal subjects. E. and F. Dorsal hippocampal subjects. G. and H. Ventral hippocampal subjects.


A AMYG
B AMYG
C SEPT
D SEPT
AD DURATION (SECONDS)
STIMULATION DAY (second site)

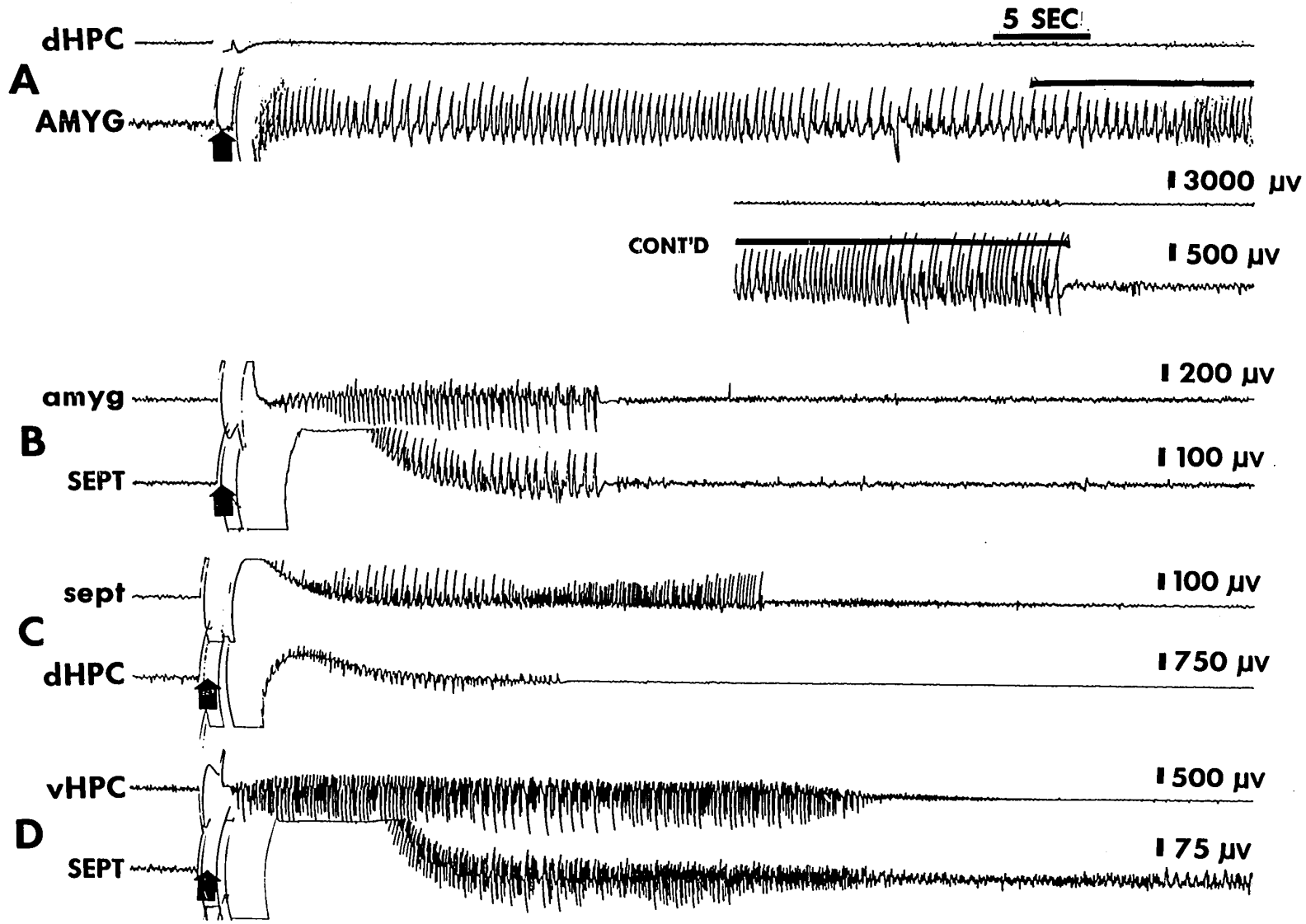
(Figure 18)


E dHPC
G vHPC
F dHPC
H vHPC
AD DURATION (SECONDS)
STIMULATION DAY (second site)

(Figure 18)

Figure 19

Discharge propagated from secondary to primary sites. (Vertical arrows indicate site and time of stimulation. Heavy horizontal lines indicate seizure activity.) A. Secondary discharge causes a seizure without causing reactive discharge in the primary site. B. - D. Secondary discharges cause reactive discharges in primary sites without causing seizures.


