LOCALIZATION STUDIES ON THE MOTOR AND SUPPRESSOR AREAS OF THE CEREBRAL CORTEX OF THE DOG

by

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INTRODUCTION

This investigation was undertaken (a) to remap the so-called "motor" areas on the lateral surface of the cerebral hemisphere of the dog using a square wave, long duration type of electrical pulse as the means of exciting the cortical cells and fibers, and (b) to attempt to locate the "suppressor" areas of the lateral surface of the cerebral hemisphere of the dog through cortical stimulation induced by rigidly controlled electrical pulses.

The production of skeletal muscular response by electrical stimulation of the cerebral cortex of the dog was first demonstrated in 1870 by Fritsch and Hitzig. An abstract of their study by Ferrier (30) indicated that they localized cortical regions which were centers for evoking muscular responses in definite parts of the body. An inconstant center for the neck muscles was discovered to lie on the lateral portion of the anterior sigmoid gyrus about opposite the tip of the cruciate sulcus. The more lateral part of the anterior sigmoid gyrus contained the area for the extensors and adductors of the fore-limb. Posteriorly on the lateral part of the posterior sigmoid gyrus lay the center for flexion and rotation of the fore-limb. The hind-leg focus was located on the more medial portions of the posterior sigmoid gyrus, and the facial area appeared on the middle part of the suprasylvian gyrus.

Ferrier (30), using a faradic type of electrical stimulus instead of the galvanic type employed by Fritsch and Hitzig, reported somewhat different results for the motor centers of the dog. On the most medial portion of the posterior sigmoid gyrus movements of the tail could be induced. As the stimulating electrodes were moved laterally respective centers were found for responses in the hind-limb, for retraction and adduction of the fore-limb, and for elevation of the shoulder and extension of the fore-limb.

Instead of dectecting movements of the fore-limb and neck from the lateral parts of the anterior sigmoid gyrus, observations were recorded which indicated that this area was responsible for opening the eyelids, dilatation of the pupils and movements of the eyeballs and head to the side opposite that of stimulation. Almost the entire extent of the coronal gyrus served as a center for responses in the orbicularis oculi and zygomatic muscles with associated divergent movement of the eyeballs. The area for retraction and elevation of the angle of the mouth, for opening the mouth and for movements of the tongue was found on the anterior composite gyrus and the tip of the anterior ectosylvian gyrus. The anterior ectosylvian gyrus served as another region for retraction of the angle of the mouth, while movements of the ear were elicited by stimulation of the middle ectosylvian gyrus. A second center for producing movements of the eyeball and occasionally of the head to the opposite side was located in the middle suprasylvian gyrus.

Numerous studies were subsequently carried out by other investigators in an attempt to accurately delineate the "motor" areas of the cerebrum of the dog. Smith (60) in his extensive review of the literature reported widely differing findings. The principal controversy occurred regarding the excitability of the medial portion of the anterior sigmoid gyrus and the excitability of the gyrus proreus with the remainder of the cortex anterior to the sulcus praesylvius.

In 1933 Woolsey (67) reported his findings regarding the motor cortex of the dog as elicited by stimulation through a monopolar electrode of an induction current or a house circuit 60 cycle a.c. current with a suitably reduced voltage under either ether or nembutal anesthesia. It was found that the gyrus proreus, the medial half to two-thirds of the anterior sigmoid, and the cortex lateral to the coronal sulcus were not responsive to electrical stimulation. Stimulation of the lateral third of the anterior sigmoid gyrus yielded responses in the facial muscles instead of neck, fore-limb, eyeball, or head muscles as reported by Fritsch and Hitzig and by Ferrier. Opposite the tip of the cruciate sulcus excitation produced neck responses, and as the exploration was carried onto the posterior sigmoid gyrus, from the lateral to the medial parts, respective areas were encountered for flexion or occasionally extension of the entire fore-leg, for simultaneous flexion of fore- and hind-leg, and for movements of the hind-leg. The hind-limb area covered the medial half and mesial surface of the gyrus. Histological examination of the brains of the animals revealed that the responsive area slightly overlapped the granular sensory cortex posteriorly and the agranular area 6 anteriorly.

The latest studies on the electrically excitable cortex of the dog have been done by Smith (59,60). The animals were anesthetized with ether and were stimulated with an ordinary 60 cycle alternating current reduced to 3 volts. The current was passed to the cortex through a platinum wire monopolar electrode. As in Woolsey's experiments Smith was unable to obtain muscular responses from the medial half of the anterior sigmoid gyrus or from the cortex anterior to the sulcus praesylvius. Contralateral and ipsilateral movements of the hind-legs and contralateral movements of the tail were obtained from an area of the cortex adjacent to the medial edge of the hemisphere on the posterior sigmoid gyrus. In the adjacent lateral portion of the posterior sigmoid gyrus bilateral movements of the fore-legs resulted from stimulation. In the lateral and posterior region of the anterior sigmoid gyrus stimulation produced responses in the neck muscles, while in the more lateral and rostral portion of the anterior sigmoid gyrus excitation produced an opening and closing of the mouth which resembled chewing movements. The chewing movements could be obtained also around the tip of the coronal sulcus and even on the upper part of the anterior composite gyrus. The statement is made that there was some overlap between the regional divisions of the excitable area. It was the author's contention that the entire excitable area lay in structural area 4 on the basis of a series of comparisons of histological preparations with the areas delineated by means of electrical stimulation. On the basis of chromatolysis and degeneration studies following high cervical section of the corticospinal tracts in the cord, Holmes and May (39) concluded that the fibers of the corticospinal tracts originated from the 5th or giant cell layer of the cortex in the region of the posterior sigmoid gyrus and from only a very small portion of the posterior and lateral part of the anterior sigmoid gyrus of the dog. Undegenerated giant cells were found in a wider area of distribution on the anterior sigmoid gyrus and "lateral to the sulcus coronalis" from which it was assumed that cortico-bulbar fibers arose.

Ward and Clark (66) in 1935 reported their experiments on the motor cortex of the cat. The animals were anesthetized with ether, nembutal or a combination of these two chemicals. Stimulation was produced by means of an inductorium, the primary of which was energized by a 60 cycle alternating current whose voltage was reduced through a transformer. A unipolar electrode was used to explore the cortex. By this method it was possible to divide some of the larger subdivisions of the motor cortex into smaller areas for more specific responses. They were able to distinguish separate regions in the fore-leg area for extension and flexion of the contralateral forefoot, for abduction of the contralateral fore-limb, and for rhythmic batting and rhythmic digging movements.

More recently Garol (32) investigated the motor cortex of the cat. These animals were under the influence of Dial anesthesia. The lateral surface of the cerebral hemisphere was explored with an entirely different type of electrical stimulus than had been used by any of the other investigators. The source of the electrical energy was a thyraton whose frequency, pulse duration and voltage could be rigidly controlled. The current was passed to the cortex through bipolar Ag-AgCl electrodes with an interelectrodal distance of 2mm. With the use of these carefully controlled factors for stimulation Garol was able to divide the motor cortex of the cat into numerous discrete regions. On the medial portion of the posterior sigmoid gyrus he was able to distinguish ankle, knee and hip sectors in the hind-leg area. In the arm area sectors for the shoulder, elbow, fore-arm and wrist could be discerned by using stimuli of low frequency. If, however, the frequency of the pulses was increased to 30 to 60 pulses per second, an extension of the contralateral fore-limb could be obtained from the medial portion of the arm area, whereas a flexion of the contralateral fore-limb could be obtained from the lateral portion of this same area instead of the discrete responses which occurred with the low frequency. The neck section was found along the anterior border of the anterior sigmoid gyrus just posterior to the sulcus praesylvius. The face region was largely confined to the anterior composite gyrus and the anterior extremities of the coronal gyrus. This corresponded in general to the face area which Ward and Clark had discovered, but Garol was able to distinguish separate narrow strips for the upper face, the upper lip and vibrissae, the jaws, the tongue and the lower lip. He also found a second motor area in the lower portion of the anterior ectosylvian gyrus in which bands were isolated for the upper face, the lower face, the neck, the contralateral arm and ipsilateral leg, and the ipsilateral arm and the contralateral leg. The upper face band was most superior and the ipsilateral arm and the contralateral leg band most inferior in this region. A region for the pinna was discovered around the superior extremity of the anterior ecotsylvian gyrus.

None of the reported experiments on either the cat or the dog indicated that responses of individual muscles in the extremities were ever obtained, which is in contrast to the findings which Chang et al. (16) have demonstrated from the motor cortex of the monkey.

It long has been known that stimulation of the brain under experimental conditions may result in a diminution in an observable response or a complete lack of activation in an effector instead of the activation or an increase in the observable response that is usually assumed to follow the application of a stimulus to nervous tissue. The lack of response subsequent to active stimulation of excitable nervous tissue has been observed in many effector systems. The most common one in which it has been noted is the skeletal muscle system, but reduction of response has also been observed in cerebral electrical activity, the respiratory apparatus, the heart rate, the blood pressure, and the activity of smooth muscle masses in various visceral organs.

When using the general skeletal muscle system as the indicator of the excitability or the physiological processes occurring in the cerebral motor cortex and related regions, it is possible to distinguish at least four different varieties of diminution or absence of skeletal muscle response ensuing from cortical electrical stimulation. These four types have been defined and segregated by various authors (24,25,34,50) as (a) neural "fatigue or exhaustion", (b) inhibition, (c) extinction, and (d) suppression.

Garol and Bucy (34) in their classification defined neural fatigue or exhaustion as "the state of failure of response to a previously adequate stimulus, delivered singly or in a volley, because of immediately preceding generalized neural overactivity". This was characterized by the unresponsiveness that immediately followed a period of after-discharge in the muscle.

Inhibition induced from the cerebral cortex has been defined as the "disappearance of an existing muscular contraction on stimulation of a cortical focus from which an antagonistic response may be elicited" (24). This is the recriprocal inhibition of an antagonistic muscle during the cortical activation of the agonist muscle.

The third type of diminution of skeletal muscle response is that of extinction. This is in many ways closely related to the phenomenon of facilitation which, however, tends to produce an exactly opposite effect––an increase in observed muscular response instead of a decrease. Since these two phenomena are so intimately related they shall be discussed jointly.

In Dusser de Barenne's and McCulloch's paper on the factors for facilitation and extinction (24) the factors for facilitation were defined as "any changes of the CNS caused by antecedent excitation and causing a fall in threshold, a decrease in latency, and increase in amplitude or any combination of these" characteristics of the muscular response to subsequent stimulation or "test" stimulation of the cerebral cortex. In other words to elicit facilitation it was essential to stimulate the cerebral cortex at least twice. The first stimulus or "antecedent stimulation" produced the control response and so altered the functional condition of the cerebral cortex that the second or "test stimulation" was able to change the characteristics of the muscular response so that there was an increase in the amount of contraction, that there was a decrease in the time between the application of the stimulus and the appearance of the muscle response, and/or that the amount of energy required to just produce a discernable response was decreased below the level required to initiate the response to the first stimulus.

Dusser de Barenne and McCulloch (18,19,21,24,48,50) have illustrated in a series of papers that the parameters of stimulation have a profound bearing upon whether repetitive stimulation of the same cortical point will result in facilitation or extinction of the motor response. It was shown that longer periods of application of an electrical stimulus to the cortical surface tended to enhance extinction. It was found that if all parameters of stimulation were maintained constant except the number of electrical pulses delivered to the cortex per second, the lower frequencies produced facilitation of response to themselves and facilitation of responses whose antecedent stimuli were of a higher frequency. Higher frequencies of test stimuli, however, produced extinction of response when the antecedent stimulus was of the same high frequency, but facilitation when the antecedent stimulus was of a lower frequency. Moreover, if the parameters of stimulation were so arranged that the only variable was the duration of each individual pulse, then it was shown that longer pulses always result in extinction, but stimulation with shorter pulses only extinguished responses whose antecedent stimuli had been those of long duration pulses. Short duration pulses in the test stimuli facilitated responses whose antecedent stimuli had been those of the same short duration type of pulses. When only the voltage of the electrical stimulus was varied, it was found that stimulation with lower voltage always facilitated, while stimulation with higher voltages facilitated responses to stimulation of lower voltage and extinguished the responses to itself. The conclusions that were reached by these authors were that increasing or decreasing the total energy of stimulation respectively increased or decreased extinction.

When all the parameters of stimulation were held constant except the time interval between the application of the antecedent and the test stimulus, it was discovered that within certain limits, which depended upon the depth of anesthesia and condition of the animal as well as the electrical parameters of stimulation employed, that the shorter the time interval between the two sets of stimuli, the more likely one was to produce facilitation. As the time interval was increased the more likely one was to produce extinction. When using the usual surgical level of anesthesia under Dial or ether, and a frequency of stimulation around 50 per sec. with the duration of application of the stimuli being approximately 5 sec., it was shown that the optimal interval for the appearance of extinction was in the neighborhood of 13 seconds. Under deeper anesthesia extinction was demonstrable up to 3 minutes. In the absence of anesthesia the optimal interval for the appearance of extinction was 4 seconds. Besides the optimal time of onset of extinction being partially controlled by the depth of anesthesia, it was found that poor circulation, cooling and other changes in the animal which tended to depress or impair the functional activity of the cortex prolonged the interval in which extinction could be maximally demonstrated. After a period of one or two minutes the effects of the antecedent stimulus which produced the alterations in the physiological function of the cerebral cortex essential for extinction had worn off, and nothing except a response similar to the control or antecedent response would result from the test stimulus.

Within the few seconds immediately following the antecedent stimulus and prior to the onset of extinction, a second or test stimulus applied to that cortical point induced a facilitated response. During the facilitatory period changes occurred in the electrical and chemical relationships within the cerebral cortex. Accompanying facilitation there was increased cortical electrical activity in the facilitated regions with a negative electrical potential with respect to some distant, non-facilitated focus. At the same time the $_pH$ increased in the facilitated areas. During the extinguishing period just the opposite effects occurred in these areas. The electrical activity decreased, the electrical potential became positive and remained that way for a minute or so, slowly returning to normal, and the $_pH$ became decreased (24).

T. Graham Brown (8,9,10,11,13,14,15) and Dusser de Barenne and McCulloch (21,24,48,50) have likewise shown that facilitation and extinction could only be produced by stimulation within certain definite limited areas on the cerebral cortical surface. Both were most easily produced by repetitive stimulation of the same point in area 4 of the motor cortex; however, these same effects might result if the antecedent stimulus was applied to a cytoarchitectonic area which was structurally and functionally related to the area of the motor cortex to which the test stimulus was applied. Another interesting observation was that facilitation and extinction would occur in only one functional subdivision of the sensory-motor cortex at a time. The phenomena would not cross the functional boundaries between the leg, arm or face subdivisions of the cortex unless the antecedent stimulus had been so strong that an after-discharge had been initiated which was capable of crossing these boundaries. Therefore if one applied an antecedent stimulus to the arm sector of area 4 and then applied the test stimulus to the leg sector of area 4, the response from stimulation of the leg sector would be unaltered (24).

