THE EFFECTS OF ISCHEMIA ON SPONTANEOUS AND EVOKED ELECTROCORTICAL ACTIVITY IN THE CAT

by

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Dedicated to

JERRY

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TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

LIST OF ILLUSTRATIONS

LIST OF TABLES

INTRODUCTION

Cerebral anoxic events have been common to man since the beginning of his history. Down through the ages there have been numerous reports reflected in myths, legends, folk tales and newspapers of suffocation, mechanical strangulation, and drownings. Modern medicine today is still confronted with the old problem of cerebral anoxia even more frequently due to carbon monoxide poisoning, stratospheric aviation, and the injudicious use of anesthetic agents.

The treatment of cerebral anoxia today is largely a watch and wait proposition. The rational therapy of any pathological state evolves from an understanding of the basic pathophysiological events leading to that condition. It is the author's hope that this study will contribute to the understanding of the heretofore unknown physiological changes that take place during cerebral ischemia.

REVIEW OF THE LITERATURE

Early Studies Concerning Cerebral Ischemia

The first important experimental study on cerebral ischemia was performed on dogs by Sir Astley Cooper(1) in 1836. He tied the vertebral arteries at their origins, and at the same time ligated the carotid arteries. Following this he noted generalized tonic-clonic convulsions which were soon followed by the cessation of respiration.

Magendie and Poiseuille(2) in 1837, Kussmaul and Tenner(3) in 1857, and Brown-Sequard(4) in 1851, repeated Sir Astley Cooper's experiments and tried to measure the resistance of the brain to ischemia. The first two observers found that it was impossible to revive their animals after 2-3 minutes of ligation. However, the animals were not maintained on artificial respiration. Brown-Sequard noted that one of his dogs survived arterial occlusion for 17 minutes. This was the first in a long series of variations found in the measurement of the survival time of the brain following ligation of the four main cerebral vessels. In 1878, Mayer(5) again conducted the above experiments with great care. He found by observing neurological changes in the animal that the vasomotor and respiratory centers lost their excitability later than higher cerebral centers. This was the first experimental evidence showing that some areas of the brain are more resistant to ischemia than others.

In 1888, Hayem(6) studied the effects of ligating the vertebral and carotid arteries of the rabbit. He found that in most of his animals 10-11 minutes of ischemia resulted in permanent neurological deficits. However, this was not true in all the rabbits tested. Some were able to resist the ischemia longer. He suggested that this was probably

the result of variation in the completeness of ischemia secondary to collateral circulation set up around the arterial ligatures.

The Problem of Collateral Circulation

Numerous other studies followed the work of Mayen substantiating the idea that incomplete cerebral ischemia occured following ligation of the vertebral and carotid arteries in species other than the rabbit. In 1900, Hill(7) tied the four main cerebral vessels in various species of animals. He showed that cerebral collateral anastomosis must exist in dogs and cats. It was his finding that most dogs cannot be killed by permanent ligation of the carotids and vertebrals, and that only one of three cats died after similar ligations. Hill suspected the anterior spinal artery was responsible for the collateral circulation in dogs. In 1916, Brown(8) confirmed this idea by demonstrating that the spinal vessels readily carry dye to the brain following ligation of the vertebrals and carotids. Hill also showed that horses and goats could be killed by ligation of the carotids alone.

The importance of preventing collateral circulation to the brain was emphasized by d'Etchepare,(9) Batelli,(10) and Cannon and Burket(11) who showed that the presence of stagnant blood significantly reduced the vulnerability of nerve cells to ischemia.

Most of the workers at this time were striving to correlate the duration of ischemia with resulting neurological and histological changes. The problem confronting them was how to create a complete ischemia and still keep the animal alive long enough to observe the subsequent neurological and histological changes. It was a difficult problem, and was not solved until 1940. However, it is helpful to

examine the results obtained by workers who were unable to obtain complete ischemia.

In 1906-1908, Stewart et al(12, 13) studied the neurological deficits resulting from combined ligation of the vertebral and carotid arteries in 93 cats. Detailed observations were made on changes in reflex activity, blood pressure, respiration, and muscle tone, but little attention was paid to behavior changes. The authors concluded that irreversible damage to the cerebral and medullary centers resulting in death occured after 15-20 minutes of ischemia. They also concurred with Mayer(5) that the cerebral cortex was more sensitive to ischemia than the vasomotor and respiratory centers.

In 1909, Gomes and Pike(14) studied the histological changes in the brains of the animals used in the experiments by Pike, Stewart et al(12, 13). The cats were killed at various periods after the termination of occlusion, and the brains fixed appropriately and stained using the Nissl, Pal Weigert, and Marchi stains. They demonstrated histologically that nerve cells from different areas in the same animal showed variation in their susceptibility to ischemia. Small pyramidal cells of the cerebral cortex were the most sensitive to ischemia. Purkinje cells of the cerebellum, medullary cells, cervical cord cells, and spinal ganglion cells exhibited progressively greater resistance. Neuroglia were unaffected by ischemia of the durations used in their experiments. They also demonstrated that the animals must remain alive for several hours following decocclusion in order to demonstrate any histological changes. Those animals dying during ischemia showed no histological change, those dying soon after ischemia showed "swollen cells", and those dying many hours after restoration of the circulation showed shrunken, irregularly outlined cells with vacuolization of the

cytoplasm.

In 1910, Hill and Nott(15) conducted a similar set of experiments in England. They permanently ligated the vertebral and carotid arteries of cats and monkeys and then studied the histological changes at various intervals following ligation. Using Nissl's method, they were able to demonstrate slight swelling and chromatolysis of cortical cells after as short a period as 10 minutes following ligation. As yet this has not been confirmed by any other observers. In animals that died within 24 hours, the cortical cells showed diffuse staining, absence of Nissl bodies, and coagulation necrosis. In those animals that died after 24 hours, swollen, vacuolated cells with large eccentric nuclei were present. Finally, those animals that were able to survive permanent ligation, showed cell swelling, nuclear enlargement, and nuclear displacement. Hill and Nott suggested that the latter changes were of a reversible nature.

In 1930, Gildea and Cobb(16) undertook a series of experiments similar to those of Stewart et al(12, 13) in order to obtain additional information about the histological lesions occuring in the cerebral cortex of cats secondary to ischemia. They hoped also to correlate these lesions with the symptoms that occured as the result of ischemia. Gildea and Cobb recognized that they were not getting complete ischemia by ligating the vertebral and carotid arteries. It was necessary for them to establish some criteria for adequate occlusion. If they found that the animal showed a prompt cessation of respiration within from 1-2 minutes after the onset of ischemia and convulsions during the occlusion period, the ischemia was adequate. Of the 90 cats operated on, only 20 survived for 24 hours or more. Failure of normal respira-

tions to return was the most common cause of death.

Gildea and Cobb examined the post-ischemic brains histologically using the Nissl technique. The animals were allowed to survive at least 24 hours before the histological studies were made. In general, they concluded that no one type of lesion can be said to be pathognomonic of cerebral ischemia. Like Gomez and Pike(14), and Hill and Mott(15), these observers found areas of chromatolysis and homogeneous staining cells immediately following a period of cerebral ischemia which was sufficiently complete and prolonged to cause death. The most severe lesions were areas of focal necrosis requiring at least 24 hours to appear. The most marked changes occured in laminae III and V of the cerebral cortex. They concluded that 10 minutes of severe cerebral ischemia was sufficient to impair cortical cells permanently.

Other less successful techniques were employed to create complete cerebral ischemia, such as stopping the heart(17), and exsanguinating animals to the point of clinical death(18). There are many obvious reasons why these techniques were not successful.

Findings Associated With Complete Ischemia

Histological and neurological findings: It is, of course, technically easier to produce complete ischemia of the spinal cord. It would be helpful, therefore, to examine the functional and histological changes in the spinal cord motor neurons following complete ischemia.

In 1901, de Buck and de Moor(19) reviewed all the experimental data available on spinal cord ischemia, and concluded that Nissl's method of staining was the most sensitive and satisfactory, and that

any prior studies not using Nissl's technique should be disregarded. They observed that the animal must survive at least 3 hours after the beginning of occlusion or no lesion could be found. On histological examination of the spinal cord following ischemia, they noted that nerve cell changes began with chromatolysis, formation of reticulum, and later, a loss of affinity for staining. They observed that the majority of cells atrophied rather than becoming swollen. The nucleus appeared to be more resistant than the cytoplasm. They also reported neurophagia and lymphocytic infiltration. Like Gildea and Cobb(16), they concluded that there was no characteristic histological change associated with ischemia.

In 1936, L. L. Tureen(20) was the first to document the reversible cell changes following a given period of ischemia. He occluded the abdominal aorta of cats for one hour, and then killed the animals at varying intervals following the offset of ischemia. The histological changes observed are summarized in Table I below:

Table I

DURATION OF SURVIVAL FOLLOWING DEOCCLUSION

7 HOURS	28 HOURS	36 HOURS	48 HOURS	5 DAYS	11 DAYS
Chromatolysis.	Elongated cell nuclei and spindle-shaped cell bodies.	Amorphous appearing cytoplasm. Dark staining nuclei and cytoplasm.	Inflammatory reaction at maximum. Round cell infiltration and capillary budding.	Nissl flaking and chromatolysis.	Normal.

Tureen made the important observation that the neurological deficits were at a minimum when the histological picture looked the worst (48 hours). He suggested that there was little correlation between the reversible histological changes and the observable neurological deficits. Tureen failed to make any observations earlier than 7 hours, but suggested that the initial histological change prior to chromatolysis was probably cell swelling.

In 1949-1950, Eric Krogh(20) confirmed Tureen's prediction by demonstrating in a series of similar experiments that the earliest cell change following ischemia was "acute swelling". He described the consecutive stages of degeneration leading to the death of the cells as: "acute swelling, liquifaction of Nissl substance (chromatolysis), ischemic cell degeneration of Spielmeyer, pseudosclerotic dark-colored shrunken cell, and finally, the non-stainable cell shadow which disappears completely".

Turning once again to the studies of cerebral ischemia, we note that in 1940, Weinberger et al(22, 23) finally solved the problem of incomplete cerebral ischemia. They occluded the pulmonary artery via an intrathoracic approach in 24 cats, and subjected them to periods of ischemia ranging from 2-10 minutes. They employed the disappearance and reappearance of retinal artery blood flow as criterion for the adequacy of ischemia. In all cases, there was a complete cessation of retinal artery blood flow. With this technique, Weinberger et al felt that a reliable comparison of the neurological and histological changes could be made.