5 SEC
dHPC
A
AMYG
3000 µv
CONT'D
500 µv
amyg
200 µv
B
SEPT
100 µv
sept
100 µv
C
dHPC
750 µv
vHPC
500 µv
D
SEPT
75 µv

(Figure 19)

Figure 20

Afterdischarges accompanying primary site stimulation during the period of post-transfer seizure suppression. A., B. and C. illustrate the wide range of durations seen in a single group (the primary septal group after secondary stimulation of the amygdala).

(Figure 20)

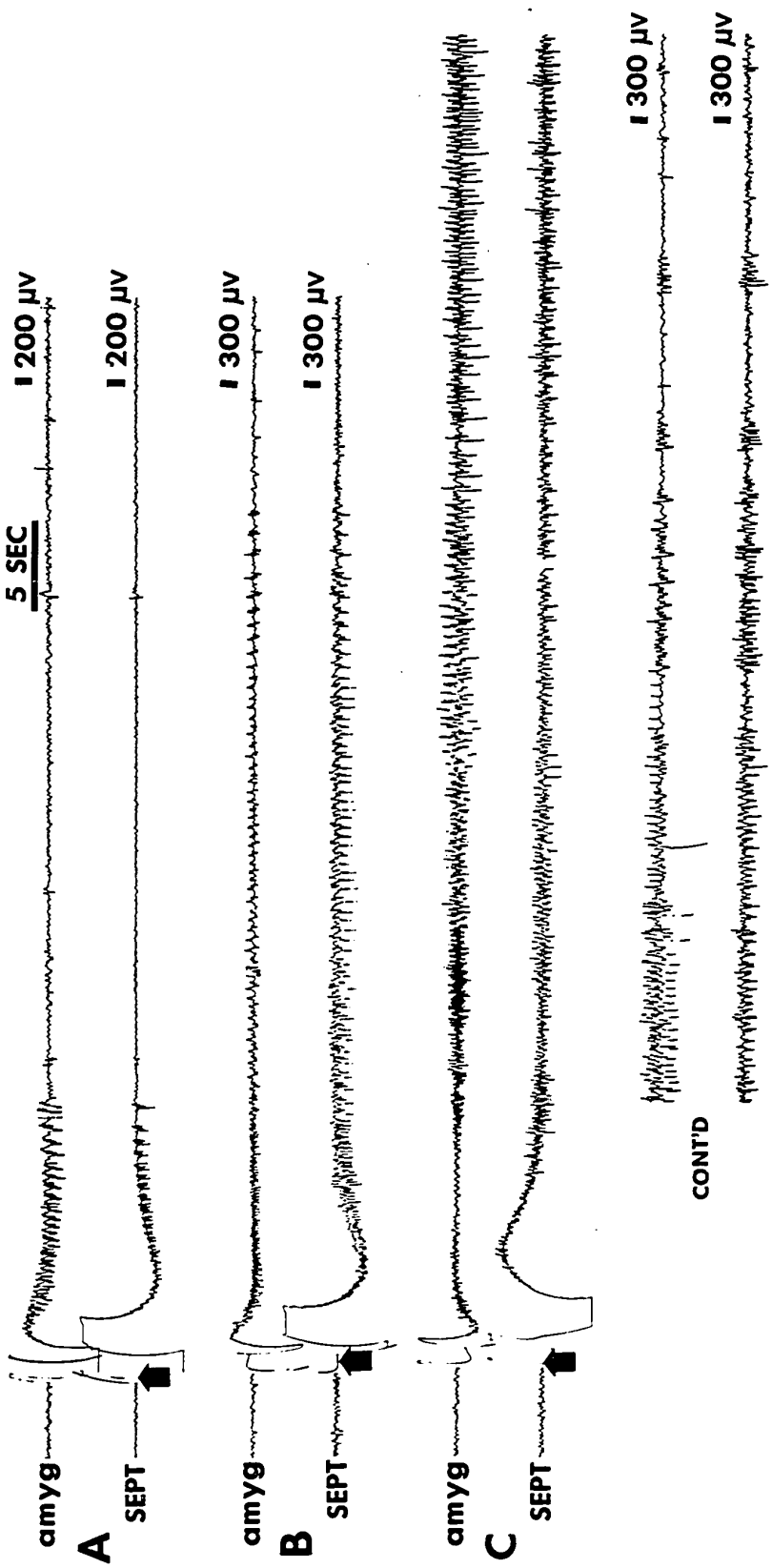

5 SEC
200 µv
200 µv
300 µv
300 µv
300 µv
300 µv
amyg
SEPT
A
amyg
SEPT
B
amyg
SEPT
C
CONT'D

Figure 21

Patterns of response to the lowering of stimulation intensities. ("Filled in" circles indicate discharges or stimulations without seizures. "Open" circles indicate discharges accompanied by seizures.) Pattern A. Long afterdischarges with seizures continued unchanged until both disappeared at threshold. Pattern B. Long discharges with seizures continued unchanged until stimulating current was just above threshold at which point afterdischarges suddenly became very short and seizures usually disappeared. Pattern C. Discharge dropped to moderate levels and seizures occurred only intermittently. (Table 28 indicates the number of subjects in each group that displayed each pattern.)

(Figure 21)