T. Graham Brown (8,9,11,14,15) has shown in a series of papers that facilitation—particularly "secondary facilitation" — was a process that was dependent upon transcortical fibers in the grey matter or through short association fibers in the white matter directly adjacent to the under surface of the cortical grey substance. He has demonstrated that small incisions placed perpendicular to the cortex and just extending into the white substance between the regions to which the antecedent and test stimuli were applied would block the action of the antecedent stimulus in its facilitation of the region to which the test stimulus was directed.

Dusser de Barenne and McCulloch (21) likewise showed that extinction was a cortical phenomenon for which the outer three layers of the cortex were not essential, as laminar thermocoagulation at 70°C. for three seconds killed these layers, yet it was still possible to obtain extinction from the thermocoagulated area. However, if the entire thickness of the motor point on the cortex had been killed by thermocoagulation or if the entire thickness of the grey matter at the point had been surgically excised, extinction from the point was no longer obtainable. Further study on the problem seemed to indicate that the large and giant pyramidal cells were primarily responsible for the process of extinction. It was also observed that if repetitive stimuli, which would result in extinction when applied to the cortical surface, were applied to the white matter directly underlying this cortical point that the process of facilitation resulted, instead of extinction. In 1915 T. Graham Brown (12) also pointed out that facilitation could be induced anywhere in the corticospinal tract from the corona radiata to the level of the mid-brain.

The fourth method through which a cortically induced skeletal muscle response can be diminished by excitation of the cerebrum has been called suppression. This phenomenon was first discovered by Marion Hines and reported in her paper on the motor cortex in 1936 (37,38). Her work was done using monkeys as the experimental animals. All of the experiments were confined to the motor cortex which was located anterior to the central sulcus. It was found that ablation of a 3 to 5 mm. strip of cortex from the anterior portion of area 4, a strip which passed through the superior precentral fissure from the inferior precentral fissure to the callosomarginalis fissure on the medial surface of the hemisphere paralleling the curve of the central sulcus, and which involved the anterior border of the face subdivision of area 4 as well, resulted in the immediate production of the phenomena of "release" and a transient paralysis of the contralateral extremities. The phenomena of "release" likewise transiently appeared in the ipsilateral extremities. Included in the phenomena of "release" were (a) hypertonicity of the skeletal muscles. The hpertonicity was maximal in the contralateral flexors of the elbow, the extensors of the knees and the addustors of the thigh. (b) The second characteristic of release was a typical jacknife rigidity in which passive motion at the joints in a direction opposite the maximal hypertonicity elicited no resistance to the first few degrees of motion, great resistance to the next few degrees of motion, and then suddenly the disappearance of all resistance. There was also an associated "supporting reaction" which meant that pressure applied to the hand or foot caused a forceful extensor response in the contralateral extremity. (c) The third feature of release was the ability to produce clonus of muscle groups in the contralateral extremities by suddenly and continuously maintaining a stretch on the tendons of the particular group. (d) The fourth feature of release was the presence of brisk tendon reflexes in the exremities affected by the lesion. If the ablation was small and incomplete, it was followed by a transient appearance of some or all the phenomena of release in both contralateral extremities, regardless of the fact that the ablation had been done opposite the arm or the leg subdivision of area 4. Complete bilateral removal of the strip areas resulted in permanent release in all four extremities.

Ablation of area 6, which lies anterior to 4s, did not result in any paralysis or release, but a "grasp reflex" was produced. This was not a permanent result unless there had been a bilateral removal of the area. If ablation of area 6 was combined with area 4s, there was some passive resistance throughout the range of motion as well as the grasp reflex, clonus and brisk reflexes, but the jacknife resistance was gone.

Following the removal of the posterior portion of area 4 there was temporary paralysis in the contralateral extremities without the phenomena of release. When area 4 was combined with the strip area, the contralateral limbs were not used to initiate independent or discrete movement -- rather they aided or followed the movements of the opposite extremity, and the release factors were present.

Electrical stimulation of area 6 gave relaxation of tonic flexion and grasp, while the electrical stimulation of 4s gave relaxation of tonic extension.

Following this contribution by Marion Hines a whole series of papers have appeared in the literature dealing with the delineation, the function and the anatomical connections of the cerebral cortex from which "suppression" can be produced. Some of the earliest and most extensive work on the suppressor areas was done by Dusser de Barenne, McCulloch and their co-workers (20,22,23,25,26,27,29), and subsequently further investigations have been undertaken on this subject by Bailey, Kennard, McCulloch, Garol, Ward and Smith (3,5,31,32,33,34,41,49,63,65).

The animals on which the anatomy and the function of the suppressor areas have been studied are the monkey, chimpanzee, and the cat. In almost all instances the animals have been anesthetized with Dial, which was either given intraperitoneally or intraperitoneally and intramuscularly, the dose being divided between the two sites. The latter method has been preferred in the monkey and chimpanzee because it eliminated a peculiar jerkiness of response and it raised the threshold for after-discharge which occurred when all of the drug was given I.P. (21). In Smith's work on area 24 of the monkey ether was used as the anesthetic.

There have been two principal methods of stimulation and study employed in the research on suppressor bands. The first has been one in which a skeletal muscle response has been induced from electrical stimulation of a focus in area 4 of the cortex at one minute intervals with a pulse frequency between 30 and 60 per second. Then a second electrical stimulus of approximately the same frequency has been applied to other areas of the cortex and the effect upon the muscle response observed. The second method of investigation of the suppressor areas has consisted of recording the electrical activity of the cerebral cortex before, during, and after the local application of strychnine solutions to the cortical surface by means of small soaked squares of filter paper. The pieces of filter paper have been allowed to remain on the cortex for a period of one minute after which they have been removed along with any excess solution. It has been reported that local applications of strychnine to the cortex were responsible for typical changes in the electroencephalograph (EEG) which occurred as follows: First within a few seconds after the application of the drug there was a generalized increase in the cerebral electrical activity at the strychninized site. Within 1/2 to 1 minute later sharp, high, voltage fluctuations, or so-called strychnine spikes, appeared in the EEG from the strychninized point. The spikes reached their full height in about 2 or 3 minutes. As the spikes developed the background activity markedly diminished. After 15 minutes or so the spikes began to decrease in size and the background activity increased. The EEG usually returned to normal in 20 to 40 minutes. The changes in the EEG were not restricted to the local area strychninized, but might be transmitted to other regions of the cortex and the brain stem. The area of distribution of the spikes depended upon the cytoarchitectonic area and the various major subdivisions of the sensory cortex strychninized (22).

It has been shown that the local application of strychnine results in strictly local reaction where synapses occur on nerve cells and that the reaction is propagated dromically and never antidromically. The conducted impulses have been shown never to pass the next synapse without dispersion and delay (28,33).

When strychnine has been locally applied to a suppressor band on the cerebral cortex, it has been found that typical spikes might appear in the band throughout its entire extent having no regard for the functional boundaries segregating the arm, leg and face subdivisions of the cortex of the primates. Twelve to 20 minutes after applying the strychnine it has been observed that a wave of decreased electrical activity began to spread over the remainder of the cortical hemisphere. Reports indicated it took approximately 15 to 20 minutes for the wave of depression to completely cross the cortex, and that the suppression could have a duration at any one point of from 6 to 20 or 30 minutes. It has not been possible to reproduce the suppression of electrical activity for from 35 to 45 minutes after the first application of strychnine to the band (25).

After electrical, mechanical or chemical stimulation of a suppressor band, the threshold of cortically induced skeletal muscle responses elicited from area 4 at one minute intervals has been raised considerably above its original value after a latency of from 2 to 20 minutes, depending on the factors of stimulation to the band and the depth of anesthesia. The suppression of motor response lasted from 6 to 20 or 30 minutes. It has also been found that electrical or mechanical stimulation of any of the bands would immediately hold in abeyance any cortically induced motor after-discharge. With the suppression of muscle movement there was a concomitant relaxation of muscle tone (25,26,31,32,34,65). Barker and Gellhorn (6) have studied the influence of electrical stimulation of the suppressor areas on afferent impulses to the cerebral cortex. They showed that the afferent impulses induced by electrical stimulation of the sciatic nerve or the vagus nerve and auditory or visual stimuli were considerably reduced following stimulation of a suppressor band. However, it was also shown by Gellhorn (35) that various nociceptive stimuli applied to parts of an extremity led to excitation of the suppressor areas as well as to excitation of the sensori-motor and projection areas of the cortex. No effect on the patellar reflex, however, has resulted from stimulation of a suppressor band (25,28).

In the monkey and chimpanzee five cortical suppressor areas have been located. They are 8s, 4s, 2s, 19s, and 24 (3,5,20,22,23,25,26,27,28,29,31, 32,41,49,65). Four cortical suppressor areas have been described in the cat which are 8s, 3s, 2s, and 19s (32,33). These were reported as being located as follows on the cortex of the cat: (a) 8s laid near the sulcus between the anterior sigmoid gyrus and the gyrus prereus in an area which, upon electrical stimulation, was also found to yield eye movements; (b) 2s extended from the junction of the suprasylvian and anterior suprasylvian sulci to the junction of the lateral and ansate sulci; (c) 3s extended from the rostral portion of the postcruciate sulcus to the caudal portion of the coronal sulcus; and (d) 19s laid in the posterior margin of the posterior suprasylvian gyrus.

The distinction between extinction and suppression has been made by Dusser de Barenne and McCulloch (25). The differences were as follows: (a) Cortical suppression could only be obtained from one of the suppressor bands, while extinction could be obtained only by antecedent stimulation of the same focus to which a test stimulus was applied, or by antecedent stimulation of an area whose discharges actually involved the area excited by the test stimulus. (b) Except where the antecedent stimulus had been so violent as to cause the after-discharge to spread across the functional boundaries for the face, arm and leg subdivisions of the motor cortex, extinction had always remained localized to the subdivision stimulated.

However, suppression could be elicited by antecedent stimulation of any of the functional subdivisions of the suppressor area. (c) The Phenomenon of extinction had a relatively short latency -- being a matter of seconds -- and had a very maximal duration of 1 to 2 minutes. Suppression on the other hand had a latency which measured in minutes and had a duration of several minutes.

Garol and Bucy (34) were able to distinguish a portion of area 4s in one human upon whom they were operating because of a persistant tremor on the right side of the body. The effects of stimulating the area at the time of operation were exactly similar to the muscular effects following stimulation of suppressor areas in lower forms.

Although Hines (38) was able to produce the phenomena of release after the total ablation of 4s in monkeys, it was observed by Ward (65) that unilateral ablation of areas 24, 8, 4s, and 19 resulted in no spasticity in the contralateral extremities. Mettler and Pool (54) reported the removal of the rostral border of area 4 in human cases, and they found that unilateral removal of area 6, area 6 plus the rostral portion of 4, and area 6 plus both the rostral and caudal parts of area 4 produced no noticeable spasticity in the subjects unless there was also some subcortical damage.

Functional and anatomical connections of the suppressor bands have been investigated in the monkey, cat and chimpanzee. There were described two distinct pathways for the suppression of cortical electrical activity and for the suppression of cortically induced motor response. In neither case were intracortical connections essential as a deep lesion through the cortex down to the level of the caudate nucleus failed to prevent the suppression (23,25,28). Undercutting the cortex in the suppressor regions did prevent the occurrence of both types of suppression

(25,28). The neural circuit involved in the suppression of electrical activity has been described as starting in one of the cortical suppressor bands from which the impulses were conducted to the caudate nucleus. From the caudate nucleus the impulses were relayed to the thalamus and from the thalamus the tracts conducted the impulses back to the cortex. Lesions in any one of the structures prevented the appearance of the suppression (23,28). Using the Marchi technique (42) myelinated nerve fibers have not been traced to the caudate nucleus following ablation of area 4s, but by using a new silver technique Glees (36) has shown in the cat that fibers arising in 2s, 3s, and 8s pass to the caudate nucleus as non-myelinated cortico-caudate fibers arising as collaterals from cortico-fugal tracts.

The neural elements involved in the suppression of motor response have been described as not using the same circuit as for the suppression of cortical electrical activity (25). It was found that lesions in the caudate nucleus and thalamus failed to prevent the suppression of motor response while they still prevented the suppression of electrical activity. Dusser de Barenne and McCulloch also determined that the putamen, globus pallidus, corpus callosum, anterior commissure, commissura mollis, the substantia nigra and the cerebellum were not involved, as destructive lesions of these structures or their removal did not prevent suppression of motor response (25). McCulloch, Graf, and Magoun (51,52) have cited evidence that descending paths from 4s, 24, and 19 leave the cortical spinal tracts at the level of the pons and pass into the bulbar reticular formation. Hines (39) reported the finding of hypotonicity with paralysis in the extremities following division of one of the pyramids, whereas a lesion in the cortex involving both area 4 and 4s resulted in paralysis and in the phenomena of release. This indicated that the pathways from the two areas must have dissociated before they reach the level of the pyramids. Ward has traced degenerated myelinated fibers through the brain stem and cortex of monkeys after bilateral ablation of area 24. Cortical fibers went to the superior frontal, the arcuate fasciculi and throughout the extent of the cingulum bilaterally, apparently ending posteriorly in area 31 or the medial part of area 19. Some fibers seemingly went to area 19 and 18 and to the pre and postcentral regions. Descending fibers were traced bilaterally in the region of the anterior commissure to the lateral septal nuclei and through the posterior two-thirds of the internal capsule. In the midbrain the fibers were confined to the ventral and medial portions of the cerebral peduncles. In the pons fibers were found scattered among the pontine nuclei and in both medial longitudinal fascicluli. From the level of the superior olive to the region of the decussation of the pyramids degenerating fibers were seen in the medial reticular formation (65).

The medial bulbar reticular formation has been implicated in influencing skeletal muscle and other responses by further evidence. Allen in 1927 demonstrated the course of fibers from the cortex which conveyed the impulses for decreasing respiratory movements. He found that the impulses went by way of the corticobulbar and corticospinal fibers to the reticular nuclei of the pons and medulla. The axones of the nuclei were described as descending crossed or uncrossed in the anterior columns or in the ventral and medial part of the lateral columns as reticulospinal tracts (1).

Magoun and Rhines (47) found by stimulating the ventral medial portion of the bulbar reticular formation with a 60 cycle sine wave current at 3 to 5 r.m.s. volts that the patellar, flexor and blink reflexes could be promptly stopped. Upon withdrawal of the electrical stimulus the reflexes promptly returned. The extensor tone of decerebrate rigidity was also abolished by stimulation in the bulbar reticular formation. The return in extensor tone was often prompt and vigorous, resembling rebound. Thirdly, stimulation of the bulbar reticular formation would immediately stop movement initiated by excitation of the cortical surface or the internal capsule. The effect on the cortically induced movement was bilateral. Rhines, Magoun and Windle (58) have also pointed out the fact that the hyperreflexia following cerebral concussion was associated with a depression in the excitability of the bulbar inhibitory mechanism, suggesting that the release from the bulbar inhibition may be a factor in the production of hyper-reflexia. Bach (2) stimulated the bulbar reticular formation of cats and was able to simultaneously stop the patellar reflex, cause respiration to cease and the blood pressure to fall. Withdrawal of the stimuli resulted in a rebound in all three systems. It has further been shown that the bulbar inhibitory mechanism probably passes down the anterolateral portion of the cord (47), hich agrees with Allan's findings covering the path of fibers from the bulbar reticular formation (1). Impulses from the bulbar suppressor mechanism have been found to pass to the lateral portion of the intermediate pool of internuncial neurones in the ventral horn of the spinal cord, and stimulation of this group of neurones has resulted in stopping the knee jerk (46).