Following 3 minutes and 10 seconds of cerebral ischemia no ob-

servable neurological deficits were present, and no permanent lesions of the cerebral cortex were seen. After 3 minutes and 25 seconds, permanent alteration in behavior and "psychic function" occured. Histologically, frank necrosis of the cortex was observed. After 6 minutes, vision and sensation suffered some degree of permanent injury. Following 7 minutes and 36 seconds, permanent and practically complete dementia, blindness, serious sensory and auditory deficits, motor and postural defects, and reflex abnormalities were present. Histologically, widespread areas of laminar necrosis were present. After 8 minutes and 45 seconds or longer, life could not be maintained for more than a few hours.

In general, Weinberger et al observed that the motor and visual cortices sustained the earliest and most profound change. The olfactory, orbital, and temporal regions were the least susceptible. Laminae III and IV were more vulnerable than I and II. The Purkinje cells ranked next to the cortical cells in susceptibility, and then the basal nuclei in the following order: lateral geniculate, hypothalamus, thalamus, globus pallidus, and caudate. The brain stem and spinal cord nuclei were uninjured by periods of ischemia compatible with continued survival of the animal.

In 1938-1939, Kabat and Dennis(24, 25) devised a unique method of arresting completely the cephalic circulation of the dog, without subjecting the animal to the trauma of a complicated operation, the use of anesthetics, and the cutting off of the blood supply to all other parts of the body, as was done in Weinberger's(21) experiments. Their technique consisted of a simple preliminary surgical procedure involving the removal of both laminae and spines of the second cervical vertebra,

thus exposing the vertebral arteries. After an interval of two days, the trachea was cannulated with a metal tube to insure an adequate airway during occlusion, and a large blood pressure cuff was wrapped around the dog's neck. The pressure in the cuff was raised quickly to 700 mm. Hg., completely arresting the circulation to the brain. Using this technique, Kabat, Dennis, and Baker(26) observed that the animals "lost consciousness" in a very few seconds, and that the corneal reflex disappeared in from 20-40 seconds, and that spontaneous respirations ceased in 40-90 seconds. They concluded that animals subjected to 6 minutes of ischemia or less recovered completely, but that stasis for 8 minutes or longer resulted in permanent neurological deficit.

In 1946, Grenell(27), using the technique of Kabat and Dennis(24, 25), attempted to correlate the neurological and histological changes with the duration of ischemia. He observed that following 2 minutes or less of circulatory arrest, the animals were in coma for 12-18 hours, and they exhibited some slight ataxia for a week or more. Histologically, relatively little damage was seen. After 4 minutes of occlusion, the animals were unconscious for 18-24 hours. At first, they showed lack of interest and curiosity, apathy, and a paucity of spontaneous movements, but after several weeks they returned completely to normal. Histologically, the cortex showed many areas of severe injury. Following 6 minutes of occlusion, there was a gradual return of consciousness over a 24-48 hour period. Similar neurological deficits, as found in 4 minute animals, were present but disappeared after several weeks or a month. Histologically, again there was "severe brain damage" present. Adult dogs rarely recovered consciousness after 8 minutes of

vascular occlusion. In general, Gremell's histological studies revealed that various nuclei appear to behave as units in their resistance to ischemia. He found that damage was remarkably uniform throughout a nucleus, and that adjacent nuclei might show marked differences in susceptibility. He suggested that a group of neurons constituting an anatomical unit may also share specific metabolic characteristics.

Using the blood pressure cuff technique, Kabat et al(25, 26) were able to demonstrate that young and pregnant or lactating dogs were more resistant to ischemia than the normal adult dog. In evaluating the experimental results of Kabat et al and Gremell, the possibility must be borne in mind that the early recovery period may have been complicated by cervical cord trauma.

In 1928, Spielmeyer(29) and in 1953, Courville(30) summarized their studies on human brains coming to post mortem after episodes of cerebral anoxia. It is of interest that they demonstrated histological lesions similar to those described in the animal experiments above.

Inadequacies of these studies: In general, most of the experiments appearing in the past literature have dealt with the neurological and histological changes that occur secondary to ischemia. There are some serious shortcomings and inadequacies that result from using these criteria. First, numerous experiments have shown that there is a lack of correlation between the histological picture and the observable neurological changes(20, 31, 32). Second, it is difficult to determine how much functional recovery is due to reversible neuron changes, and how much is due to compensation and relearning. Finally, inadequate histological preparation and trauma to the brain during

removal from the skull can cause histological changes which can mimic some of the early ischemic changes(33, 34).

Conclusions

From the past literature we are able to conclude that irreversible histological changes appear after 3½-4 minutes of complete ischemia in the cat and dog. Complete ischemia for 9 minutes or more is apparently incompatible with survival. There seems to be little correlation between the anatomical picture and the functional status of the animal. It is difficult to predict from the histological picture the degree of subsequent recovery because of compensation and relearning.

STATEMENT OF THE PROBLEM

Lucas and Strangeways(33), Horvath et al(35), Lennox et al(36), and Kabat et al(26) have demonstrated that there is a "sudden loss of consciousness" following the onset of ischemia. During this period no histological changes have been observed(33, 27). The question naturally arises as to the physiological mechanism underlying this very early functional change. At present, there is no information available to answer this question. It is the aim of this research to try to find a solution to this intriguing problem.

Ideal

The ideal way to solve this problem would be to examine experimentally the objective correlates of the loss of consciousness following the onset of cerebral ischemia. This is obviously impossibly for several reasons. First, and most important, no adequate definition of consciousness is available at this time. Consciousness is difficult to define specifically because it is based on a complex central nervous system function integrated at many levels. There are, therefore, many variations in degrees of consciousness. According to Cairns(37), Stanley Cobb defined consciousness as "an awareness of environment and self". Therefore, if there is little or no awareness, the patient has some degree of unconsciousness. The normal man can indicate by speech and movements that of which he is aware, but lower animals cannot. It is obvious that lower animals must be used in experiments designed to explain the mechanisms underlying the loss of consciousness. We are therefore left with the problem of observing

speechless behavior in response to various stimuli, and this cannot possibly provide information about awareness. Finally, there are obvious humane reasons for not subjecting unanesthetized animals to cerebral ischemia.

Second Choice

Another aspect of central nervous system function: Since the ideal is at present unattainable, the next best choice would be to study a central nervous system function with the following attributes. First, it must be based on a complex functional interaction between neurons, comparable to that which forms the basis for consciousness. Second, it should occur spontaneously in unanesthetized animals. Third, it should be observable by objective means. Finally, the mechanisms of abolition of the function by ischemia should be susceptible to analysis.

Spontaneous spindling fulfills requirements: Most observers who have studied spontaneous spindling(38, 39, 40) agree that it is apparently produced by an interchange of activity between cortical and thalamic neurons. These authors have observed that the activity occurs in the form of bursts of repetitious discharges in both cortical and thalamic neurons. Some of the cortical neurons active are those giving rise to corticospinal fibers. In 1939, Adrian and Moruzzi(38) were the first to record spindle bursts in the motor cortex and simultaneous bursts of activity in the pyramidal tract. This work was later confirmed by Zanchetti and Brookhart(41) and in the microelectrode studies of Calma and Arduini(42).

Spindling activity is found in normal sleeping animals and in animals with mesencephalic transections which do not need anesthesia. Bremer(43), in 1935, was the first worker to demonstrate that an animal with a lesion of the tegmentum at the collicular level appeared for all intents and purposes like the normal sleeping animal. He called his preparation the "cerveau isole". Lindsley, Bowden, and Magoun(44) recorded simultaneous burst activity in the cortex and thalamus following mesencephalic transection. They suggested that a link or factor was present associating the burst activity in the two regions. By abolition studies, they were able to demonstrate a corticothalamic interdependence. Magoun(45, 46) and Staral, Taylor and Magoun(47) have demonstrated the importance of the activity of the reticular formation in the aroused state. Bremer(48), in 1953, suggested that a mesencephalic lesion interrupts the tonic functioning of the reticular formation resulting in what appears to be a sleep state, which is apparently very similar to that occuring in the normal animals.

Spindling can be recorded easily on the electroencephalograph. According to Gibbs, Davis, and Lennox(49) and Jasper and Carmichael(50), the electroencephalogram changes in sleep were first observed by Berger in 1929. Since then numerous other investigations have confirmed his observation(51, 52, 53).

The cells of origin of corticospinal fibers can be stimulated in pure culture antidromically. The antidromic activity results in the production of an electrocortical complex which is detectable at the surface of the cerebral cortex. The first observers to study this

complex were Woolsey and Chang(54) in 1947. The purpose of their study was to determine the origin of the pyramidal tract fibers in several species of animals. In the cat, they described two types of responses recorded from the pericruciate gyri following pyramidal stimulation. The authors were uncertain about the interpretation of the components of the wave complex, but suggested that the positive deflections might represent conduction in three different sized fiber groups with different conduction velocities. Woolsey and Chang also suggested that the negative deflection might be due to the spread of electrical activity in the apical dendrites or to activation of pyramidal axon collaterals.

In 1955, Chang(55), in a series of carefully controlled experiments, studied the cortical response to stimulation of the medullary pyramids in the rabbit. He recorded an electrocortical complex from the motor cortex which consisted of two initial positive deflections followed by a long negative wave. From the evidence he presented in his work, there was reason to believe that the initial positive deflection was the result of electrical activity in the axon, that the second positive deflection was due to somatic activity, and that the negative deflection was due to activity in the apical dendrites. Chang was able to show that the negative component was very susceptible to anoxia and asphyxia, and that the positive components were far more resistant.

Other studies have been done on peripheral(31, 56) and cranial nerves(57) and the spinal cord(58, 59) which indicate that the soma is more sensitive to anoxia than the axon. On the other hand, Woall

17

and Chinn(60) and Sugar and Gerard(61) in studying the visual pathways found that in the retinal and geniculate ganglia, conduction across the synapse and cell body failed only seconds before the axon became inexcitable. Bronk and Larrabee(62) and Bargeton(63) found the same thing true in their studies on the superior cervical sympathetic ganglion. The differences in the results of the two groups of observers can probably be explained by the fact that the work on the spinal cord and cranial nerves was based on the antidromic activation of the cell bodies, while the studies on the retinal, geniculate, and sympathetic ganglia were based on orthodromic transynaptic excitation of the cell bodies.

We see, therefore, that spindling consists of spontaneous activity which is dependent upon complex interneuronal exchange in unanesthetized animals, and should be abolished early in ischemia. Spindling activity involves corticospinal neurons which may be studied independently of the spindling using antidromic activation. Certain portions of the response thus produced have been noted to be abolished early in anemia and asphyxia. It would seem worthwhile to compare the effects of ischemia upon the complex activity called spindling, and upon the response of the corticospinal cells to antidromic activation. Measurement of the duration of ischemia required to abolish these signs of neural activity could be used as criterion of relative susceptibility. Such correlation or lack of correlation as might appear could then be used to guide our attempts to understand the early functional results of ischemia.