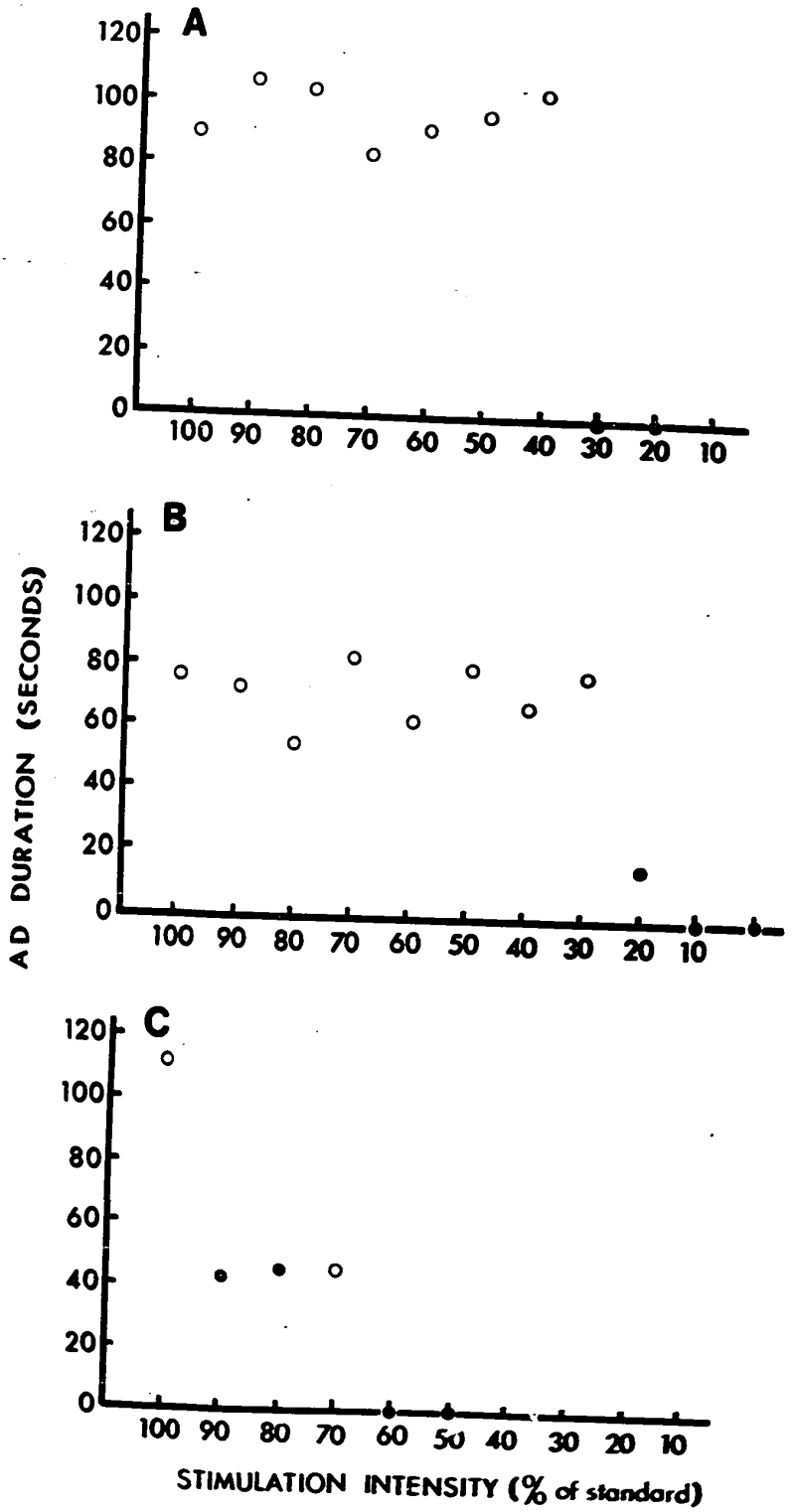

A
B
C
120
100
80
60
40
20
0
100 90 80 70 60 50 40 30 20 10
AD DURATION (SECONDS)
STIMULATION INTENSITY (% of standard)

Figure 22

Seizure caused by a brief amygdaloid afterdischarge evoked by near threshold stimulation. (The vertical arrow indicates the time of stimulation. The heavy horizontal line indicates seizure activity.) Note the absence of propagation.

(Figure 22)