Strychninizations of areas 24, 8s, 4s, 2s and 19s in the monkey and chimpanzee have established that secondary strychnine spikes from any one of the areas would always appear in areas 31 and 32, which indicated that the suppressor bands were at least functionally related to those areas (5).

Mettler et al. (53) have stimulated various portions of the extrapyramidal system while observing cortically induced movement in an extremity of cats and monkeys. Stimulation in either the caudate nucleus, putamen or the claustrum stopped cortically induced movement. The effects were largely ipsilateral, but occasional contralateral results were observed.

Tower (64) has contributed further facts on the methods and cortical sites from which skeletal muscle response or activity can be diminished. The observations were made on cats which were under ether anesthesia of such a depth that spontaneous activity was existant or that extensor muscles were in a state of increased tone. The experiments were performed on the cortex before and after unilateral or bilateral section of the pyramids at the level of the medulla. The stimulating device delivered a 60 cycle sine wave with a voltage of 0.02 to 10 volts. Excitation of the cortical extrapyramidal system resulted in two main types of decreased muscle activity which were a diminution of muscle tone or a cessation of movement. Diminution of muscle tone could be evolved from two overlapping fields on the sigmoid gyri about the cruciate sulcus, and was manifest by a palpable relaxation of muscles or by collapse of a tonic extremity. The effects were most easily produced after section of the pyramids. There were certain general characteristics of this decreased tone: (a) Unless the existing tone was very weak, the decrease in the tone operated only during the time of application of the stimulus. (b) Return of the original tone during the stimulation and rebound following stimulation were common. (c) Painful stimuli applied to the skin summed with the cortical stimuli to produce a reduction of tone. (d) A positive supporting reaction, which occurred when area 4 was ablated in the monkey by Hines, prevented the cortical stimulation from reducing muscle tone in Tower's preparations. (e) The strength of the stimulus and the tonic contraction of the muscles determined the latency, rate of progress, completeness, and the duration of the resulting reduction of tone.

Cessation of movement could be induced from cortical areas which were entirely different from those from which muscle tone was reduced. There were two main fields from which cortical inhibition of movement could be elicited: (a) The frontal field on the gyrus proreus, and (b) the lateral field whose center was apparently on the anterior sylvian gyrus. The frontal field was the stronger of the two. A third and much weaker area was found on the tentorial surface of the cortex. Spontaneous movements in light anesthesia, movements produced in light anesthesia by proper stimulation or the rhythmic movements of respiration were all stopped by stimulation of the above fields. If the spontaneous activity was very vigorous, the cortical stimulus produced a state of attention "with the animal's eyes front, head raised, back and tail straight and legs fixed". The "state of attention" could be held for about one minute. If the spontaneous activity was at a minimum, the stimulus simply made the animal droop.

It is also interesting to note that when Tower was studying the motor effects of stimulating the cortical extrapyramidal areas, three regions on the cat's cortex were found which gave rise to "adversive" responses. The three regions corresponded in their location to Garol's areas 19s, 2s, and 3s from which he was able to show suppression.

Leao (43,44,45) has reported another type of reduced response to cortical stimulation. Using rabbits anesthetised with Dial he demonstrated that weak cortical faradic stimulation caused a depression of electrical activity to spread out over the cortex in all directions. The depression spread to the opposite hemisphere only with the use of "supraminimal" stimuli, appearing first in the point symmetrical to the one stimulated. It took 3 to 6 minutes for the depression to involve the entire cortex, while 5 to 10 minutes was required for recovery of the electrical activity at any one depressed point. The spreading depression also involved cortical responses evoked by tactile stimulation, electrical stimulation of afferent nerves, illumination of the retina, ipsilateral or contralateral cortical electrical stimulation, and the electrical changes elicited by the local application of strychnine or of eserine plus acetylcholine. During the period of depression large slow waves followed by faster components occasionally appeared in the record. Accompanying the spreading depression was a marked vasodilatation and increased blood flow in the pial vessels. Similar findings occurred in the pigeon and in the cat whose brain stem had been transected.

In the monkey, dog, cat and rabbit areas have been discovered which when stimulated have a depressant effect on respiratory movements (1,4,17,45,61,62,63,65). In some instances the decrease in rate and amplitude of respiratory excursion or the complete cessation of all respiration seemed to be the sole observed effect of the stimulus. Stimulation of the areas, nevertheless, failed to maintain cessation of respiration beyond a 20 to 30 second period. In some cases other effects also appeared during stimulation of the respiratory depressant areas. This was particularly true from area 24 on the cingular gyrus where either an associated rise or fall in blood pressure, a slowing of the cardiac rate, piloerection, pupillary dilatation, and a marked suppression of electrical and skeletal muscle activity was noted to occur.

In an unpublished thesis (55) a report was made of a partial exploration of the cerebral cortex of the dog for suppressor areas, using both the strychnine and electrical pulse techniques. With neither method were suppressor bands found. Suppression of electrical activity was observed from several points on the cortex, but it did not have the characteristics which have been described for suppressor bands in other animals. The onset of the electrical suppression varied from 2 minutes to 2 hours and 15 minutes after applying the strychnine and had a duration of about 3 to 15 minutes.

The electrical suppression spread over the cortex, but it did not always commence near the strychninized point, and the strychnine spikes often, but not always, disappeared from the strychninized point. A rather strong 60 cycle sine wave stimulus applied to the coronal gyrus or the inferior portions of the postcruciate and sigmoid gyri, usually facilitated, extinguished and caused a rebound of a cortically induced one per second twitch at the scapulo-humeral joint. Cessation of respiratory movements occurred from application of the a.c. stimulus to the anterior composite gyrus — the same area from which Smith (61,62) obtained respiratory inhibition.

METHODS

Sixteen dogs were used in the experiments on the localization of the motor cortex. With the exception of three, all of the animals were anesthetized with Dial (0.5 cc./kg. of body weight) one half of which was injected intraperitoneally and one half intramuscularly. Three of the animals were originally anesthetized with Nembutal (0.5 cc./kg. of body weight) and were subsequently switched to Dial during the course of the experiment by giving numerous, small intraperitoneal doses of the drug. No animal was allowed to reach a plane of anesthesia in which there was evidence of spontaneous activity.

The operation was started by cannulating the trachea so as to provide a free airway at all times during the experiment. The dog's jaws were then clamped in a brace which prevented any movement of either the jaws or the head. An extensive craniotomy was done on the right side of each animal with excision of the entire orbital content so as to provide for subsequent adequate exposure of the frontal portion of the lateral surface hemisphere. Efforts were made to prevent as much blood loss during the course of the operation as possible. Care was taken to prevent injury to the cerebral blood vessels -- particularly those near the medial aspect of the hemisphere emptying into the superior longitudinal sinus. All of the exposed tissue around the margins of the craniotomy were finally covered with cotton packs soaked in warm Ringer's solution.

Each animal was then transfered to a rather high, wooden frame with a wide slot through the entire middle of the structure. Four straps were placed across the slot, and the animal was suspended on them in such a manner that its legs hung down free of all restraint. The headholder was attached to the frame so that no movement of the head or jaws was ever possible. The tongue was brought out the left side of the mouth where it could be readily visualized, and an eyelid retractor was utilized on the left side so as to expose the left eyeball for obervation.

The electrodes for stimulating the cortical surface were placed in a rigidily supported holder which could be moved in two planes by screw adjustments. An exploration of a portion of each animal's cortex was carried out, moving the electrodes in 1 or 2 mm. coordinate steps. An electrical square wave type of pulse with a duration of 15 msec. was employed as the exciting stimulus. The strength of the stimulus was controlled by a variable resistor connected in series on the output of the stimulator. The resistor was adjustable from 0 to 100,000 ohms. For each point of the cortex explored a very weak stimulus was first tried in an effort to obtain a muscular response. If no response was discernable after 3 or 4 seconds of stimulation, an interval of 20 to 30 seconds was allowed to elapse before a second series of somewhat stronger stimuli were applied to the point. This procedure was continued until the first response was detectable, and the character and location of the response was recorded in the protocol. If possible the strength of the stimulus was again increased at intervals until a maximal response was obtained. Any variations in the response with the increasing strength of the stimulus were all recorded. An interval of 30 or 40 seconds was then allowed to elapse before stimulation of the next point on the cortex was attempted, and then the process was repeated. In all sixteen of the animals a pulse frequency of 1/sec. was used with the square wave stimulator; however, in six of the dogs frequencies from 10 to 30/sec. were also used. At each cortical point of the six animals the effects of each separate frequency were investigated over the full range of strength of the stimulator.

All responses were detected by visual observation and palpation of the muscles.

The cortical electrodes were constructed from rather stiff stainless steel wire. The tips of the electrodes were filed as free of jagged points and rough edges as possible. Plastic holders were used for rigidly maintaining the relationships of the electrodes to one another and as an aid in maintaining their position on the cortex. Most of the electrodes were insulated except at the tips. The first type of electrode assembly which was tried was of a concentric type in which there was a small central wire with an indifferent surrounding ring of wire at a radius of 2mm. It was soon found that fluid collected between the central and peripheral electrodes which tended to shunt the current across the surface of the cortex thereby preventing the appearance of uniform results. Therefore, this type of assembly was quickly abandoned. Bipolar electrodes with an interelectrodal distance of 2 mm. were next tried, but it was soon apparent that a monopolar assembly would give rise to somewhat different results. Consequently 15 animals were explored, using a monopolar cortical electrode with the indifferent electrode being placed in the saturated cotton surrounding the craniotomy, on the lips, on the tongue, under the abdomen or in the rectum. In 7 of the 15 animals a comparison was made between the results when using a monopolar and a bipolar electrode assembly. On four of the animals another type of assembly was tried in which the two electrodes were placed side by side but in such a manner that when they were applied to the cortex one of the electrodes penetrated the cortex to a depth of 3 mm. of an inch while the other remained on the surface.

During the exploration of the cortex a map was plotted of the gyri and sulci of the region being stimulated on the basis of the coordinate positions of the electrode carrier. At the conclusion of the experiment the results were transferred to accurately enlarged charts of the cortical area explored on the animal. Enough charts were prepared for each experiment to demonstrate each of the significant variables.

In the second set of experiments on the localization of the "suppressor" bands of the dog's cortex, a total of 16 dogs and 4 cats was used. All of the cats were anesthetized with Dial (0.5 cc./kg. of body weight) which was given intraperitoneally. The dogs were also anesthetized with Dial but in this group of experiments the total dose was given intraperitoneally and for seven of the animals the dose was cut from the usual 0.5 cc./kg. of body weight to 0.35 to 0.4 cc./kg. of body weight. Instead of waiting the usual half to one hour after giving the anesthetic before starting the surgical procedure, in almost half of the animals a period of 6 to 8 hours was allowed to elapse between the injection of the anesthetic and the performance of the operation. Prior to doing the right sided craniotomy drills were placed in the upper and lower portions of the left humerus. The tendons of the left biceps and triceps muscles were isolated and freed from their attachments with precautions being taken not to injure their nerve or blood supply. Long cords were then transfixed to the tendons of the muscles. The remainder of the operative procedure was essentially the same as that described above. No operative work was done on the extremities of the four cats; the drills were not placed nor the tendons isolated.

Following the operation the animals were transferred to the frame, described above, where the drills in the humerus were fastened to braces attached to the frame in such a manner that the bone was almost absolutely immobile and would not transmit nor be affected by movements of other parts of the body. The cords from the muscles of the upper arm were then passed over freely movable pulleys and attached to fixed coil springs. The springs were adjusted so that there was moderate tension on both of the muscles. The cords from the tendons were then fastened to horizontally moving, ink-writing, muscle levers from a motor driven paper kymograph. A signal marker and an electrically driven one per second timer were also attached to the kymograph, which was run at a velocity of approximately 1 cm. per second.

Two sets of bipolar stainless steel electrodes were arranged for stimulating the cortex. One pair of the electrodes, with an interelectrode distance of 3 mm., was used for stimulating the motor cortex, and the other pair was used in the exploration for suppressor bands. A switch was arranged in the circuit of the stimulator so that the current could be passed to either pair of electrodes with ease. Both sets of electrodes were attached to adjustable carriers. The carrier for the exploring electrodes was a converted microscope mechanical stage with thumb-screw adjustments possible in three planes along millimeter scales. When the electrodes had been arranged, a hurried exploration of the motor cortex was performed to determine the point from which responses in the biceps, triceps or both muscles could be most easily elicited. The motor electrodes were then permanently placed on this point.

The electrical stimulator produced a square wave pulse whose duration was generally held at 15 msec. The strength of the stimulus was controlled by the resistor described above, and all stimuli to the motor point were considerably above threshold at the start of the experiment. In the first three experiments the frequency of the pulse delivered to the motor cortex was 1/sec. and continuous 1/sec. responses from the muscles were recorded on the kymograph. For the remainder of the experiments the pulse frequency for the motor point was set at 30/sec. The motor point was stimulated with this frequency for period of 2 to 5 seconds once each minute during the entire experiment. The kymograph was generally run only for a short time before, during and after the application of the motor and "suppressor" stimuli. During the first three experiments of this group the "suppressor" stimulus consisted of a 60 cycle sine wave current which was applied to individual explored points at intervals of one or more minutes. For the remainder of the experiments the suppressor stimuli consisted of the square wave electrical pulses of a duration of 15 msec. and a frequency of 30/sec. The explored point was practically always stimulated with a stronger current than the motor point, and the stimulus was applied through the exploring electrodes for periods of 5 to 10 seconds. A "suppressor" stimulus was applied to the cortex oncé every 5 to 10 minutes unless the response in the muscles was appreciably altered in which event a second "suppressor" stimulus was withheld until the muscle response had returned to its previous state. The exploring electrodes were moved in 2 mm. coordinate steps and maps of the sulci and gyri covered in the experiment were constructed on the basis of the coordinates.

The room in which all the experiments were conducted was kept at a temperature of 27°C. or more and an electric lamp was placed over the animal in an effort to maintain its body temperature. One end of the frame was elevated so that the hips of the animal were always higher than its head in order to allow gravity to help maintain cerebral blood flow.

RESULTS

A: Location of "Motor Cortex"

Each part of the lateral surface of the right cerebral hemisphere was explored for possible motor activity in at least two animals. No successful attempts were made to explore the medial aspect of the hemisphere or the depths of the sulci. On 13 of the 16 dogs employed in this study a considerable part of the exploration was confined to the region of the sigmoid and coronal gyri, for it was realised that this was the most probable area from which motor responses might be obtained.

It was found that the motor area of the dog was confined largely to the entire posterior sigmoid gyrus, the posterior part of the very lateral portion of the anterior sigmoid gyrus, and to the posterior portion of the coronal gyrus (Fig. 1).

The hind-leg region extended from the medial margin of the hemisphere over 1/3 to 1/2 of the posterior sigmoid gyrus. Anteriorly it was limited by the cruciate sulcus and posteriorly by the postcruciate sulcus, if this was present. In many animals it was especially difficult to thoroughly explore the medial margins of the region because of the numerous and large cerebral veins which pass across the area to the dura a considerable distance from the superior longitudinal sinus.