METHODS

General Plan

Cerebral ischemia was produced by basilar and carotid artery occlusion. The likelihood of variations in the degree of ischemia produced in different animals was confirmed by observing the retinal artery blood flow in a number of cats following occlusion. The majority of animals had an immediate cessation of retinal artery blood flow, but showed some return of circulation in anywhere from 30 seconds to 5 minutes after the onset of occlusion. Despite these variations, it was considered that the sensitivity to ischemia of the mechanism under consideration would obviate the requirement for complete and total cessation of blood flow. Spontaneous spindles were produced by mesencephalic lesions. Antidromically conducted evoked potentials were produced at the cortex by stimulation of the medullary pyramids. The times of disappearance of the spindles and the evoked responses following the onset of ischemia were observed and recorded.

Specific Details

Production of ischemia: In preparation for combined carotid and basilar occlusion, it was found to be advantageous to tie the basilar artery at least 24 hours prior to the performance of the experiment. Several attempts to carry out all of the surgical manipulations on the same day resulted in preparations which deteriorated before the completion of the experiment. The animals were anesthetized with intraperitoneal pentobarbital-sodium, 0.5 cc./kg., and an endotracheal tube or tracheostomy tube was used to insure an adequate airway. With

the animal in the supine position, the base of the skull was approached via the parapharyngeal route. The basioccipital bone was entered with a dental bur. The aperture was enlarged with a small tipped rongeur. The dura was divided and the basilar artery was seen pulsating in the midline between the two pyramids. A fine suture was passed beneath the artery at the level of the inferior border of the pons. This point was chosen in order to preserve the circulation in the more caudal portions of the basilar artery, thus insuring an adequate blood supply to the respiratory and cardiac centers of the medulla during the periods of ischemia. In addition, the mechanical passage of the suture was facilitated by the presence of a large cistern between the inferior border of the pons and the basilar artery. The animal was given fluids and permitted to recover for at least 24 hours.

On the day of the experiment, under light ether anesthesia, the carotid arteries were isolated and loose ligatures placed around them. A small length of polyethylene tubing was slipped over the free ends of the ligature, so that occlusion could be brought about by placing traction on the ligature and sliding the tubing over the doubled-up artery. The use of this technique greatly facilitated the occluding and deocclusing processes.

Production of spontaneous spindles: Lightly etherized cats were placed in the Horsley-Clark apparatus. Bilateral bur holes were placed in the posterior parietal bones for insertion of the coagulating electrodes. The electrodes were 4 mm. apart, and the distal 4 mm. were uninsulated. The electrodes were stereotaxically oriented to enter the tegmentum of the mesencephalon at the intercollicular level. The

lesions were produced by a radiofrequency generator operating at 8.7 megacycles. Ninety milliamps of current were passed between the coagulating electrodes for 20 seconds, producing a lesion 4 x 4 mm. Five such lesions were adequate to destroy the tegmentum and spare the central grey matter and cerebral peduncles. Two lesions were placed to the right and left of the vertical midline, oriented so that their midpoints were 4 mm. lateral to the vertical midline and 2 mm. above and below the horizontal zero plane. The fifth lesion was placed so that the midpoint was on the vertical midline and 4 mm. below the horizontal zero plane. If the lesion was complete, the pupils became slit-like within a few minutes and a soft rigidity developed in all the extremities. The incidence of cerebral edema following the production of the mesencephalic lesion was reduced to a minimum by careful avoidance of trauma to the superior sagittal sinus.

Following the conclusion of the experiment, the animal's brain was perfused with formalin through the left carotid artery. Anatomical checks were made on all lesions. The cerebral peduncles and central grey matter were spared in most cases. However, in several of the brains there was some slight encroachment upon the central grey matter.

In all cases, the anesthesia was discontinued for at least 1 hour before the recording was started.

Recording of spindles: The spindles were recorded with a Grass eight channel electroencephalograph (EEG). Unipolar electrodes were attached to the right frontal and the right and left parietal and occipital bones. Another lead was taken directly from the left frontal

cortex.

The EEG was run continuously during ischemia at a paper speed of 15mm./second. The beginning and end of ischemia were marked on the EEG paper, and the duration of ischemia was calculated using the rate of EEG paper movement as a time base.

In an attempt to represent the degree of spindling activity graphically within a reasonable space, the EEG records were measured in the following way. The record for an entire run was subdivided into two second intervals. In each of these intervals, the percentage of time that waves were in excess of 100 microvolts was measured. These percentage values were then plotted on semilog paper. The 100 microvolt amplitude was chosen arbitrarily so that the difference between spindling and interspindling activity would be apparent graphically. The total disappearance of all EEG activity was used as the ultimate criterion for measurement.

Production of the evoked response: The medullary pyramid was stimulated with a bipolar concentric electrode constructed by inserting and fixing a 29 gauge nichrome wire inside a length of 20 gauge hypodermic needle tubing. Both were insulated to the tips which were opened by brushing against fine stone. A 0.5 mm. tip separation was used.

The aperture for placement of the pyramidal electrode was made with a dental bur in the occipital bone overlying the posterior part of the cerebellum. The pyramidal electrode was stereotaxically oriented to arrive at the left pyramid using an angular approach through the cerebellum and pons. The left motor cortex was stimulated and at

the same time a recording was taken from the pyramidal electrode. When the electrode entered the pyramid, the cortically induced orthodromic pyramidal response could be recorded(37). At the same location, spindling could be heard over the audiomonitor. The use of these criteria insured an accurate location of the pyramidal electrode tip in the medullary pyramid.

Pyramidal stimuli consisted of single rectangular pulses of 5-15 volts intensity and 0.1 to 0.5 msec. duration delivered through an isolating transformer. The stimulus frequency was controlled manually and the stimuli were synchronized with an oscilloscope sweep. During the experimental period, the stimuli were timed manually to occur during interspindle lulls in order to insure a stable background and prevent interaction of the spindles and the antidromic waves.

Recording of evoked response: The antidromically evoked pyramidal response was recorded from the left frontal cortex. Under light ether anesthesia, the left frontal sinus was entered with a dental bur. Another bur hole was then cautiously placed in the thin posterior wall of the frontal sinus. This aperture was enlarged with a small rongeur in order to give a good exposure of the pericruciate cortex. The dura was left intact as long as possible prior to recording. A plastic well was constructed around the frontal aperture and filled with warm mineral oil to protect the exposed cortex. This procedure was found to be essential to the complete recording of the evoked potential complex. The recording electrode was a thin, ball tipped silver wire. Following conventional amplification, the responses were recorded photographically from a cathode ray oscilloscope. The film was developed and analysed using an enlarger.

The amplitude changes of the components of the antidromic pyramidal response were measured and plotted graphically using a semilog time base. The control values were determined by obtaining the mean amplitudes of the components of 10-15 responses prior to the period of ischemia.

The period of ischemia: Before each period of ischemia, a series of 10-15 control records were photographed. The onset of ischemia was taken as that moment when both carotid arteries were occluded. During the period of ischemia, an assistant observed the cortical changes, checked the contact of the electrode with the cortical surface, and applied warm mineral oil to the well when needed. The conclusion of ischemia was taken as that moment when one of the two carotid arteries was deoccluded.

The recovery period was not studied in detail because it was complicated by cerebral edema, probably having its origin in reactive hyperemia. These conditions undoubtedly caused local changes that were severe enough to retard the normal recovery cycle.

Statistical treatment of data: The mean disappearance times of the EPS and components of the pyramidal response were determined and subjected to "t" test analysis(64). This was done to determine whether any of the means were significantly different. Correlation coefficients were also determined, comparing the EPS disappearance times with the disappearance times of the pyramidal response components(65). Scatter diagrams with Xy and Yx regression curves were drawn for each of the comparisons made.

RESULTS

The results to be described have been based upon experiments on 51 cats. Of this total number, the data from 10 have been used in preparing this description. From these 10 cats, 14 ischemia series were obtained. The remainder of the animals were used for various purposes not productive of data adequate for analysis. A number were used to gain familiarity with recording equipment and techniques of preparation. Still others were used in an attempt to evaluate the probability of the occurrence of collateral circulation which would offset the ischemia produced by the combined arterial occlusions. Still others were non-contributory because of the early onset of cerebral edema, equipment failures and other technical difficulties.

Preischemic Activity

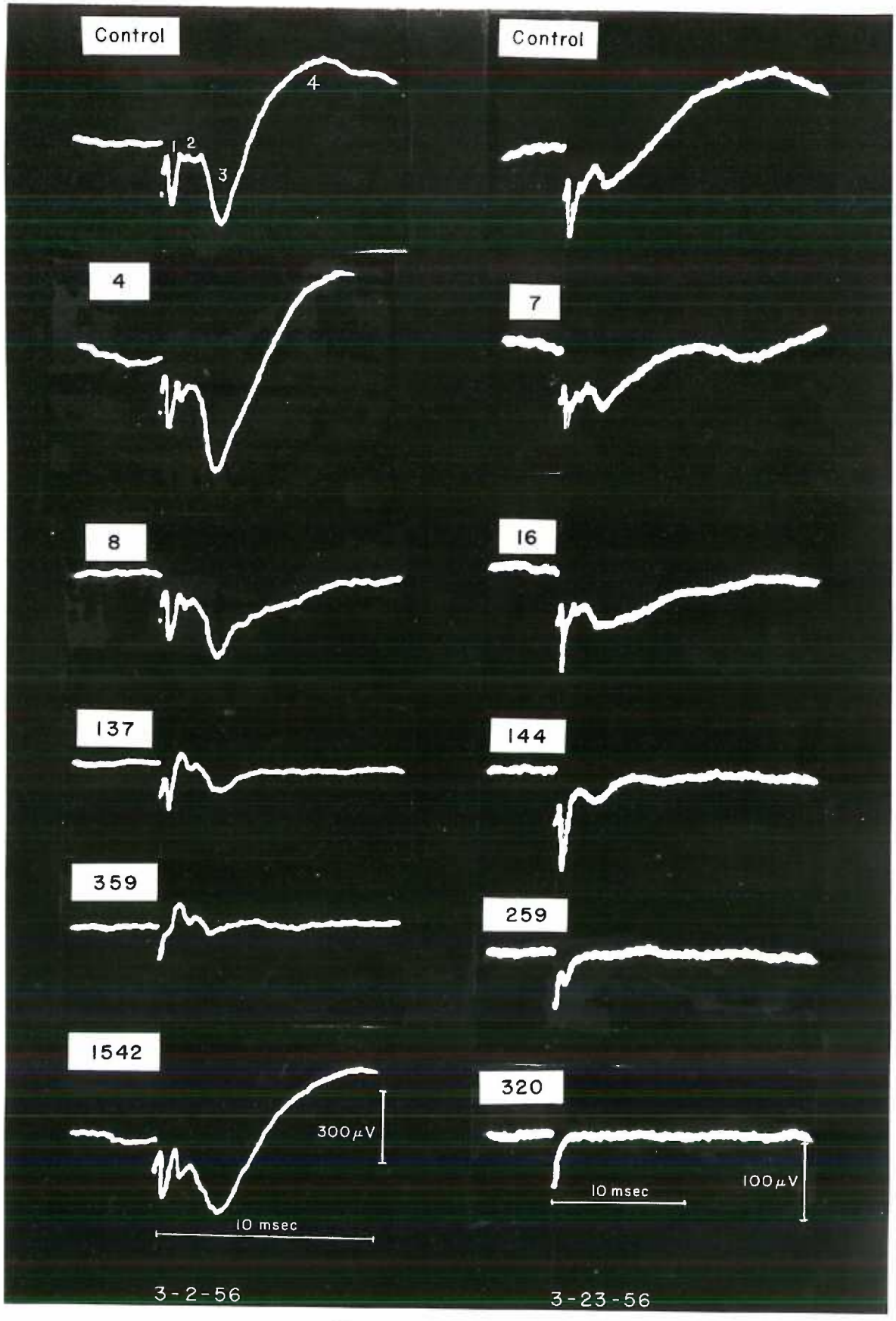
Evoked response: The antidromically evoked cortical response was best recorded from the cortex surrounding the lateral portion of the cruciate sulcus. The response consisted of three positive deflections and a later-occuring negative deflection. These components have been designated 1, 2, 3, and 4. Photographic reproductions of the typical preischemic response may be seen in Figure 1 (control). The ranges of latencies and durations of their components as recorded in 14 ischemia series are summarized in Table II.