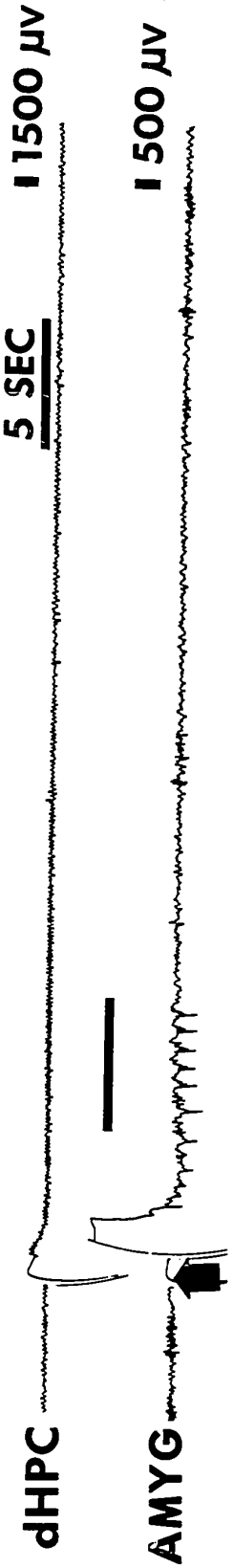
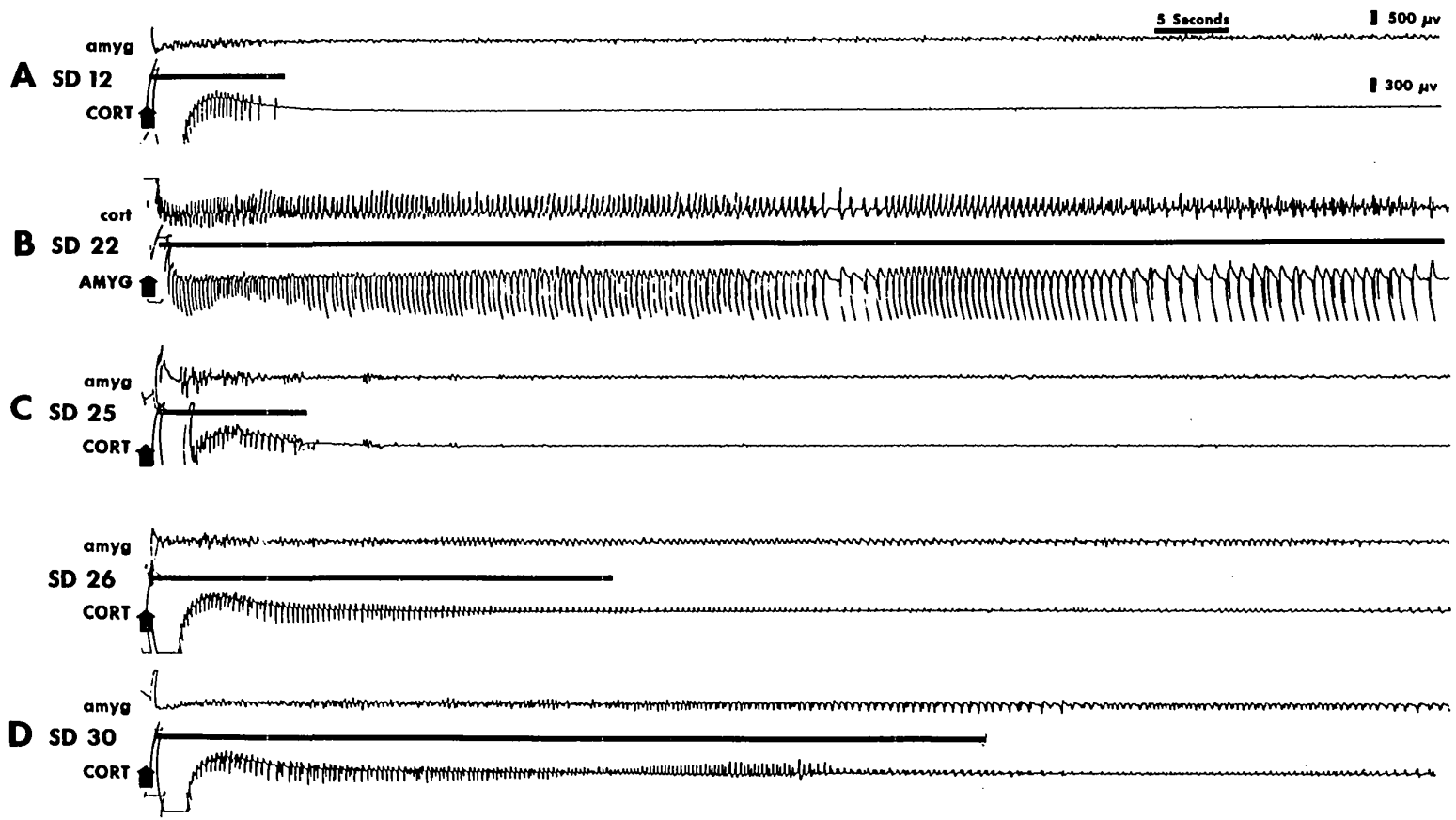