Seven animals showed a variable sized band across the mid-portion of the posterior sigmoid gyrus from which simultaneous responses would be obtained from both the hind-leg and the fore-leg. This band likewise did not extend beyond the cruciate sulcus anteriorly or the postcruciate sulcus posteriorly.

The fore-leg region was found on the lateral 1/2 to 3/5ths of the posterior sigmoid gyrus and occasionally extended around the tip of the cruciate sulcus onto the posterior part of the most lateral portion of the anterior sigmoid region. Fore-leg responses were never obtained from stimulation across the coronal sulcus on the upper part of the coronal gyrus.

Eyelid contractions and movements of the left ear resulted from excitation of the posterior and mid-portions of the coronal gyrus and very occasionally from the adjacent anterior and superior border of the anterior ectosylvian gyrus. In most instances eyelid responses were observed from a larger segment of this region than the ear responses, and they usually had a lower threshold. In one animal, on which the penetrating type of bipolar electrode was being used, a few points also yielded movements of the upper lip as well as the eyelid or ear. From one point in one animal contractions of the left temporalis muscle were observed.

In one animal contractions of the left part of the trunk were noted following stimulation of the mid-portion of the posterior sigmoid gyrus, and in another animal responses of the left temporalis muscle were noted from excitation of the most lateral part of the posterior sigmoid gyrus approximately opposite the lateral end of the cruciate sulcus.

With the exception of the responses mentioned above no movements of the trunk, head, neck or face were found from stimulation of the sigmoid gyri.

Movements of the eyeball were looked for carefully, particularly when the electrodes were placed about the medial part of the praesylvian sulcus, but no responses were seen. Movements of the eyeball were frequently seen but they appeared spontaneously and could not be correlated with the application of an electrical stimulus.

The responses were mainly contralateral. Occasional ipsilateral movements of the extremities could be seen, but these were very rare and were not constantly obtained from any one cortical point in one animal or the group as a whole.

At the end of one exploration an experiment was set up designed to determine if there were any intracortical connections between eyelid and ear areas and the area for the extremities, which were essential for eliciting a response from either region. Both areas were successively stimulated and adequate responses seen at a low threshold. Then a vessel in the coronal sulcus was coagulated by electrocauterization and an incision was made with a blunt instrument to a depth of about 1.5 cm. in the sulcus between the two fields. Each region was again stimulated and responded, indicating that there were no intracortical connections essential to the production of either response.

When the cortex was stimulated with square wave pulses at a frequency of 1 per sec. the responses consisted of single, sharp contractions of a group of muscles which usually produced movement of at least two joints of an extremity. In numerous instances, however, it was possible to detect movement at only one joint; this was especially true with near threshold strengths of stimuli, but could be produced from some points in some animals with stronger currents. Stimulation of some cortical points resulted in movement at even three or more joints, and the responses were not necessarily all of the same type such as a massive flexion, extension, abduction or rotation but might be any combination of these. No experiments were performed to determine if responses of single muscles occurred.

It was impossible to subdivide the areas for the fore and hind-legs into regions for the wrist, elbow, shoulder, ankle, knee and hip joints as there was considerable variation in the location of the response from point to point in the same and different animals. It was also impossible to subdivide these areas into regions for one specific type of movement such as a flexion or extension at a joint. It was easier to get responses in the proximal part of the limb than in the distal.

When the frequency of the pulse was raised to 30 per sec. one was no longer able to obtain simple twitches of muscle groups. In their place a relatively smooth, gradual contraction, of muscles acting on all joints of an extremity occurred, culminating often in a tonic and clonic reaction in the extremity, especially if the stimulus was applied for more than 3 or 4 seconds. With the use of maximal currents at a frequency of 30/sec. the excitable area for the arm and leg region increased very slightly in extent; whereas in one case the size of the region for eyelid and ear responses was decreased (Fig.6).

The regions with the lowest thresholds were the fore-leg and eyelid areas. The first detectable responses were obtained from the centers of these fields with minimal stimuli. As the current was then increased responses could be seen in the center of the hind-leg field, and by gradually increasing the stimulus to its maximum, the excitable cortical regions expanded to the limits described above, but seldom beyond them (Fig. 2 & 4).

The impression one received from switching the type of electrode assembly in the various animals was that the most discrete and isolated muscular responses were observed with the use of the bipolar penetrating system (Fig. 7). However, this was not used a sufficient number of times nor compared to the bipolar surface electrode system so that this impression could be definitely established as a fact. In general the lowest threshold for obtaining responses was found with the use of the monopolar cortical electrode, but the responses were not as discrete as with the surface bipolar electrodes as movements could be seen at more joints (Fig. 3,4 & 5). When the variable resistor in the output of the stimulator was set anywhere between 10,000 and 3,000 ohms, very complex reactions occurred with the use of the monopolar system. There were bilateral movements of the neck, fore-legs, face, tongue and occasionally of the hind-legs which would result from stimulation of practically any point on the surface of the hemisphere. This never occurred with the use of either of the bipolar electrode systems. To determine if these complex responses were the effect of impulses descending in pathways through the brain stem the following work was done at the conclusion of one of the experiments: The motor area for the fore-leg was stimulated with weak currents which gave nothing but fore-leg responses on the contralateral side after which the current was increased to the point at which the complex reactions were occurring from many regions of the cortex. Then an incision was made through the occipital pole of the cortex so as to cut through the brain stem at about the level of the mesencephalon. After the lesion was made, the cortex was restimulated with both strengths of current, and responses confined to the contralateral fore-leg could not be observed, while those of the complex variety were still obtainable.

Changing the location of the indifferent electrode from the cotton around the craniotomy to the lips, tongue, abdomen or the rectum had no effect on the complex reaction.

B: Results on Attempts to Locate Suppressor Areas

In the group of experiments designed to locate the "suppressor" bands of the dog's cortex by recording kymographically the effect of electrical stimulation on cortically induced individual muscle responses, the explorations were confined to rather small sections of the cortex. The explorations were conducted around the ansate sulcus and its adjacent gyri, the coronal, the anterior ectosylvian and the posterior portion of the anterior composite gyri, and on the gyrus proreus with particular emphsis on the cortex on both sides of the sulcus praesylvius.

When a one per second pulse was applied to the cortex a single, sharp contraction of the muscle with a rapid rise and fall occurred (Fig. 8). When the frequency of the pulse was raised to 30/sec. and the stimulus was applied for a period of 2 to 5 seconds to the cortex, a gradually increasing amplitude of contraction ensued throughout the stimulation. Often superimposed on the gradually rising contraction were small amplitude, jerky twitches of the muscle (Fig. 9,10 & 11). In some cases after-discharge of the muscle could be seen following the withdrawal of the 30/sec. stimulus (Fig. 9).

During the application of the 1/sec. stimulus to the motor point, the stimulation of points on the coronal gyrus directly across the coronal sulcus and opposite the posterior sigmoid gyrus with a 60 cycle alternating current for a period of 10 or 12 seconds would sometimes produce facilitation, extinction and rebound of the muscle response (Fig. 8).

Throughout the records of all the experiments of this group it was noted that there many periods in which the amplitude of the contractions was markedly decreased or almost negligible and that the latency of the decreased responses became considerably prolonged. However, the periods of decreased responses could not be correlated with the application of a "suppressor" stimulus as the decreased responses appeared anywhere from 1 minute to 4 hours and 10 minutes after applying the "suppressor" stimulus. The duration of the suppressed response was from 1 minute to 42 minutes.

In some animals in which "suppression" of the muscular response ensued within 1 to 5 minutes after the "suppressor" stimulus had been applied to a cortical point, the point was restimulated almost one hour later and usually no effect on the response would be seen following the second "suppressor" stimulus (Fig. 10 & 11). In some cases the same spot was restimulated 3 or 4 times during the course of the experiment with different results each time. As many as 8 increases and decreases in the amplitude of the response have been observed in a 33 minute period.

When the lighter doses of anesthetic were used, spontaneous activity was conspicuous throughout the record. Motor stimuli during the spontaneous activity abolished it for a few seconds during and after the stimulus (Fig. 11). The motor responses were always easily obtainable and of good amplitude when spontaneous contractions were present. As the spontaneous activity disappeared from the record there was a tendency for the motor responses to decrease in amplitude and with the reappearance of the spontaneous fluctuations there was generally an increase in the amplitude of the motor response.

An effort was made to find the suppressor bands of the cat in the positions described by Garol. On 4 cats 19s and 2s were explored, while 3s was also explored on two of the animals. Using the methods and stimulator described above, it was impossible to discover evidence of suppression from the areas.

DISCUSSION

To my knowledge the dog's brain has not previously been explored for motor points using a square wave pulse or a thyratron discharge. Previous investigators have employed a galvanic stimulus or the discharge of an inductorium or a reduced 60 cycle sine wave current. None of the previous experiments has been done using Dial as the anesthetic, but instead ether, nembutal or some other anesthetic has been used. These changes in the experimental procedure may account for some of the differences encountered in this investigation as compared to the results of others. The area from which fore- and hind-leg responses could be indused agrees closely with the findings of Woolsey (67), but no tail responses could be detected from the medial margin of the posterior sigmoid gyrus as had been done by Ferrier (30) and Smith (60). The findings in regard to the lateral portion of the anterior sigmoid gyrus are not in agreement with those of any of the other authors' (30,59,60,67), since neck, face, jaw, head, eyeball or pupillary responses were not found when the area was stimulated. The fact that the head and jaws of the animals used in this set of experiments were absolutely immobile, of course, interfered with detecting responses in these structures. It is very possible that many of the movements that were interpreted as flexor responses at the shoulder would have resulted in contractions of the neck or movements of the head had they been free. The finding of a center on the posterior and mid portions of the coronal gyrus for responses of the eyelids, ear and occasionally the upper lip is not in agreement entirely with the findings of Ferrier or Fritsch and Hitzig (30). Woolsey (67) and Smith (59,60) did not state whether responses were observed from the region or whether it was even explored in their experiments.

Neither was it possible on the dogs to divide the regions for the hind- and fore-legs into specific bands for the ankle, knee, hip, shoulder, elbow and wrist joints as had been done for the cat by Garol (32), who used Dial anesthesia and a thyratron discharge of a frequency of 1/sec. and a falling phase of 20 msec. as the stimulus. Moreover, no motor responses of the face, tongue, lips and jaws were obtained from the anterior composite gyrus and the anterior extremity of the coronal gyrus -- an area from which they had been observed in the cat. Also no second motor area such as Garol found in the cat at the anterior extremity of the anterior ectosylvian gyrus could be detected in the dog. The only significant effect noticed from changing the frequency of the pulse from 1 per sec. to 30 per sec. in exploring the cortex of the dog was that the responses changed from simple twitches of muscles to gradual slow contractions of larger groups of muscles which frequently culminated in a tonic and clonic reaction. Garol reported observing eyeball and other responses from stimulating the cortex of the cat in the region about the medial tip of the sulcus praesylvius with a pulse whose frequency was 30 per sec.; however, stimulation of this area in the dog failed to produce any noticeable results.

Rather frequently throughout the experiments it was noted that responses occurred in one muscle group acting across one joint. Others have reported this as happening only occasionally when stimulating the cortex of the dog.

Although the exploration of the cortex of the dog for suppressor bands was performed largely in regions which would correspond to the location of bands 8s, 3s, and 2s of the cat, they could not be found in the dog with the methods employed. As a matter of fact when using the same methods on the cat, it was impossible to locate bands 19s, 2s, or 3s as described by Garol (32). The differences between the methods employed by Garol on the cat and those used in the present experiments are as follows: (a) Garol used a thyratron stimulator whose discharges had a falling phase of 20 msec. and whose frequency was set at 20 or more pulses per second. The stimulator used most often on the dogs and cats during this work delivered a square wave pulse with a duration of 15 msec. and at a constant frequency of 30 per sec. (b) While Garol used bipolar Ag-AgCl electrodes on his cats, stainless steel bipolar electrodes were used in the present experiments. (c) The electrodes for stimulating the motor cortex of the dogs were placed in a holder and carrier so that they could be left permanently in place on one spot throughout the experiment instead of trying to manually apply them to exactly the same point on the cortex at one minute intervals as was done on the cat. (d) The exploring electrode was also placed in a mechanical carrier with screw adjustments so that it did not have to be manually applied as was done in the cat. (e) The "suppressor" stimulus was applied for a 2 to 3 second interval on the bands of the cat, but on the dog they were applied for a 5 second period. (f) Kymographic records of the cortically induced muscle responses of the contralateral biceps and triceps were taken from all of the dogs in these experiments; whereas only visual observation of the change in response or contraction in a whole extremity were used for determining the results of the "suppressor" stimulus applied to the cat. However, even visual obervation of the responses of the extremity was also used on the four cats which were explored in the present work, and still the suppressor bands could not be identified in these animals. It is conceivable that by simply changing the wave shape of the stimulus that the factors were sufficiently altered to prohibit the finding of a suppressor band as it has been shown that by simply altering the frequency of a cortical or cerebellar stimulus either facilitation or extinction of a cortical motor response can be produced from the same point (24,55). It is possible that the suppressor bands are just as susceptible to changes in the parameters of stimulation.

It is interesting to note, however, that Gellhorn had difficulty finding the suppressor areas of the cat, even though he was using exactly the same method and equipment as Garol, until approximately 18 hours after the animals had been operated upon.

Although no suppresser bands were found in our experiments, it was often noted throughout the records that the muscular response decreased or became almost absent for varying periods of time. That this was not a typical "suppression" was indicated by the fact that the onset of the decreased responses bore no constant relationship to the time of application of the "suppression" stimulus; absent or decreased contractions appeared from 1 minute to 4 hours after the stimulus. As many as 8 periods of depressed responses have occurred in a 33 minute period, whereas true "suppression" has only been reported to be trimodal at the most (25). Also it was impossible to produce decreased responses from stimulation of the same point twice although an interval of an hour was allowed to elapse between the application of the two stimuli.

The periods of decreased response in the biceps and triceps induced by cortical stimulation come closest to simulating the periodic fluctuations in the motor response to uniform electrical stimulation of the cerebral cortex which has been observed in the monkey and cat. In these animals Brodsy and Dusser de Barenne (7) and Hovland and Dusser de Barenne (40) have shown that stimulation of the motor cortex for a specific muscle response at one minute intervals with constant stimuli of a "supraminimal" strength, would give rise to spontaneous variations in the amplitude of the response. During hyperventilation the spontaneous variations were found to disappear and the amplitude of the contractions to increase in 2/3 of the cases. When the excitability of the cortex was increased by the injection of non-convulsant doses of strychnine or the local application of strychnine to the cortex, the spontaneous variations again disappeared. At the same time the amplitude of the contractions increased and the latency of the response decreased. Following the stimulus there was some appearance of after-discharge. It will be recalled that when the dogs of the present study showed evidence of spontaneous movement and activity, the amplitude of the cortically induced responses was practically always increased. However, there were wide variations in the duration of the spontaneous activity, the amplitude of the spontaneous contractions and the period in which no spontaneous activity was present. Even though the fluctuations of responses in these dogs was sometimes much more marked and had a much wider variation in its periodicity than the fluctuation reported for the monkey and cat, it is felt that they are similar phenomena.