TABLE II

	Latency of onset (msec.)	Duration (msec.)
Component 1	0.2-0.3	0.3-1
Component 2	1-1.5	1
Component 3	2-3	3-6
Component 4	5-7	8-15

FIGURE 1

Series of oscillographic records of the cortical response to stimulation of the medullary pyramid taken during two typical experiments on 3-2-56 and 3-23-56. The "control" responses were obtained during the preischemic periods. The numbers above each response indicate the seconds elapsed after the onset of ischemia. The last two responses in each column were taken during the postischemic periods.


Control
1
2
3
4
4
8
137
359
1542
300 μV
10 msec
3-2-56
Control
7
16
144
259
320
10 msec
100 μV
3-23-56

It was necessary to use fast oscilloscope sweep speeds in order to separate clearly components 1 and 2. The use of fast sweep speeds would sometimes throw the later-occuring fourth component off the oscilloscope screen. In those experiments where all the components were clearly visible, component 2 was very small and difficult to measure with any accuracy. Therefore, under the conditions of this experiment, no reliable information could be obtained about the susceptibility of component 2 to ischemia.

The cortical response was evoked during interspindle lulls because amplitude variations in the response occured when it was evoked during spindling activity.

In all experimental preparations, a variation in the pure antidromic pyramidal response could be obtained if the stimulus intensity was increased to 30-40 volts, and the recording electrode placed over the sensory cortex. A long high amplitude positive wave with a latency of 8-10 msec. and duration of 5-7 msec. would appear. The characteristics of this wave corresponded closely with those of the "sensory response" of Chang(49). It is reasonable to believe that increasing the stimulus intensity allowed the spread of the stimulus to the lemniscal system which is located just dorsal to the pyramids. In three of the experiments, the sensory response was an unavoidable complication occuring at the same time as components 3 and 4. The overlap of the sensory and antidromic responses obviated satisfactory analysis of the later portions of the antidromic response. Subsequent examination of the bipolar concentric stimulating electrodes revealed that there was a 1½ mm. separation between the tip of the core and the

shield. The wide tip separation undoubtedly was responsible for the spread of the stimulus to the lemniscal system. This difficulty was not encountered with tip separations of 0.5 mm. or less.

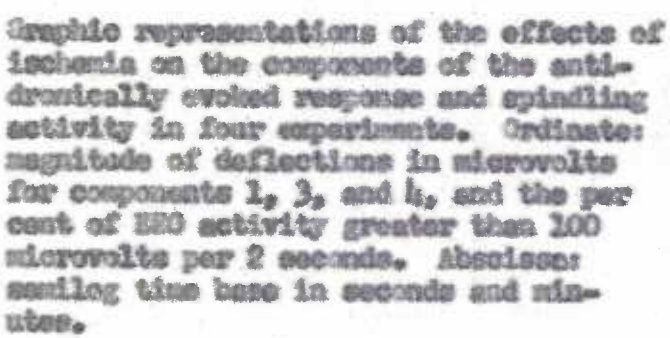
Spindling activity: Preischemic spindling activity consisted of trains of slow waves (8-10/sec.), which reached a maximum amplitude of 500 microvolts near the middle of each burst. The spindles occured as frequently as one every 2 seconds and as infrequently as one every 5-6 seconds. In general, the individual spindle waves had an initial positive deflection followed by a large negative deflection.

The Effects of Ischemia on Electrical Activity

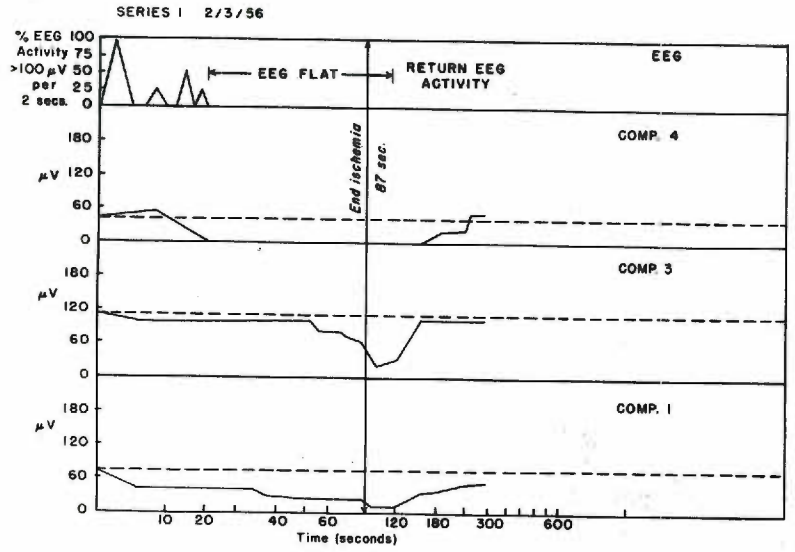
Antidromically evoked response: Figure 1 contains photographic reproductions of the antidromic pyramidal response at varying intervals during the periods of ischemia recorded in two typical experiments. It will be noted that in both of these experiments the fourth component is the most sensitive to ischemia, disappearing eight seconds after the onset of ischemia in the experiment dated 3-2-56, and 16 seconds after onset of ischemia in the experiment dated 3-23-56. In the latter experiment, component 1 is the most resistant to ischemia being still present after 259 seconds of arterial occlusion. The ischemia lasted for 330 seconds in this experiment. None of the responses reappeared following deocclusion. Marked cerebral edema appeared during the recovery period. On the other hand, in the experiment dated 3-2-56, component 1 and 3 persist, though with decreased amplitude throughout the entire ischemic period of 370 seconds. The recovery of all the components is complete 1542 seconds after the onset of ischemia.

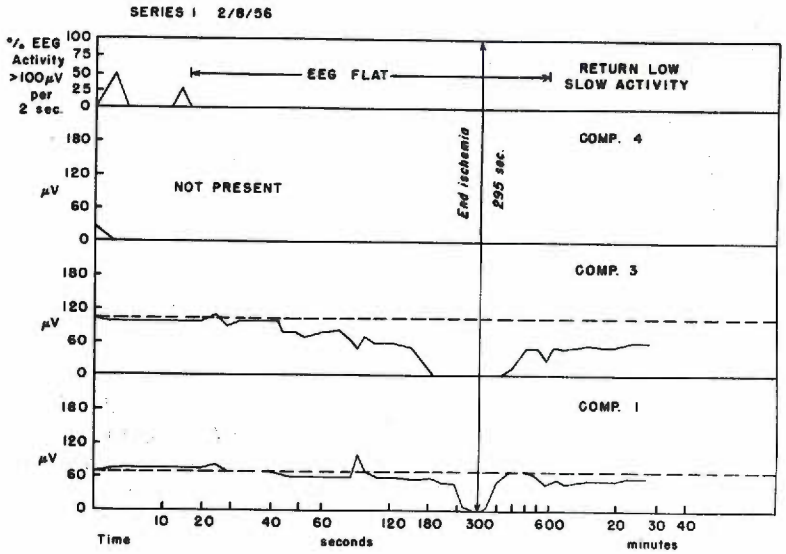
Figures 2, 3, 4, and 5 graphically summarize the effects of

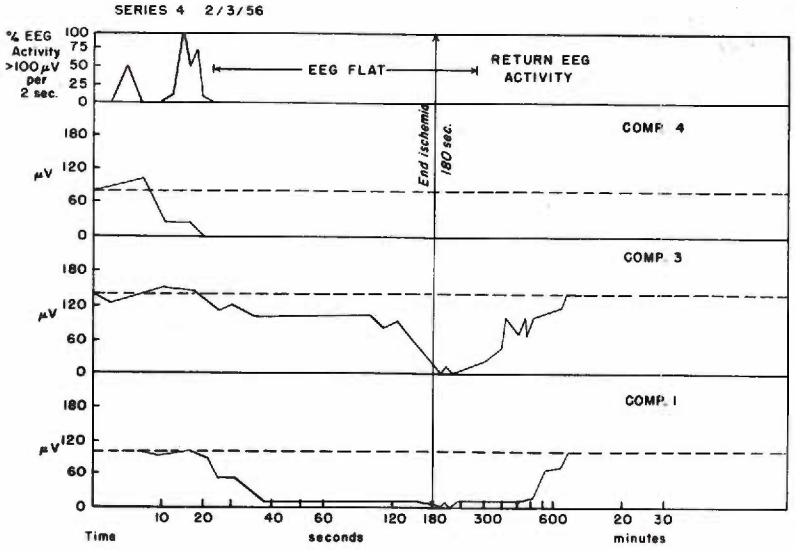
FIGURE 2



Graphic representations of the effects of ischemia on the components of the antidromically evoked response and spindling activity in four experiments. Ordinate: magnitude of deflections in microvolts for components 1, 3, and 4, and the per cent of EEG activity greater than 100 microvolts per 2 seconds. Abscissa: semilog time base in seconds and minutes.