Figure 23

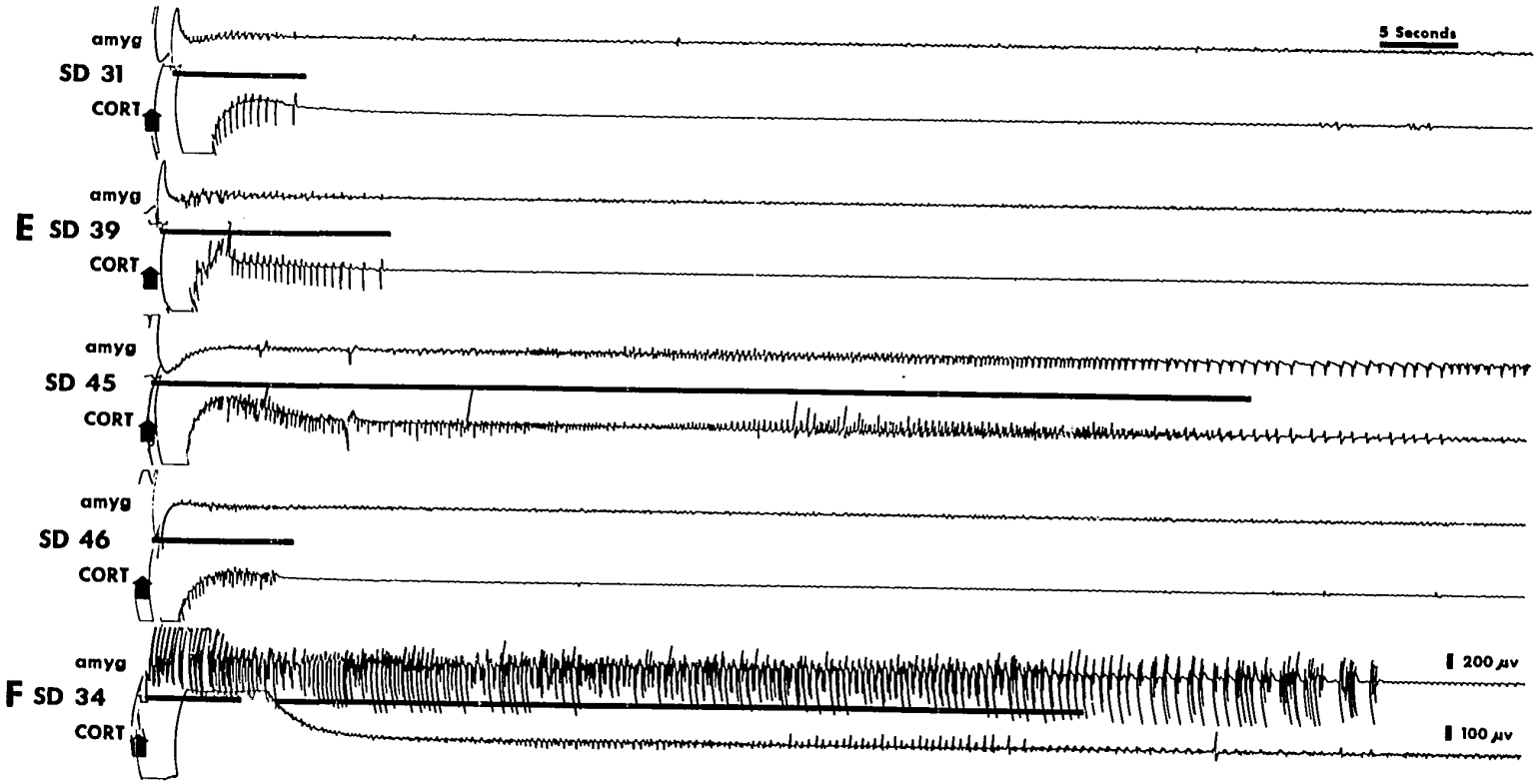
The subcortical "generalization" of cortical afterdischarge and seizures. (Vertical arrows indicate the site and time of stimulation. Heavy horizontal lines indicate seizure activity.) A. A cortical discharge and seizure seen during original stimulation of the primary site. B. An amygdaloid discharge and subcortical seizure seen during transfer testing. C. Cortical afterdischarge and seizure unchanged after transfer testing (SD 25). Sudden appearance of lengthened cortical discharge and subcortical seizure activity on the following day (SD 26). Note the absence of reactive discharge in the amygdala. D. Cortical stimulation produced a long afterdischarge and "subcortical" seizure when an amygdaloid seizure was evoked 24 hours earlier (SD 30), but a brief afterdischarge and "cortical" seizure when an amygdaloid seizure was evoked one-half hour earlier. E. A brief "cortical" afterdischarge and seizure seen with near threshold stimulation (SD 39). Lengthened afterdischarge and "subcortical" seizure seen when stimulation was raised again to the standard intensity (SD 45). A "cortical" afterdischarge and seizure seen when stimulation was raised to three times standard intensity.

Figure 23 (cont'd)

F. A lengthened cortical afterdischarge in another subject. Note the presence of reactive discharge in the amygdala and the two seizure episodes, a brief "cortical" episode and a long "subcortical" episode.


5 Seconds
500 µv
300 µv
amyg
A SD 12
CORT
cort
B SD 22
AMYG
amyg
C SD 25
CORT
amyg
SD 26
CORT
amyg
D SD 30
CORT

(Figure 23)


amyg
SD 31
CORT
5 Seconds
amyg
E SD 39
CORT
amyg
SD 45
CORT
amyg
SD 46
CORT
amyg
F SD 34
CORT
200 µv
100 µv

(Figure 23)