SUMMARY

An exploration of the entire lateral surface of the right cerebral hemisphere of the dog has been carried out using a square wave electrical pulse as the stimulus to locate the motor areas. A partial exploration also has been performed in an attempt to locate the suppressor bands of the dog. The results of this study were as follows:

(1) The motor area of the dog was confined to the entire posterior sigmoid gyrus, the posterior part of the very lateral portion of the anterior sigmoid gyrus, and to the posterior portion of the coronal gyrus.

(2) The hind-leg region extended from the superior longitudinal fissure over the medial 1/3 to 1/2 of the posterior sigmoid gyrus.

(3) There was a narrow band at approximately the mid-portion of the posterior sigmoid gyrus from which stimulation produced responses of both the fore- and hind-leg.

(4) The fore-leg region was found on the lateral 1/2 to 3/5th of the posterior sigmoid gyrus and occasionally extended around the tip of the cruciate sulcus onto the posterior part of the most lateral portion of the anterior sigmoid gyrus.

(5) Eyelid, ear and occasionally upper lip responses were detected from stimulation of the posterior and mid-portions of the coronal gyrus.

(6) Movements of the head, neck, eyeball, and lower face were not observed; however, the head and neck were limited in their motion by the brace which helped to hold the animal on the frame.

(7) On one occasion a response of the trunk musculature was observed from stimulation of the mid-portion of the posterior sigmoid gyrus.

(8) Although occasional ipsilateral responses were observed, the contractions were mainly contralateral.

(9) Movements usually occurred at two or more joints in an extremity; however, from numerous points it was possible to obtain responses at only one joint.

(10) When a pulse frequency of 1 per sec. was used, single sharp contractions of a group of muscles occurred, but if the frequency was raised to 30 per sec., the response changed to a relatively smooth, gradual contraction of muscles acting on all of the joints of an extremity. Tonic and clonic reactions often appeared during stimulation with a frequency of 30 per sec.

(11) The regions with the lowest thresholds were those of the fore-leg and the eyelid.

(12) It was the impression that the bipolar, penetrating-surface electrode system gave the most discrete responses. The lowest threshold for responses was found with the use of the monopolar electrode assembly, but with stronger currents this assembly produced bilateral responses of the neck, fore-legs, face, tongue and occasionally of the hind-legs. It was shown that a pathway through the brain stem was not essential to the production of these complex responses. Changing the location of the indifferent electrode did not alter the nature of the complex response.

(13) No evidence of suppressor bands in the dog's cortex was found in the region around the ansate sulcus, the coronal gyrus, the anterior ectosylvian gyrus, the posterior portion of the anterior composite gyrus and the gyrus proreus.

(14) During stimulation of the motor cortex with a frequency of 1 per sec., the application of a 60 cycle alternating current fora period of 10 or 12 seconds on the coronal gyrus would sometimes produce facilitation extinction and rebound of the muscle response.

(15) Throughout the records periods of decreased amplitude of response with an increase in latency were noted which had a duration of from 1 minute to 42 minutes. These periods of decreased response bore no constant relationship to the application of any "suppressor" stimulus.

(16) When lighter doses of anesthetic were used spontaneous activity was conspicuous. Stimuli applied to the motor cortex during the spontaneous activity stopped it during the stimulus and for a few seconds thereafter.

(17) With the techniques which were used it was impossible to find areas 19s, 2s, and 3s in the cat.

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FIGURE 1

A composite diagram of the right lateral surface of the cerebral hemisphere of the dog. The shaded areas are those from which skeletal muscle responses were obtained. The entire lateral surface of the cortex was explored except the olfactory bulb and tract.

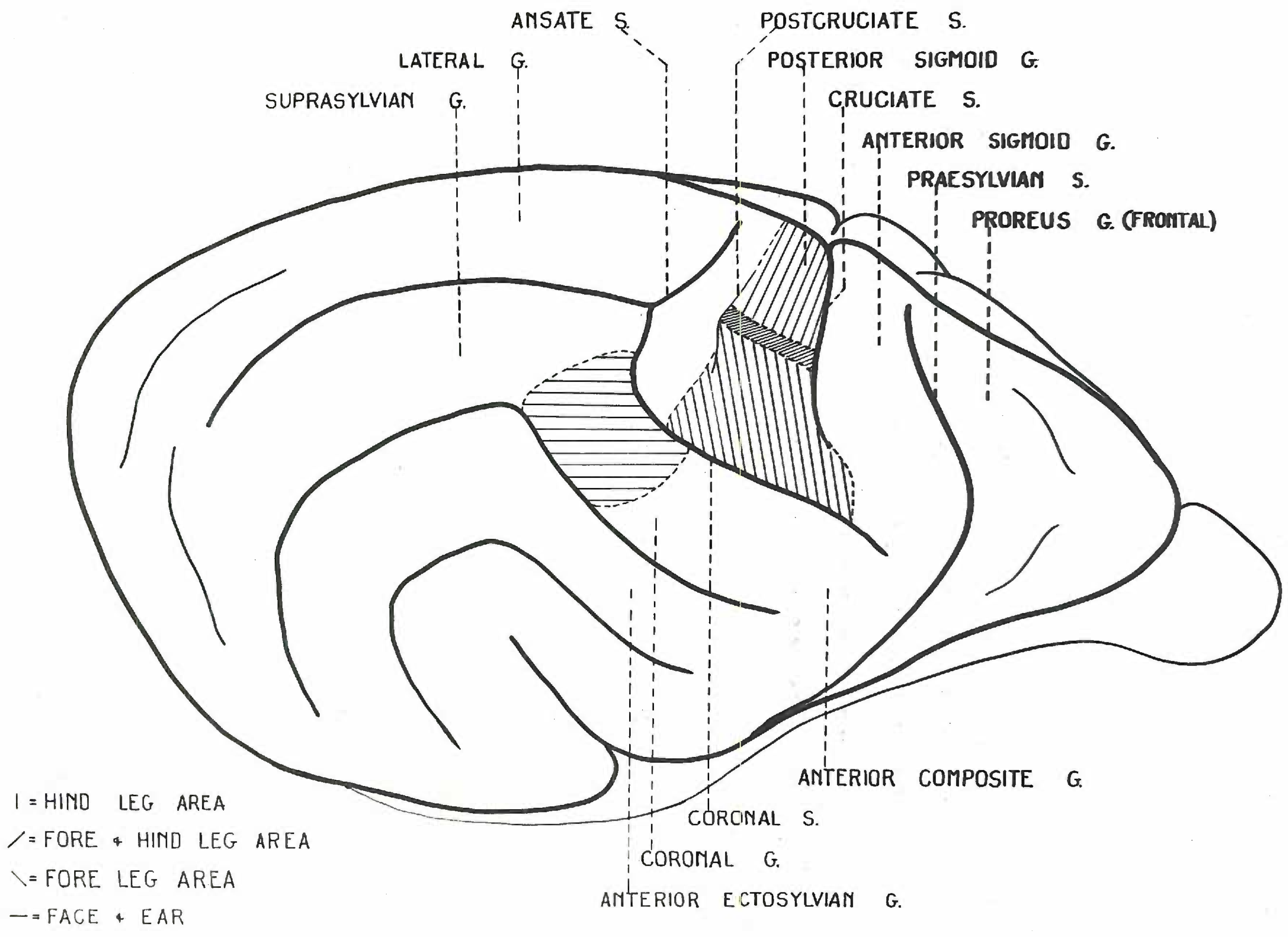
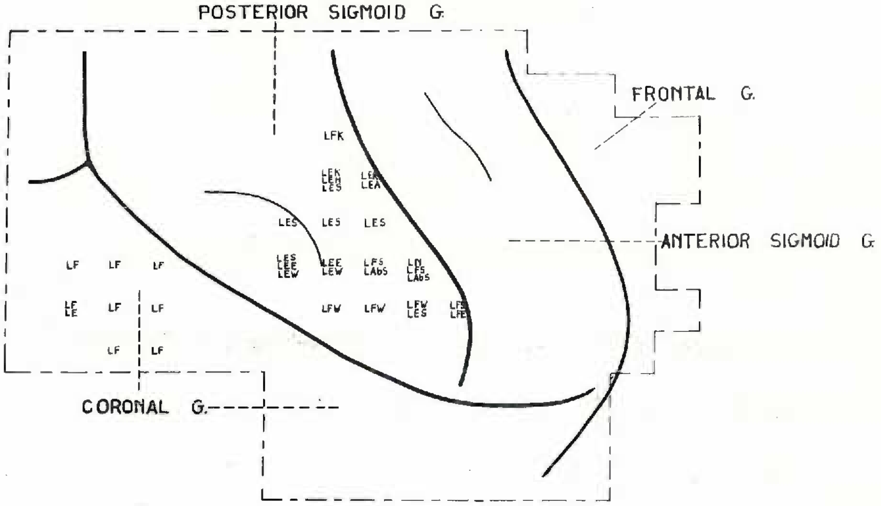

ANSATE S.
POSTCRUCIATE S.
LATERAL G.
POSTERIOR SIGMOID G.
SUPRASYLVIAN G.
CRUCIATE S.
ANTERIOR SIGMOID G.
PRAESYLVIAN S.
PROREUS G. (FRONTAL)
ANTERIOR COMPOSITE G.
CORONAL S.
CORONAL G.
ANTERIOR ECTOSYLVIAN G.
| = HIND LEG AREA
/ = FORE + HIND LEG AREA
\ = FORE LEG AREA
— = FACE + EAR

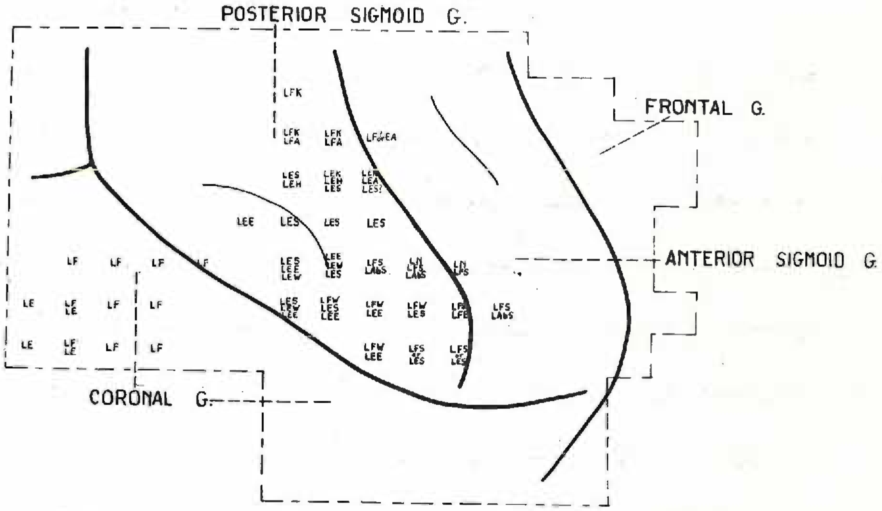
FIGURE 2

Maps of the cortical area explored for skeletal muscle response on dog #3. The cortex was stimulated with a one per sec. square wave electrical pulse of a duration of 15 msec. A monopolar electrode assembly was used. The upper map indicates the responsive points when the resistor in the output of the stimulator was set between 15,000 to 30,000 ohms; the middle map for settings between 10,000 to 30,000 ohms; and the lower map for settings between 2,000 to 30,000 ohms. The groups of letters within the explored area in these and subsequent maps indicate the responses that occurred from stimulation of that point. The distance between the centers of adjacent groups of letters is always 2 mm. unless otherwise indicated. The first letter of each group shows the side of the body from which the response was obtained; otherwise the meaning of the letters is a follows: LEH, left (omitted hereafter) extension of the hip; LAbH, abduction of the hip; LFK, flexion of the knee; LEK, extension of the knee; LFA, flexion of the ankle; LEA, extension of the ankle; LFS, flexion of the shoulder; LES, extension of the shoulder; LAbS, abduction of the shoulder; LEE, extension of the elbow; LFE, flexion of the elbow; LEW, extension of the wrist; LFW, flexion of the wrist; LF, eyelid contractions; LE, ear contractions; LN, neck contractions (these neck responses were very questionable and should not be included in the diagram as they were a part of the "complex" response described when monopolar electrodes were used). These same letters will be used in all the succeeding maps unless otherwise noted.