SERIES 1 2/3/56
% EEG Activity >100 μV per 2 secs.
EEG FLAT
RETURN EEG ACTIVITY
EEG
End ischemia
87 sec.
COMP. 4
COMP. 3
COMP. 1
μV
Time (seconds)


SERIES 1 2/8/56
% EEG Activity >100 μV per 2 sec.
EEG FLAT
RETURN LOW SLOW ACTIVITY
NOT PRESENT
End ischemia
295 sec.
COMP. 4
COMP. 3
COMP. 1
μV
Time
seconds
minutes


SERIES 4 2/3/56
% EEG Activity >100 μV per 2 sec.
EEG FLAT
RETURN EEG ACTIVITY
End ischemia
180 sec.
COMP. 4
COMP. 3
COMP. 1
μV
Time
seconds
minutes

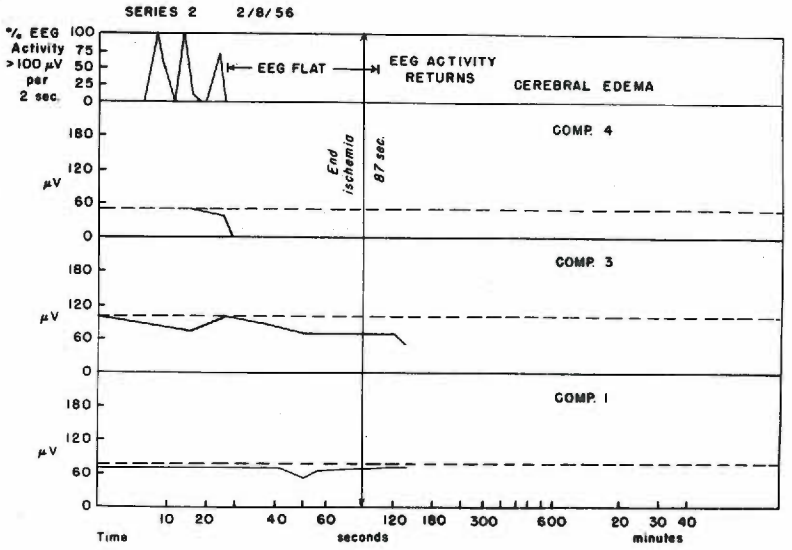
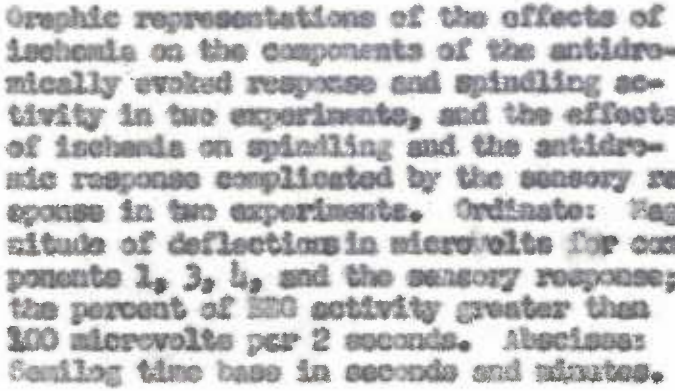
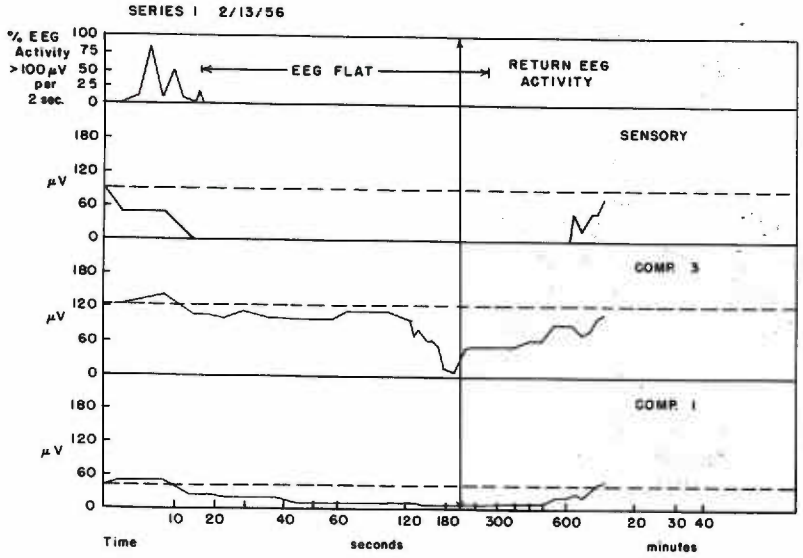
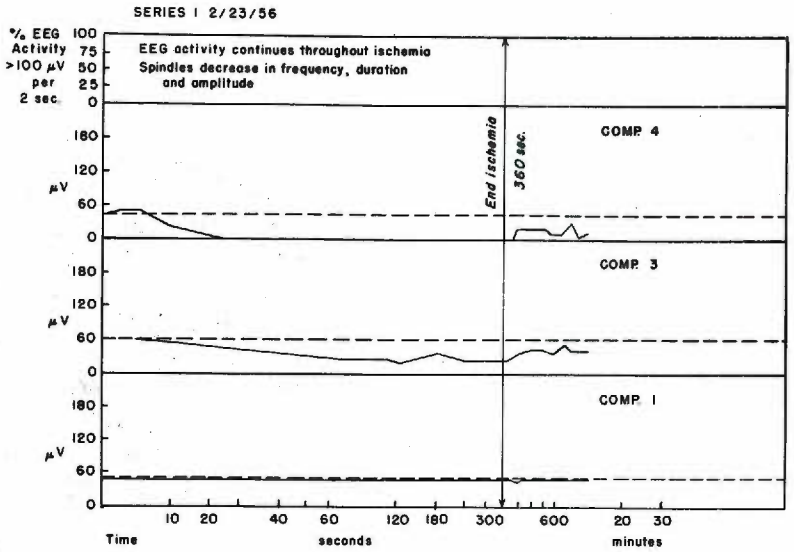

SERIES 2 2/8/56
% EEG Activity >100 μV per 2 sec.
EEG FLAT
EEG ACTIVITY RETURNS
CEREBRAL EDEMA
End ischemia
87 sec.
COMP. 4
COMP. 3
COMP. 1
μV
Time
seconds
minutes

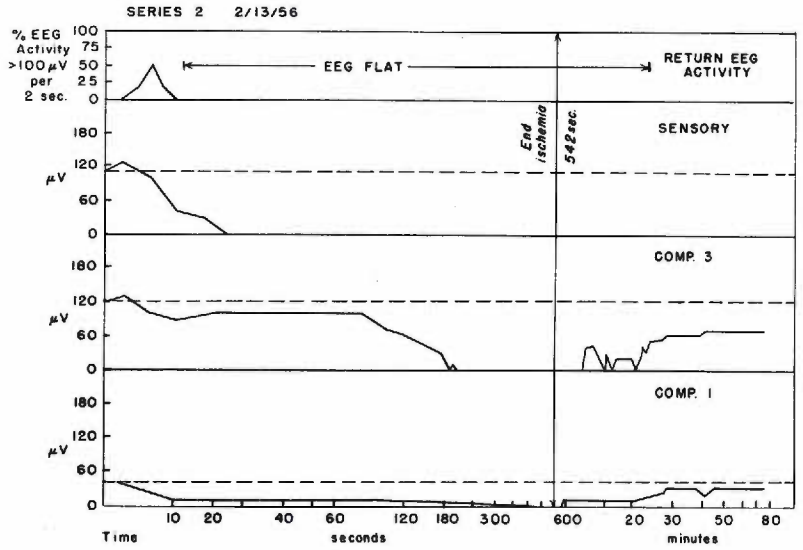
FIGURE 3



Graphic representations of the effects of ischemia on the components of the antidromically evoked response and spindling activity in two experiments, and the effects of ischemia on spindling and the antidromic response complicated by the sensory response in two experiments. Ordinate: Magnitude of deflections in microvolts for components 1, 3, 4, and the sensory response; the percent of EEG activity greater than 100 microvolts per 2 seconds. Abscissa: Semilog time base in seconds and minutes.


SERIES 1 2/13/56
% EEG Activity >100μV per 2 sec.
EEG FLAT
RETURN EEG ACTIVITY
SENSORY
COMP. 3
COMP. 1
μV
Time
seconds
minutes


SERIES 1 2/23/56
% EEG Activity >100 μV per 2 sec.
EEG activity continues throughout ischemia
Spindles decrease in frequency, duration and amplitude
End ischemia
360 sec.
COMP. 4
COMP. 3
COMP. 1
μV
Time
seconds
minutes


SERIES 2 2/13/56
% EEG Activity >100μV per 2 sec.
EEG FLAT
RETURN EEG ACTIVITY
End ischemia
542 sec.
SENSORY
COMP. 3
COMP. 1
μV
Time
seconds
minutes

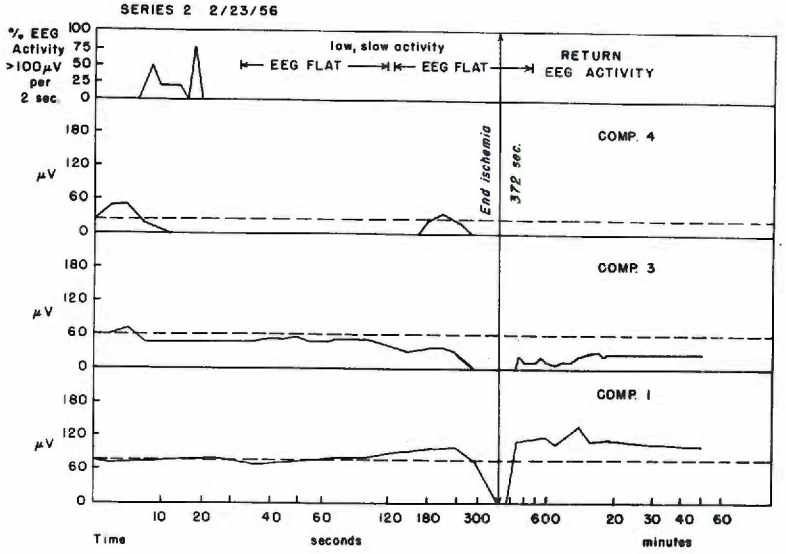
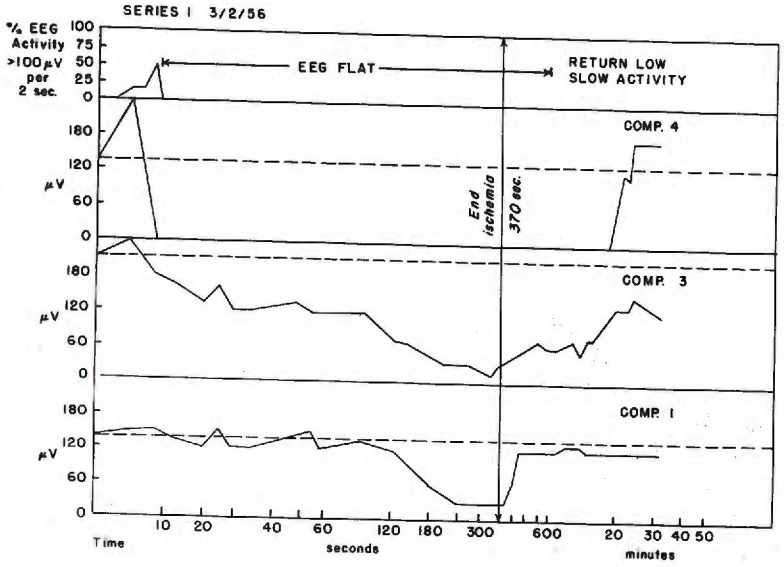
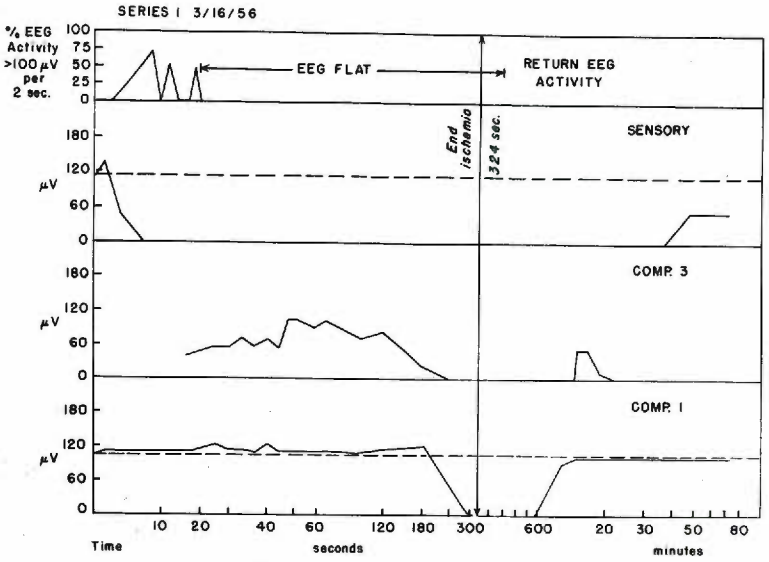
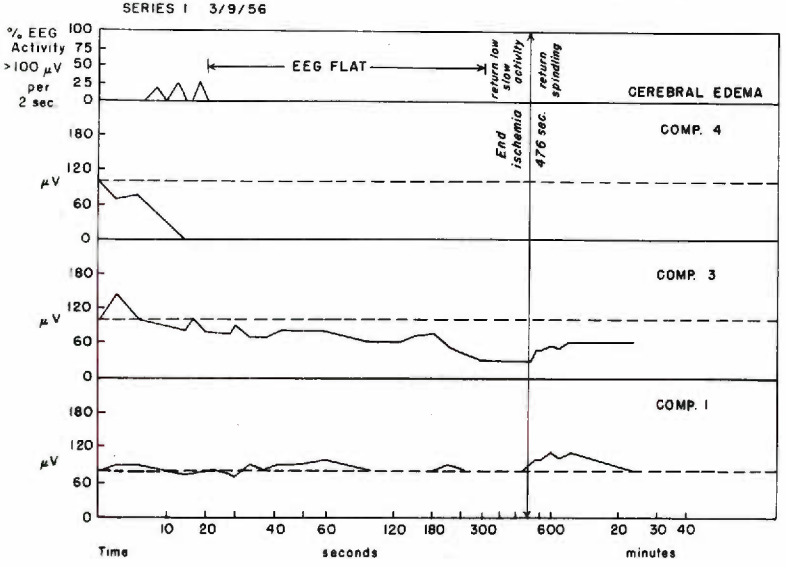

SERIES 2 2/23/56
% EEG Activity >100μV per 2 sec.
low, slow activity
EEG FLAT
EEG FLAT
RETURN EEG ACTIVITY
End ischemia
372 sec.
COMP. 4
COMP. 3
COMP. 1
μV
Time
seconds
minutes

FIGURE 4

Graphic representations of the effects of ischemia on the components of the antidromically evoked response and spindling activity in three experiments, and the effects of ischemia on spindling and the antidromic response complicated by the sensory response in one experiment. Ordinate: magnitude of deflections in microvolts for components 1, 3, 4, and the sensory response; the percent of EEG activity greater than 100 microvolts per 2 seconds. Abscissa: semilog time base in seconds and minutes.


SERIES I 3/2/56
% EEG Activity >100 μV per 2 sec.
EEG FLAT
RETURN LOW SLOW ACTIVITY
End ischemia
370 sec.
COMP. 4
COMP. 3
COMP. 1
μV
Time
seconds
minutes


SERIES I 3/16/56
% EEG Activity >100 μV per 2 sec.
EEG FLAT
RETURN EEG ACTIVITY
End ischemia
324 sec.
SENSORY
COMP. 3
COMP. 1
μV
Time
seconds
minutes


SERIES I 3/9/56
% EEG Activity >100 μV per 2 sec.
EEG FLAT
return low slow activity
return spindling
CEREBRAL EDEMA
End ischemia
476 sec.
COMP. 4
COMP. 3
COMP. 1
μV
Time
seconds
minutes

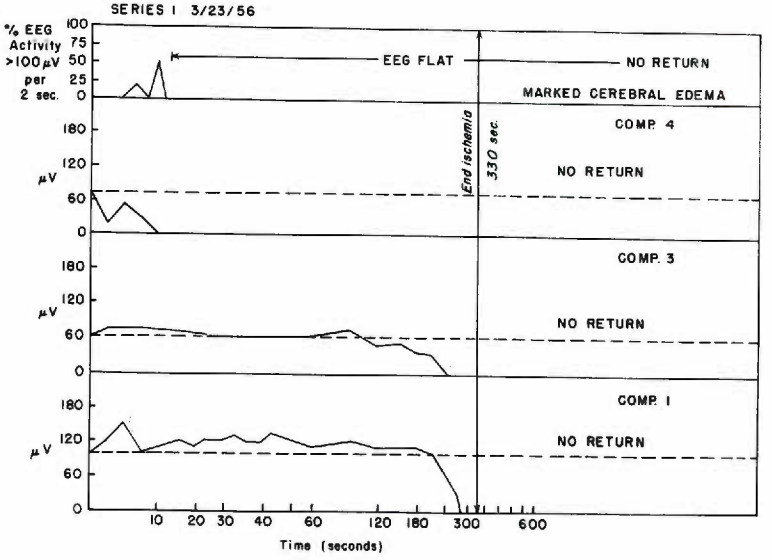
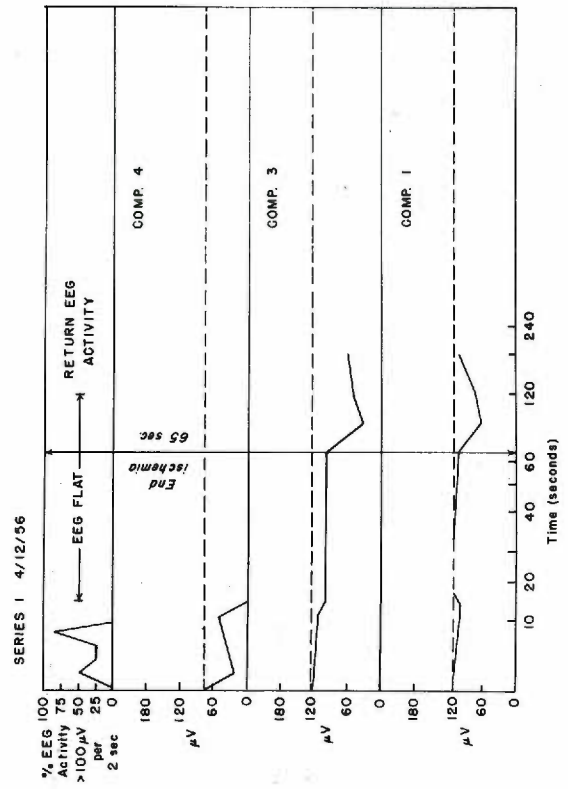
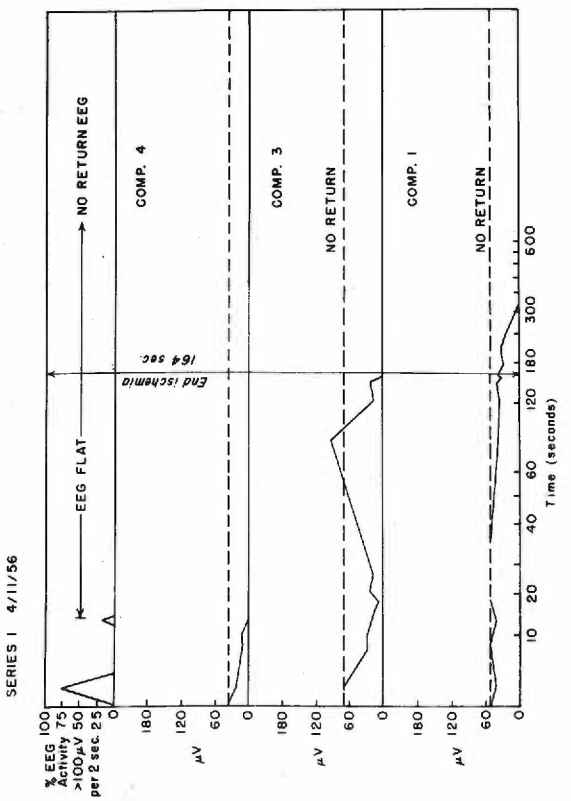

SERIES I 3/23/56
% EEG Activity >100 μV per 2 sec.
EEG FLAT
NO RETURN
MARKED CEREBRAL EDEMA
End ischemia
330 sec.
COMP. 4
NO RETURN
COMP. 3
NO RETURN
COMP. 1
NO RETURN
μV
Time (seconds)

FIGURE 5

Graphic representations of the effects of ischemia on the components of the antidromically evoked response and spindling activity in two experiments. Ordinate: magnitude of deflections in microvolts for components 1, 3, and 4, and the percent of EEG activity, greater than 100 microvolts per 2 seconds. Abscissa: semilog time base in seconds and minutes.