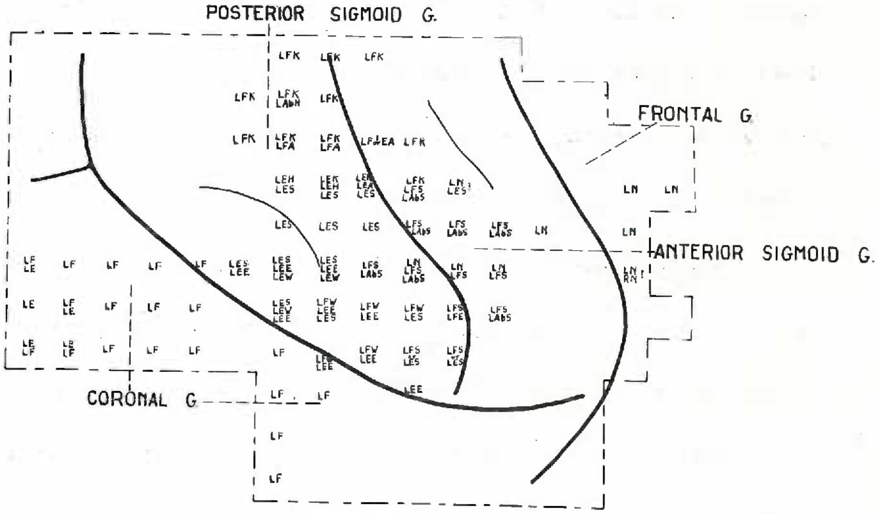
15-30K Ohms

DOG # 3 7/29/47



10-30K Ohms

DOG # 3 7/29/47

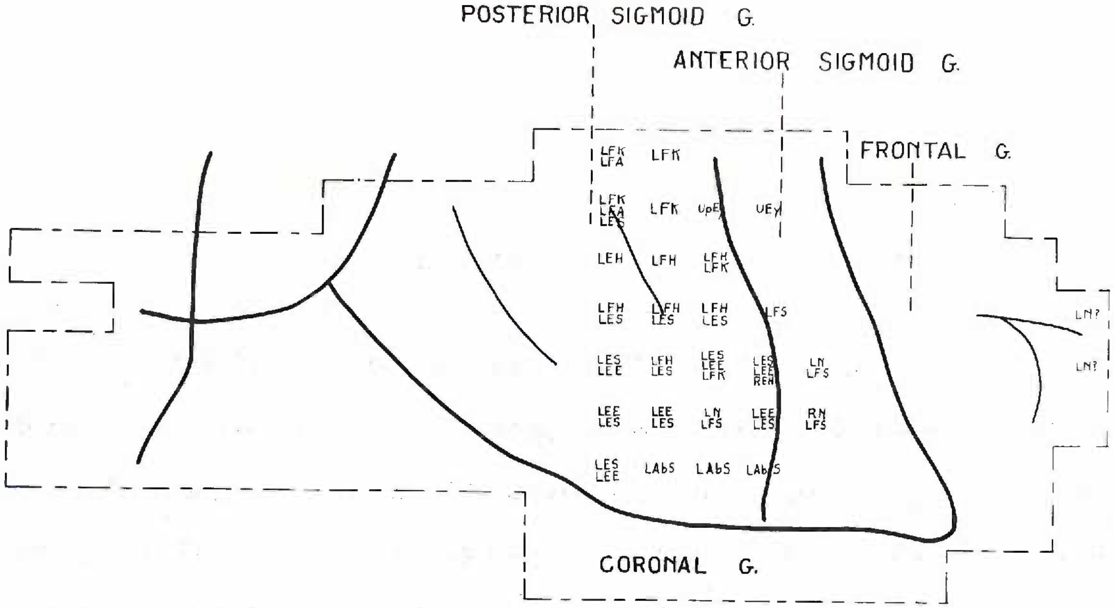


2-30K. Ohms

DOG # 3 7/29/47

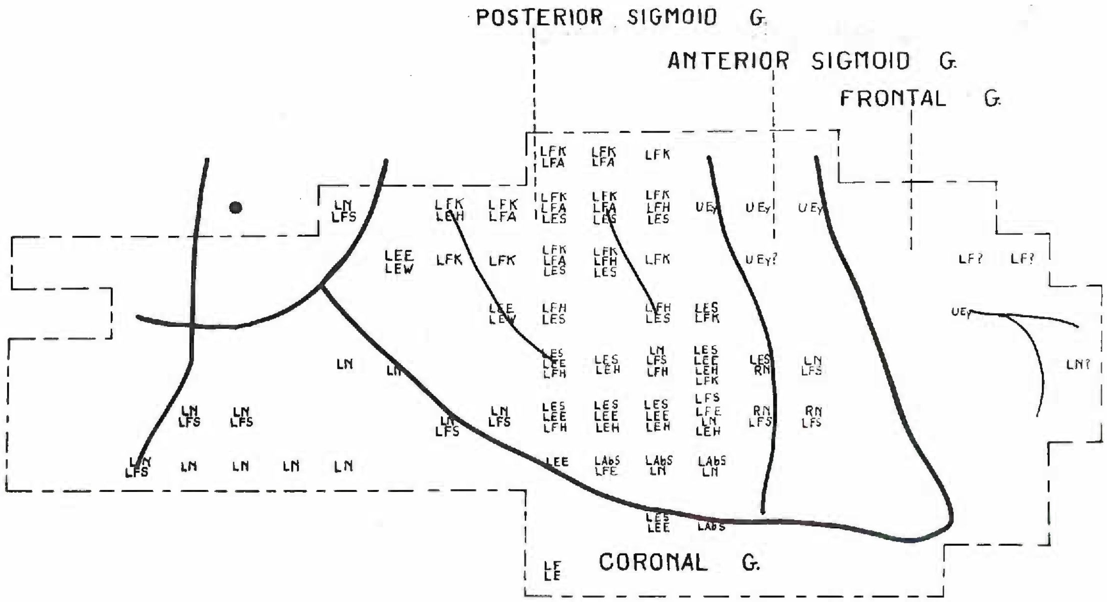
FIGURE 3

A map of the cortical area explored for skeletal muscle responses on dog #4. The stimulus consisted of a one per sec. square wave electrical pulse with a duration of 15 msec. The upper map shows the responses obtained with the use of the bipolar surface electrode assembly, and the lower map shows the responses obtained with the use of the monopolar electrode system. The meaning of the groups of letters are the same as in Fig. 2 except for the following: LFH, flexion of the hip; REH, right extension of the hip; UEy, upperward eyeball movement. The neck and eyeball movements were very, very questionable and should not be included in the diagram.



BIPOLAR

DOG # 4 0-30K Ohms 8/5/47

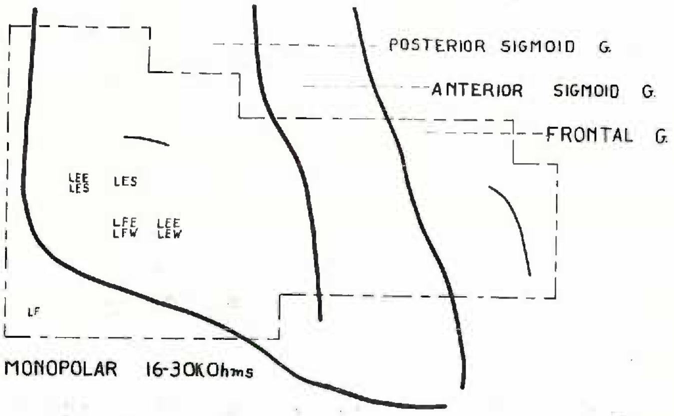


MONOPOLAR

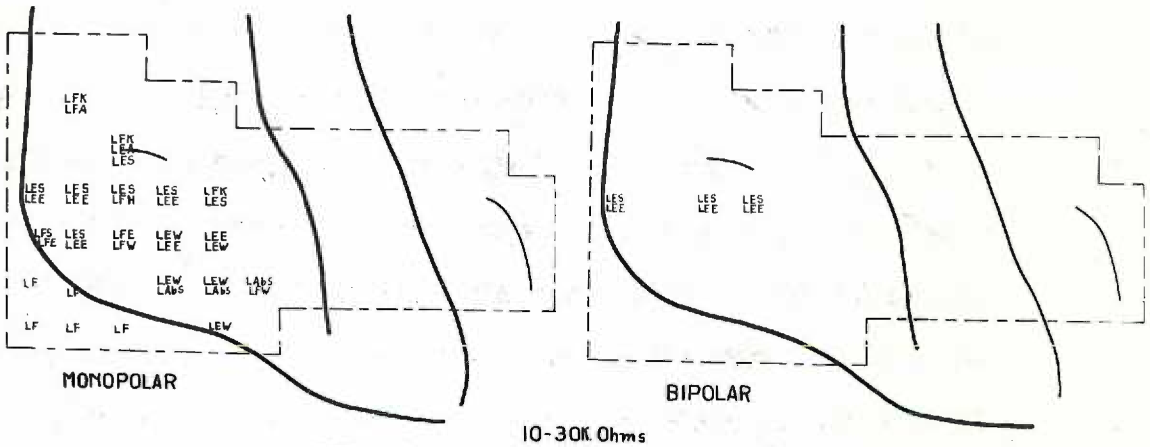
DOG # 4 0-30K Ohms 8/5/47

FIGURE 4

Maps of the cortical regions explored for skeletal muscle response on dog #5. The cortex was stimulated with a one per sec. square wave electrical pulse with a duration of 15 msec. The upper map shows the responses that were obtained when the output resistor was set between 16,000 to 30,000 ohms and a monopolar electrode system was being used; no responses were noted when the bipolar electrodes were used at these resistances. The middle and lower pair of maps show the differences between the responses obtained with the use of monopolar and bipolar electrodes. In each pair identical electrical pulses were employed. The meaning of the groups of letters is the same as in Fig. 2 & 3.



MONOPOLAR 16-30K Ohms



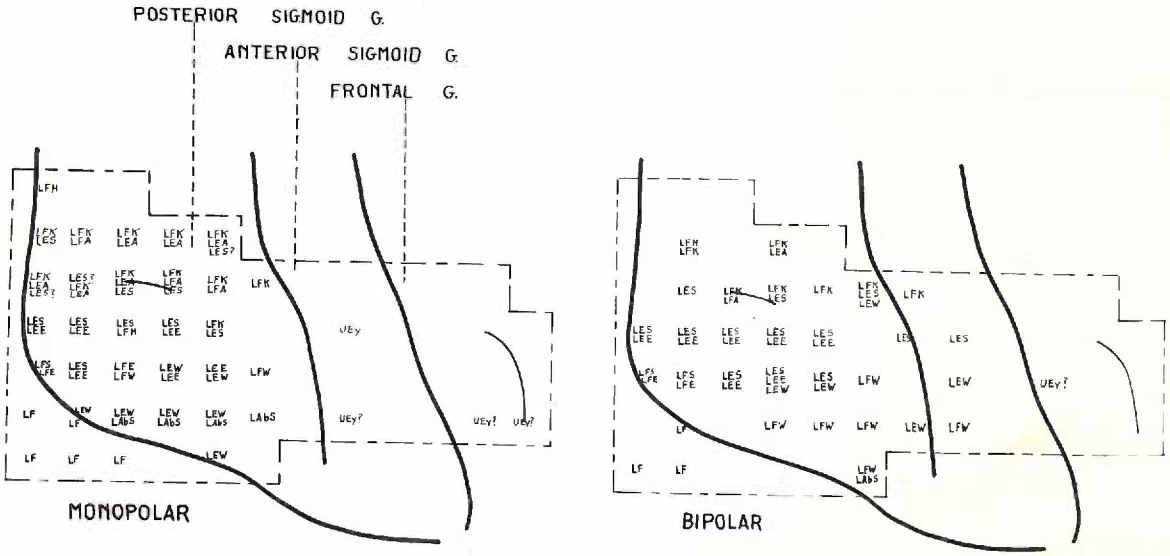
MONOPOLAR

BIPOLAR

10-30K Ohms

DOG # 5

8/26/47



MONOPOLAR

BIPOLAR

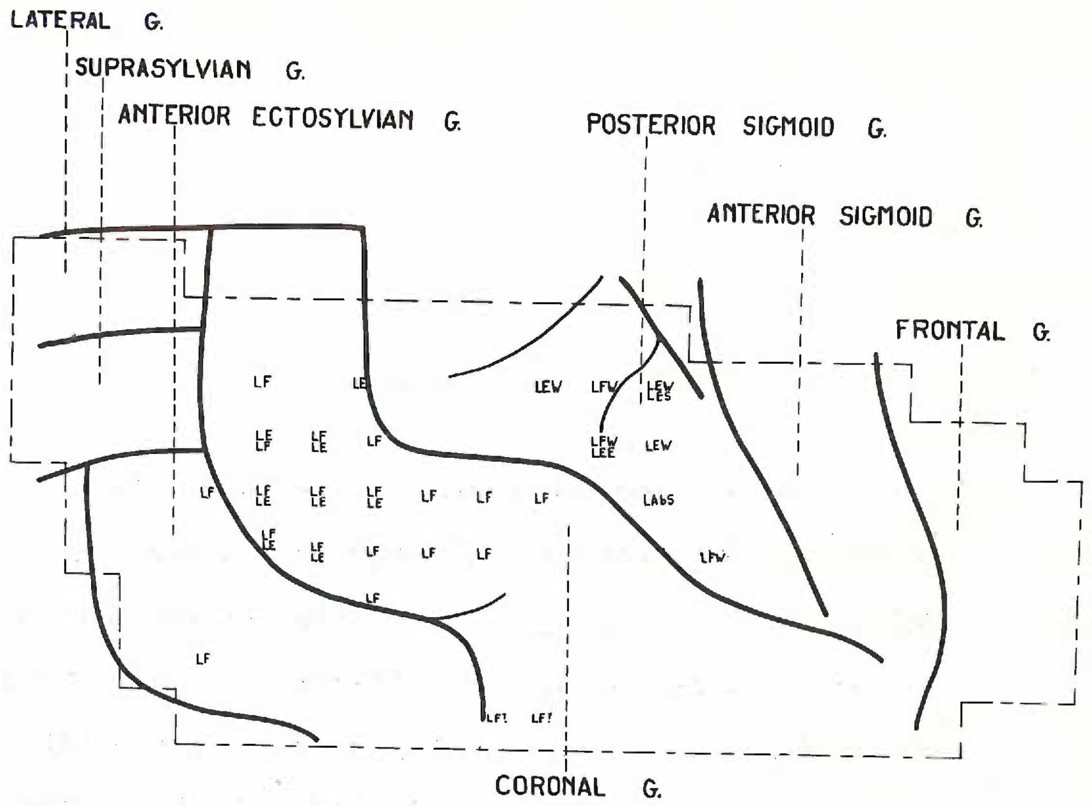
0-30K Ohms

DOG # 5

8/26/47

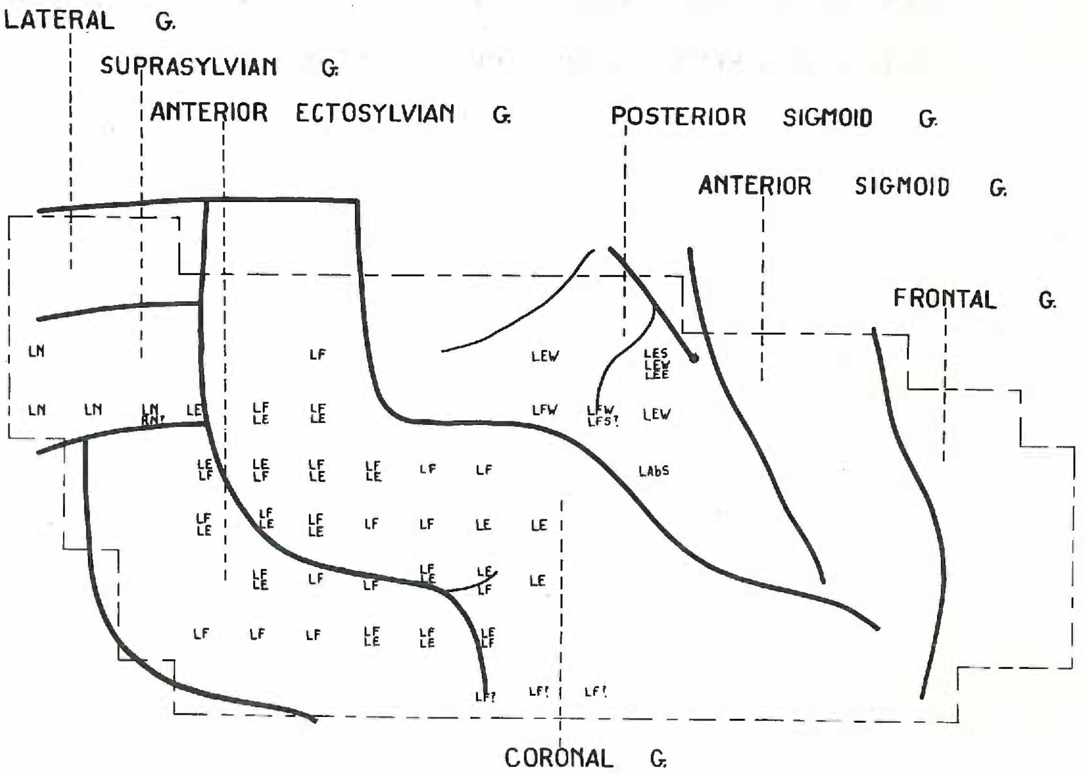
FIGURE 5

Maps of the cortical region explored for skeletal muscle response in dog #6. The cortex was stimulated with a square wave electrical pulse at a frequency of one per sec. and a pulse duration of 15 msec. The upper map indicates the responses obtained with the bipolar electrode assembly, and the lower map depicts the responses with the monopolar electrode system. The results of this experiment are included here primarily to show the extent of the area for eyelid and ear contractions. It was seldom, however, that these movements were obtained from the anterior ectosylvian gyrus. The meaning of the groups of letters is the same as in Fig. 2 & 3.