SERIES I 4/12/56
% EEG Activity >100 μV per 2 sec
100
75
50
25
0
EEG FLAT
End ischemia
65 sec.
RETURN EEG ACTIVITY
COMP. 4
COMP. 3
COMP. 1
μV
180
120
60
0
10 20 40 60 120 240
Time (seconds)


SERIES I 4/11/56
% EEG Activity >100 μV per 2 sec.
100
75
50
25
0
EEG FLAT
End ischemia
164 sec.
NO RETURN EEG
NO RETURN
COMP. 4
COMP. 3
COMP. 1
μV
180
120
60
0
10 20 40 60 120 180 300 600
Time (seconds)

ischemia on the evoked response in the other 12 series. It will be observed that most of the series follow the pattern illustrated by the experiment described above. However, in the graphs of experiments dated 2-13-56 and 3-16-56, found in Figures 3 and 4, respectively, the sensory response complicates the study of components 3 and 4. It is of interest that the sensory response is more sensitive to ischemia than components 1 and 3. This is illustrated in the graph of experiment 3-16-56. The sensory response disappears in 6 seconds and following its disappearance, component 3 becomes evident and persists for 240 seconds.

Another variation in the typical response pattern of the evoked response occured in the experiments dated 2-23-56, series 1 and 2. These experiments are depicted graphically in Figure 3. In series 1, it takes 24 seconds for component 4 to disappear. There is no change in component 1, and only a one-third decrease in the amplitude of component 3, during the period of ischemia. In series 2 on the same cat, component 4 disappears after 12 seconds only to reappear in 2-3 minutes, and finally to disappear in 4-5 minutes. Component 3 disappears in 295 seconds and component 1 in 372 seconds. The ischemia produced in this animal was obviously inadequate. These series are included to show the great variability in the degree of ischemia that can be obtained by combined basilar and carotid artery ligation.

Spindling activity: If one refers to Figures 2, 3, 4, and 5, it will be noted that in most cases there is a complete cessation of EEG activity within 30 seconds after the onset of ischemia. During the

ischemic period, there is a progressive decrease in amplitude and frequency of spindle bursts. In general, the positive component seems to be more sensitive to ischemia than the negative component.

Variations from the above pattern were found in the experiments with inadequate ischemia, dated 2-23-56. They are illustrated graphically in Figure 3. In series 1, spindling activity is present throughout the 6 minute period of ischemia. In series 2, the spindling activity disappears after 32 seconds only to reappear after 2-3 minutes for a short interval.

Summary and Statistical Analysis of Data

Summary of data: The disappearance times for spindling activity and components 1, 3, and 4 of the pyramidally evoked cortical response have been summarized in Table III for each of the 14 ischemia series. If one refers to this table it seems apparent that in any single experiment the spindling activity and component 4 of the evoked response disappear at about the same time following the onset of ischemia. It is also apparent that the other components disappear much later than the spindling activity. Finally, it appears that in each experiment component 1 is the most resistant to ischemia.

Statistical analysis of data: The above impression has been substantiated by several statistical tests. For purposes of statistical treatment, disappearance time has been defined as the period required for a reduction of amplitude to 5% or less of the control value. The use of this definition has resulted in the elimination of some of the data from the statistical analysis (see Table III). The "t" test was used to determine whether the mean disappearance times

TABLE III

SUMMARY OF DISAPPEARANCE TIMES

Date Series Number	Disappearance Times Following the Onset of Ischemia (Seconds) Spindling	Sensory	Comp. 1	Comp. 3	Comp. 4
2-3-56 Series 1	20	—	96 (20%)*	96 (20%)	22
2-3-56 Series 4	22	—	192	192	21
2-8-56 Series 1	16	—	288	186	—
2-8-56 Series 2	27	—	NC (at 87 sec.)**	87 (75%)	28
2-13-56 Series 1	16	14	200 (10%)	198 (5%)	—
2-13-56 Series 2	12	24	460	204	—
2-23-56 Series 1	NC	—	NC (at 360 sec.)	360 (33%)	24***
2-23-56 Series 2	Unable to determine	—	372	295	Unable to determine
3-2-56 Series 1	9	—	370 (20%)	370 (14%)	8
3-9-56 Series 1	20	—	NC (at 476 sec.)	476 (40%)	14
3-16-56 Series 1	20	6	312	240	—
3-23-56 Series 1	13	—	288	240	10
4-11-56 Series 1	14	—	164 (65%)	156	13
4-12-56 Series 1	15	—	60 (95%)	60 (90%)	14
s^2	24.7	—	8158	1843	46
N	12	—	6	8	8
$\bar{X}$	17		318.7	213.9	17.5

* % of response remaining
** No change
*** These figures not included in statistical analysis because of inadequate ischemia

of spindling and any of the individual components of the evoked response were statistically different. Correlation coefficients were determined in order to reveal the degree of correlation between the disappearance times of the spindling activity and the components of the evoked response.

The disappearance times of component 4 and spindling activity in the ischemia series done on 2-23-56 were not included in the statistical analysis, because in these experiment the inadequate ischemia made the measurement of the disappearance times of doubtful significance.

A summary of the "t" tests comparing the means of the disappearance times of the spindling activity and the components of the evoked response may be found in Table IV. The means and standard deviations used in making these analyses are summarized at the bottom of the appropriate columns in Table III. It will be noted that means of the disappearance times of spindling activity and component 4 can be considered statistically alike with only a 5% error of chance. The results of the other "t" tests comparing the mean disappearance times of spindling activity and components 1 and 3 are significantly different.

A summary of the correlation coefficients comparing the disappearance times of spindling and components 1, 3, and 4 may be found in Table V. It is of interest that a significant correlation with only a 5% error of chance exists between the disappearance times of component 4 and spindling. None of the other comparisons show a significant correlation. Scatter diagrams with Xy and Yx regression

TABLE IV

SUMMARY OF "t" TEST DATA

	Comp. 1		Comp. 3		Comp. 4	
	t	t.05	t	t.05	t	t.05
Spindling	11.9	1.75	16.0	1.74	0.19*	1.74
Comp. 1	—	—	2.90	1.78	—	—

* Significant at .05 level

TABLE V

SUMMARY OF CORRELATION COEFFICIENT DATA

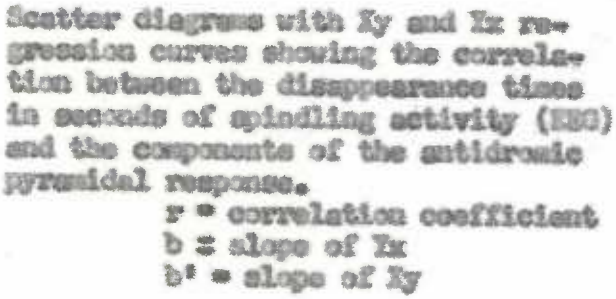
Components Correlated	r Value	Range for 95% Confidence	b	b'
Spindling vs. Comp. 4	0.937*	+0.72 to +1.0	1.0982	0.7993
Spindling vs. Comp. 1	0.292	-.6 to +.85	-9.494	-0.009
Spindling vs. Comp. 3	0.683	-0.02 to +.93	4.481	0.104
Comp. 3 vs. Comp. 1	0.301	-.62 to +.85	0.665	0.136

* Significant at .05 level

curves have been drawn for each of the comparisons made and may be found in Figure 6.

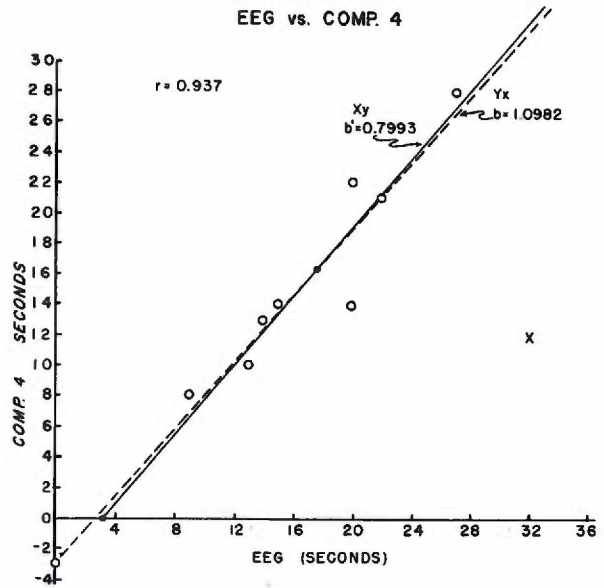
In summary then, it may be said with only a 5% error of chance, that statistically the means of the disappearance times of spindling activity and component 4 are the same, and that a correlation exists between the disappearance times of these elements. It may also be said that the mean disappearance times of spindling and components 1 and 3 are significantly different, and that no correlation exists between the disappearance times of the elements.

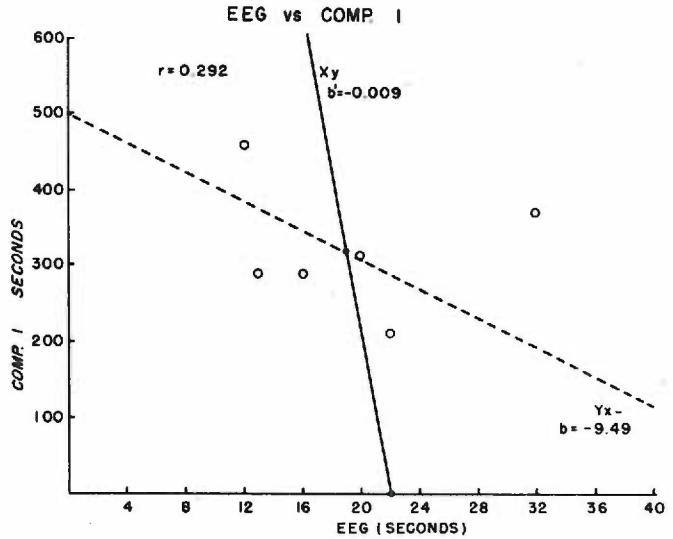
FIGURE 6

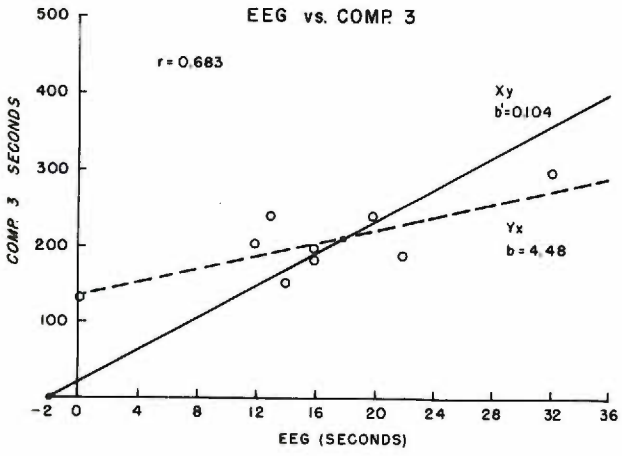


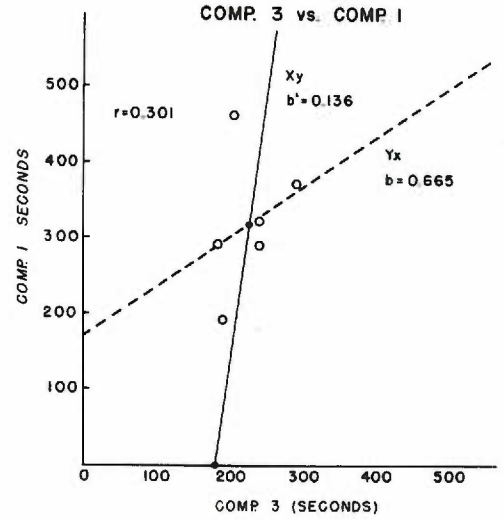
Scatter diagrams with Xy and Xx regression curves showing the correlation between the disappearance times in seconds of spindling activity (EEG) and the components of the antidromic pyramidal response.