BIPOLAR 0-30K Ohms

DOG # 6 9/4/47

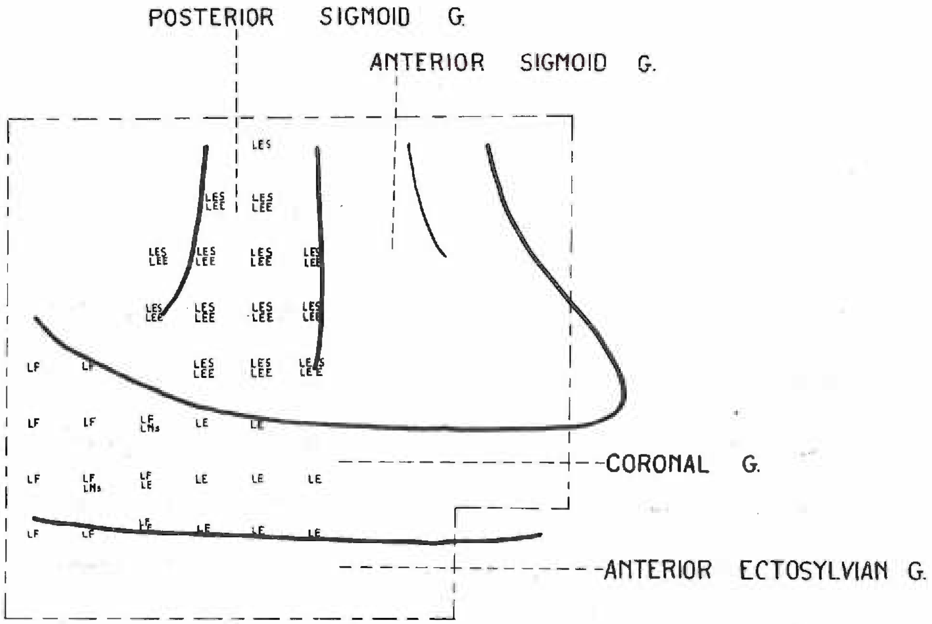


MONOPOLAR 0-30K Ohms

DOG # 6 9/4/47

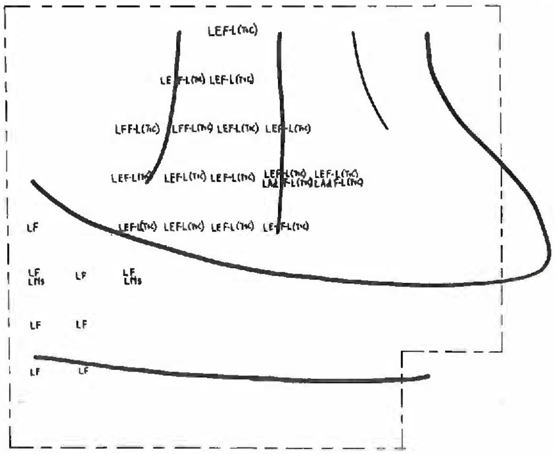
FIGURE 6

Maps of the cortical region explored for skeletal muscle response in dog #10. The cortex was stimulated with a square wave electrical pulse with a duration of 15 msec. The upper map depicts the responses observed with a pulse frequency of one per sec. The lower maps T-7 and T-11 show respectively the responses observed with a pulse frequency of 10 to 15 per sec. and 30 per sec. The meaning of the groups of letters is the same as in Fig. 2 & 3, with the following exceptions: LEF-L, left extension of the fore-leg; LFF-L, flexion of the fore-leg; LAdF-L, adduction of the fore-leg; and (T & C), tonus and clonus during the stimulation.

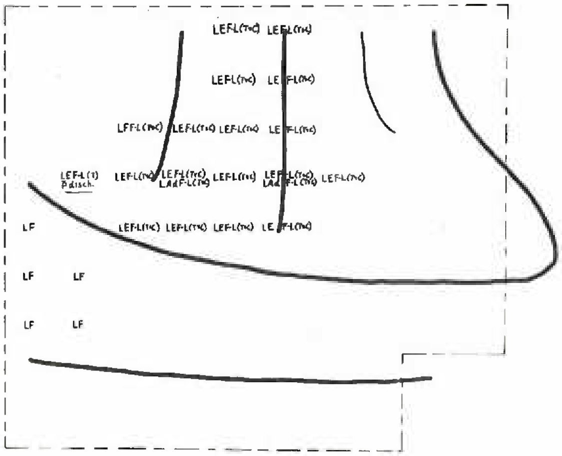


S-1 0-30K.Ohms

DOG # 10 9/25/47



T-7



T-11

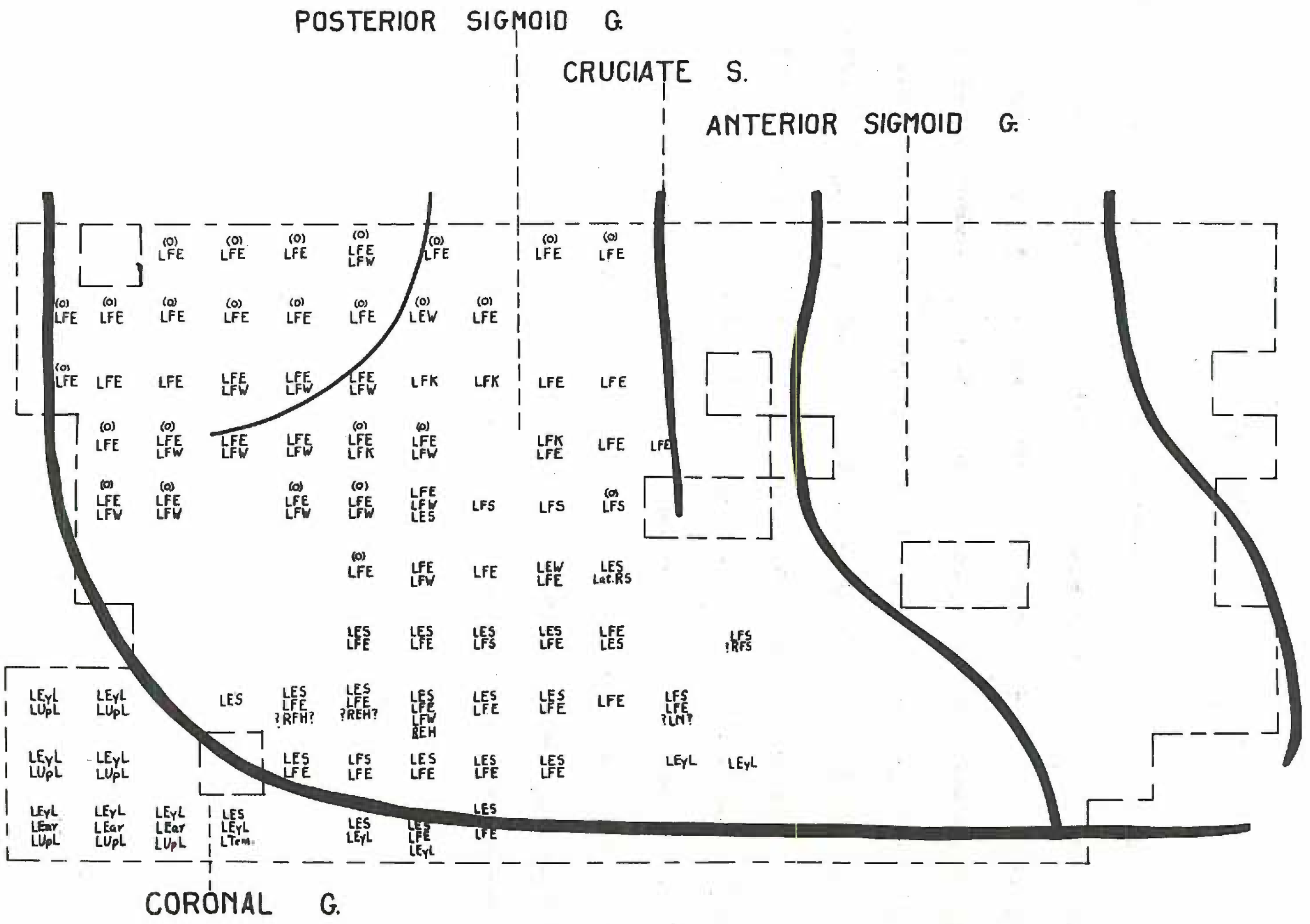
0-30K. Ohms

DOG # 10

9/25/47

FIGURE 7

A map of the cortical region explored for skeletal muscle response on dog #13. The cortex was stimulated with a square wave electrical pulse at a frequency of one per sec. with a pulse duration of 15 msec. The penetrating electrode was placed in the cortex to a depth of approximately 1/8th of an inch, while the adjacent electrode was allowed to rest on the surface of the brain. The meaning of the groups of letters is the same as in Fig. 2 & 3, with the following exceptions and additions: Lat.RS, lateral rotation of the shoulder; RFH, right flexion of the hip; RFS, right flexion of the shoulder; LeyL, eyelid contractions; LUpL, upper lip contractions; LEar, ear contractions; LTem., contractions of the temporalis muscle; and (0) contraction was only very occasionally observed and probably should not have been included in the map.



BIPOLAR ELECTRODES - 1 PENETRATING CORTEX + 1 ON SURFACE

DOG# 13 40-OK.Ohms 10/30/47

——— = 1 mm.

FIGURE 8

Kymograms of cortically induced responses of the biceps and triceps muscles of dog #18. The upper line in all of the kymograms in this and succeeding figures shows the response of the triceps muscle, while the response of the biceps muscle is shown on the second line. The third line is that of the signal marker which depicts the application of "suppressor" and "motor" stimuli to the cortex, and the fourth line shows the time signal which was marking at one second intervals. All of the individual kymograms must be read from right to left as it was necessary to arrange the recording device so that the paper was running in the wrong direction. The biceps response was induced by a square wave electrical pulse at a frequency of one per sec. and a pulse duration of 15 msec.

A. A 7 m.a. 60 cycle a.c. stimulus was applied to the coronal gyrus directly opposite the posterior sigmoid gyrus for a period of 12 sec. Notice the initial facilitation of the response followed by a period of extinction and rebound. (The recording pens were not alined exactly so the facilitation of the biceps appears about one second prior to the deflection of the signal marker).

B. The first kymogram, marked B, was taken at 11:05 during the application of a 7 m.a. 60 cycle a.c. stimulus to the gyrus proreus. The succeeding kymograms were taken at the stated intervals and illustrate the fluctuation of the biceps response.

C. The kymogram was taken at 11:26 immediately after the last one of B. For no apparent reason there was a rapid return of the response with failitation and greatly increased tonus in the muscle.

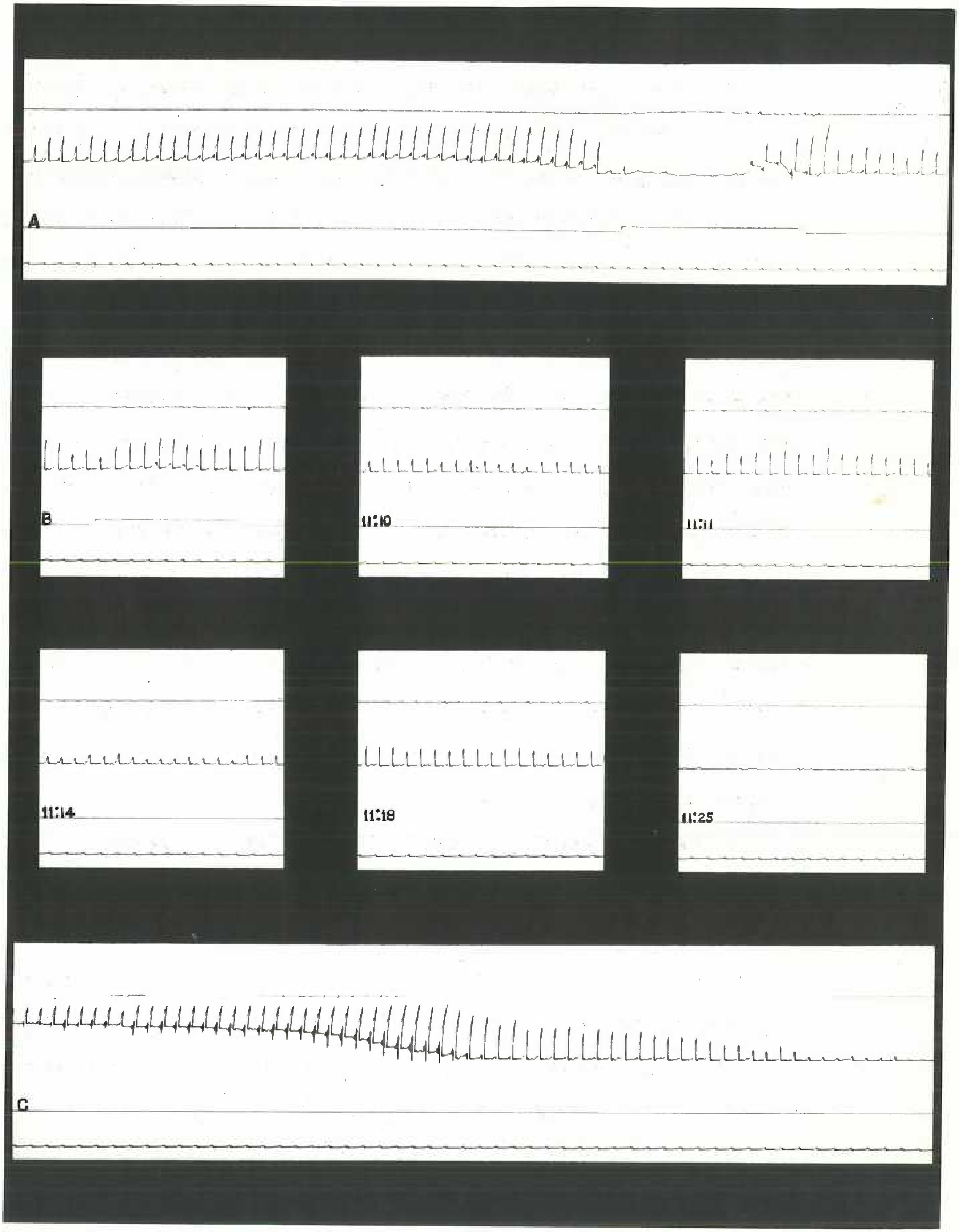
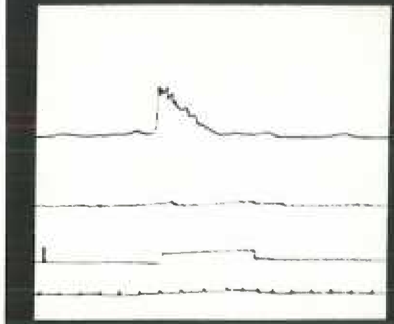