r = correlation coefficient
b = slope of Xx
b' = slope of Xy


EEG vs. COMP. 4
r = 0.937
Xy
b'=0.7993
Yx
b= 1.0982
COMP. 4 SECONDS
EEG (SECONDS)


EEG vs COMP. 1
r = 0.292
Xy
b'=-0.009
Yx-
b= -9.49
COMP. 1 SECONDS
EEG (SECONDS)


EEG vs. COMP. 3
r = 0.683
Xy
b'=0.104
Yx
b = 4.48
COMP. 3 SECONDS
EEG (SECONDS)


COMP. 3 vs. COMP. 1
r=0.301
Xy
b'= 0.136
Yx
b= 0.665
COMP. 1 SECONDS
COMP. 3 (SECONDS)

DISCUSSION

Interpretation of Results

Significance of components of the antidromically evoked cortical response: The interpretation of the results obtained in these experiments is dependent upon the validity of the explanations offered for the origins of the components of the antidromically evoked electrocortical response. Chang(55) has suggested in his studies on the rabbit that component 1 is due to electrical activity in the axon, that component 2 is due to electrical activity in the cell body and/or basal dendrites, and that component 3, the later negative deflection, is due to electrical activity in the apical dendrites. If we use Chang's explanation for the origins of the components, it would seem plausible that the interpretation of the components of the antidromically evoked electrocortical complex in the cat could be made in the following way. The initial positive deflection, component 1, may be due to electrical activity in the axon; the second and third positive deflections, components 2 and 3, may be due to electrical activity in the cell body and basal dendrite; and the slow, later occuring negative deflection, component 4, may be due to electrical activity in the apical dendrite. The latencies, signs, and time courses of the components are compatible with the above interpretation. The antidromic volleys were initiated in the medullary pyramids. Therefore, we would expect the spread of the electrical field to sequentially pass over the axon, soma, basal dendrite, and apical dendrite. It would seem to follow that component 1 with the shortest latency should represent electrical activity in the axon;

and that components 2, 3, and 4 with increasingly longer latencies should represent the spread of the electrical field to the soma, basal dendrite, and apical dendrite. According to the volume conductor theory(57), electrical impulses at a distance and approaching the recording electrode are positive in sign, and impulses that have arrived at the recording electrode are negative in sign. Therefore, electrical activity in the axon, soma, and basal dendrite recorded from the cortical surface should be positive in sign, and activity recorded from the apical dendrites should be negative in sign. The time courses of components 1, 2, 3, and 4 are in concord with previous studies on potentials attributed to the axon(55), soma(66), basal dendrite(55), and apical dendrite(55). It is possible that components 2 and 3 are complicated by electrical activity in small, slow conducting pyramidal axons. However, Gasser et al(67) have shown that the potentials generated by slow conducting fibers are very small and probably are not recordable without suitable amplification.

The sensory response is easily differentiated from the antidromic pyramidal response by its long latency of 8-10 msec., positive direction, and long time course of 5-10 msec. Chang(68) has described a late negative wave which he believes is due to antidromic activation of pyramidal collaterals in the rabbit. This response may be differentiated from the antidromic response by its long latency of 10-15 msec. and its long time course of 5-8 msec.

However, further work is necessary to definitely ascertain the exact origin of the components of the evoked antidromic response in cats.

The mechanism of the abolition of spindles: If we accept the

above explanation for the origins of the components of the pyramidally evoked cortical response, the data lead us to the inescapable conclusion that apical dendritic and spindling activities are equally susceptible to ischemia. There are three possible reasons why dendritic and spindling activities are equally susceptible to ischemia. First, there may be a direct cause and effect relationship between the two entities; that is, the disappearance of spindles may be the result of failure of the dendrites in the neurons comprising the complex interneuronal system responsible for spindling activity. Second, that the failures of spindling activity and dendritic function are both dependent upon a common factor. Finally, that this is a fortuitous relationship. The latter reason is statistically unlikely. The second reason is possible, but as yet no "common factor" has been demonstrated. We are left then, with the first reason as the most likely explanation of the relationship between dendritic and spindling failure; namely, that the failure of spindling is due to the failure of the dendrites in the complex interneuronal system which is involved in the process of spindling.

Implications

Importance of dendritic influence over the neuron as a unit: Recent studies by Bishop(69) on the cortical neuron, Brockhart and Blackly(70) on the Purkinje neuron, and Eyzaguirre and Kuffler(71) on a sensory neuron of the lobster and crayfish have demonstrated that the dendrite apparently exercises an important control over the neuron as a unit. Eyzaguirre and Kuffler(71) showed that the resting potential and excitability level of the cell soma can be set and con-

trolled over a wide range by local events within the dendrite. Bishop(69) suggested that the apical dendrites of cortical neurons have special excitability and response characteristics. They are apparently capable of "more or less" activity which modulates and controls the all or nothing discharge of the cell body. Brookhart and Blachly(70) studied cerebellar unit responses to DC polarization. They found that dendritic positivity accentuates unit activity and dendritic negativity diminishes unit activity. The present studies on the ischemic susceptibility of the components of the pyramidal neuron and spindling activity may also be interpreted to indicate the importance of the control that the dendrite exerts over the neuron as a unit

Ischemic failure of dendritic activity apparently results in the failure of transmission through the neurons of the complex interneuronal system underlying spindling activity. Perhaps then, the so-called "synaptic failure" given as the reason why multineuronal circuits are sensitive to ischemia may in reality be due to failure of the dendrites in the circuit to influence their cell bodies in the usual fashion.

Dendrites most sensitive part of neurons: Our studies substantiate Chang's(55) finding that the dendrite is the most susceptible portion of the pyramidal neuron to ischemia. Most of the studies concerning the relative ischemic susceptibility of the axon, soma, and dendrite on cranial nerves(57) and the spinal cord(58, 59) have made no effort to separate the somal and dendritic components. In general, little information is available about the relative sensitivity of the soma and dendrite to ischemia. This is indeed a fertile

field for further investigation.

In summary, these considerations lead us to the belief that the dendrite exercises an important control over the neuron as a unit and that it is the most susceptible component of the neuron to ischemia. From this, the conclusion seems evident that the early loss of consciousness following the onset of ischemia is probably the result of loss of dendritic function of the neurons which make up the complicated interneuronal circuits which are necessary for the maintenance of the conscious state.

Recovery period: The physiological mechanisms underlying the recovery of the axon, soma, and dendrite following ischemia are at present unknown. An understanding of the mechanism underlying the production of irreversible functional change following ischemia would be extremely valuable. Our experiments and others(69, 70, 71) have shown the importance of dendritic function in the maintenance of the functional integrity of the neuron as a whole. It is therefore conceivable that irreversible functional changes in the neuron may be dependent on irreversible dendritic effects. Since dendrites are so difficult to study anatomically, it may be that irreversible dendritic changes occur which have not been detected by histological study. Most observers in the past were of the opinion that irreversible functional changes occured only after there was irreversible damage to the cell body. This, too, may be true. It is safe to assume that the nutritive influence of the cell body is necessary for the dendritic integrity as it is for axonal integrity. It may be that irreversible changes do not occur until the cell body has been so seriously damaged that it is incapable of re-establishing dendritic function. Available

information is inadequate to permit conclusions with regard to these problems.

SUMMARY

This research was done with the hope that it would contribute to a better understanding of the physiological changes that take place during cerebral ischemia. Past studies evaluating the effects of ischemia on the cerebral cortex were based on post-ischemic histological and neurological changes. There was very little information available concerning the physiological mechanisms underlying very early functional loss.

The ideal way to study this neglected area of cerebral ischemia would be to examine the objective correlates of the loss of consciousness during an ischemic episode. In animal experiments, this is at present impossible to accomplish because there is no adequate definition of consciousness on which to base the objective studies. Therefore, an experiment was devised to study a complex central nervous system function similar to that which is responsible for the maintenance of the conscious state. It was necessary that this function be susceptible to analysis in order to determine the mechanisms involved in the abolition of the function by ischemia. Spontaneous spindling was found to fulfill all the necessary requirements. It consisted of spontaneous activity which was dependent upon complex interneuronal exchange, and it involved corticospinal neurons which could be studied independently of the spindling.

The ischemia was created by combined basilar and carotid artery occlusion. Spontaneous spindles were produced by mesencephalic lesions. Antidromically conducted evoked potentials were produced at the cortex by stimulation of the medullary pyramids. The time of disappearance of

the spindles and the evoked response following the onset of ischemia was observed.

The results were based upon experiments on 51 cats. Of this total number, the data from 10 were used in preparing the description. From these 10 cats, 14 ischemia series were obtained. It was found that there was no significant difference in the disappearance times of component 4 of the evoked response and spindling activity. If component 4 was due to electrical activity in the apical dendrites as suggested by Chang, the conclusion that apical dendritic and spindling activity were equally susceptible to ischemia was inescapable. It seemed most likely that a cause and effect relationship existed between dendritic and spindling failure. It was suggested that ischemic failure of dendritic activity apparently results in the failure of transmission through the neurons of the complex interneuronal system underlying spindling activity. The implications of these findings are discussed.

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