A
B
11:10
11:11
11:14
11:18
11:25
C

FIGURE 9

Kymograms of the triceps and biceps responses of dog #20. The triceps response is on the upper line. The cerebral motor point for the triceps muscle was stimulated at one minute intervals for periods of about 5 sec., as indicated by the signal marker, with square wave electrical pulses of a duration of 15 msec. and a pulse frequency of 30 per sec. The kymograms from 1 to 12 were taken at successive one minute intervals from 10:52 to 11:03 p.m. The last "suppressor" stimulus had been applied 37 minutes previously. Notice the three minute period of almost complete absence of response.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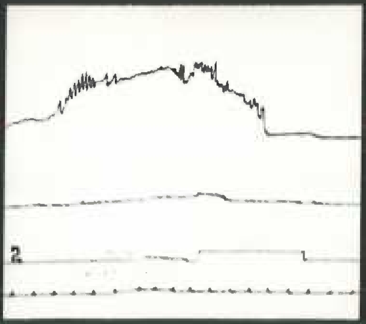
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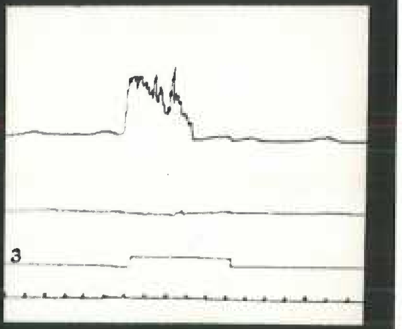
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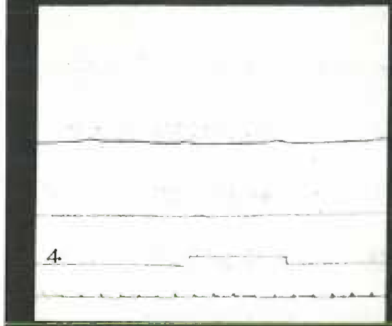
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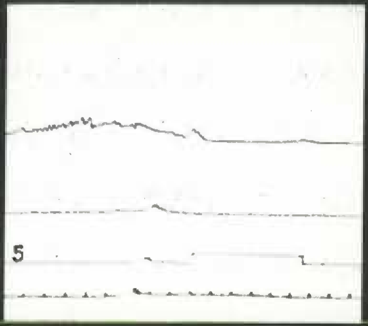
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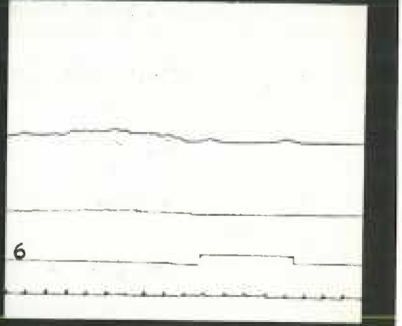
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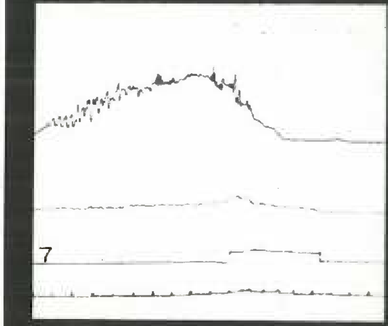
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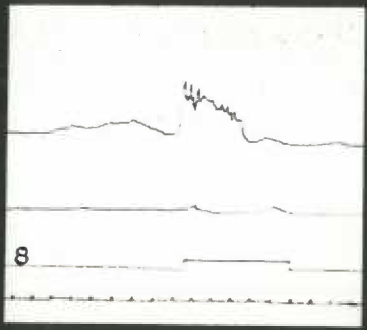
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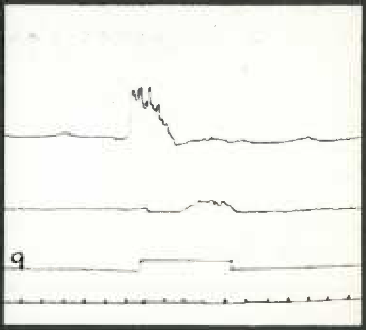
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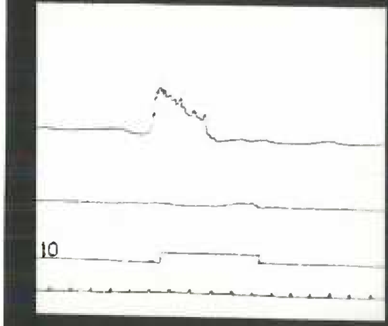
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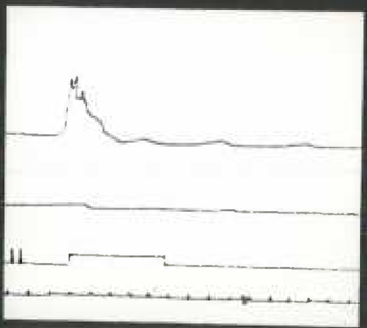
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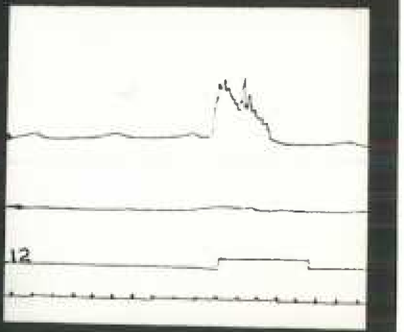
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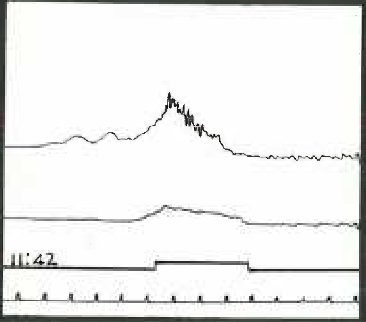
FIGURE 10

Kymograms of the triceps and biceps responses of dog #32. The triceps response is on the upper line. The motor point for the muscles was stimulated with square wave electrical pulses with a duration of 15 msec. and at a pulse frequency of 30 per sec. for a period of about 3 sec. at one minute intervals. A "suppressor" stimulus was applied to a point on the gyrus proreus for 5 sec. at 11:45. The parameters of the "suppressor" stimulus were exactly the same as those used for stimulating the motor cortex except that the resistance on the output of the stimulator was decreased. The response was decreased or absent for a period of 21 minutes.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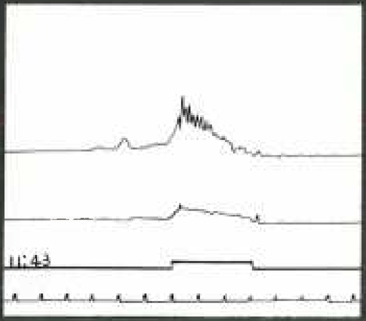
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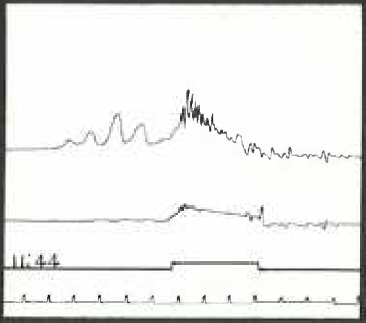
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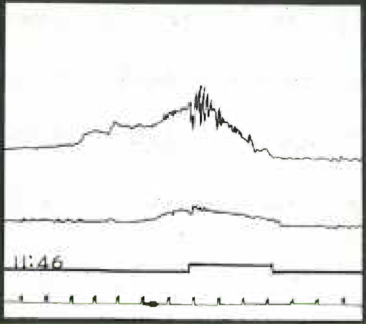
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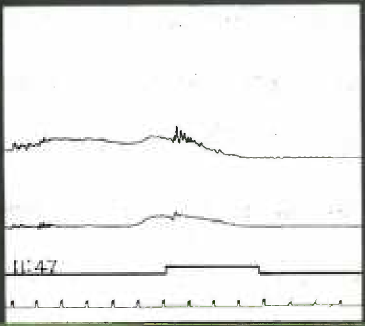
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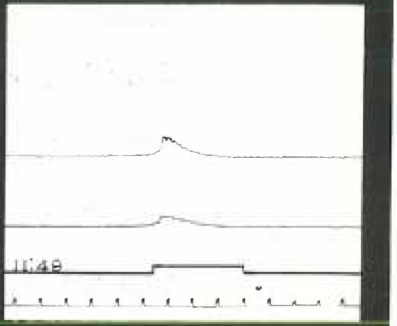
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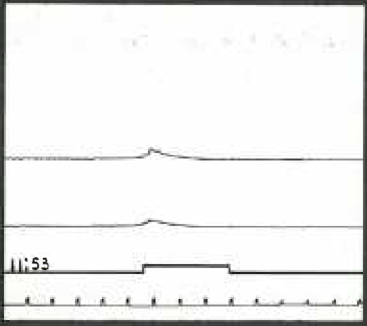
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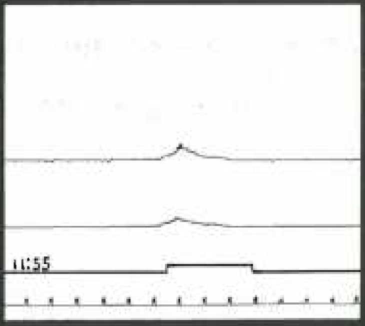
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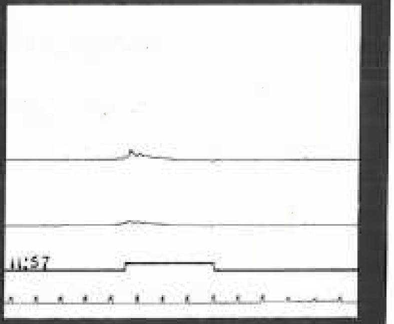
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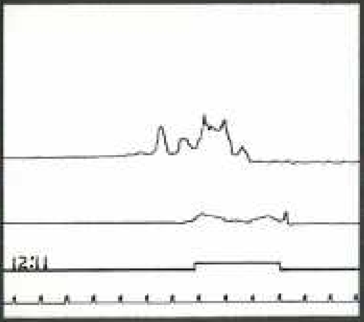
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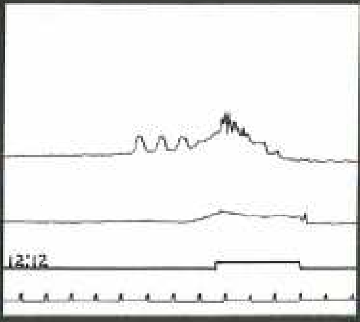
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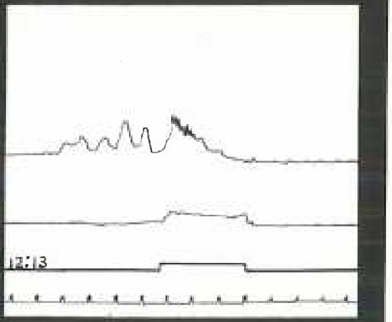
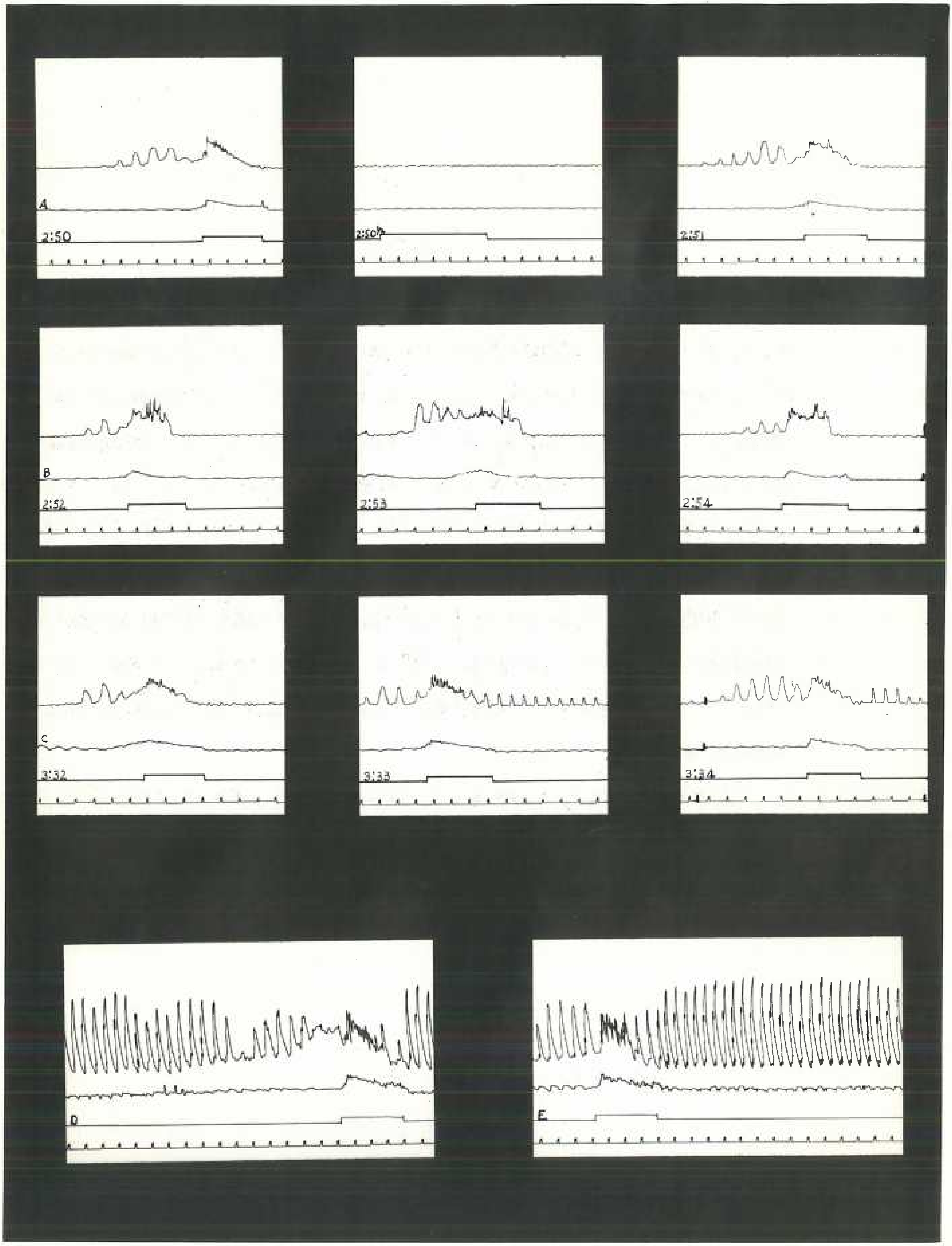

12:13

FIGURE 11

Kymograms of the triceps and biceps muscle responses of dog #32. The parameters of stimulation were exactly the same as those used and described for Fig. 10. A. to C. consists of sample kymograms taken at the stated times before, during and after the application of a "suppressor" stimulus to the identical point on the gyrus proreus from which the "suppression" for Fig. 10 was elicited. At 2:50-1/2 the signal marker indicates the period of application of the "suppressor" stimulus. It should be noted that there was no decrease in the amplitude of the contractions over a 44 minute period; whereas in Fig. 10 a 2/minute period was shown in which the contractions were almost absent.

D. & E. are sample kymograms taken from dog #32 showing spontaneous contractions of large amplitude. Notice that the spontaneous twitches disappeared during the application of the stimulus to the motor cortex.


A
2:50
2:50½
2:51
B
2:52
2:53
2:54
C
3:32
3:33
3:34
D
E