

METHODS FOR TEMPORARY AND REVERSIBLE PARALYSIS
OF LOCAL AREAS OF THE CEREBRAL CORTEX

by

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PREFACE

I am deeply indebted to Dr. Wilder Penfield for his assistance in many ways. Only Fellows of the Montreal Neurological Institute can fully appreciate how much help Dr. Penfield can be. Dr. Herbert Jasper was also helpful in obtaining financial aid and, in spite of his over-crowded days, found time to direct my work to a successful conclusion. Dr. Theodore Rasmussen kindly directed the work on local pressure until his departure to the University of Chicago. Dr. O.O. Stoland of the University of Kansas should be remembered for his encouragement and for his loan of animals and equipment for preliminary work on anodal block of peripheral nerve. Mr. Leslie Geddes, with his knowledge of mechanics and electronics, directed the making of most of the equipment used. Miss Mary Roach, R.N., assisted with surgery and animal experiments, and Mr. Charles Stephen care for the animals before and after surgery. Mrs. Elinor Christie was a great help in putting the thesis together and in typing it. Photography was done by Mr. Charles Hodge. In summary, I am indebted to the Montreal Neurological Institute, McGill University, the University of Kansas and the National Research Council (U.S.) for making possible this investigation.

TABLE OF CONTENTS

PREFACE	i
INTRODUCTION	1
<u>PART I.</u> <u>ANODAL POLARIZATION</u>	4
Review of the Literature	6
Methods	44
(See details included in results)	
Results	73
Discussion	94
Conclusions	103
<u>PART II.</u> <u>LOCAL PRESSURE</u>	104
Review of the Literature	105
Methods	111
Results	119
Discussion	139
Conclusions	142
GENERAL SUMMARY	143
BIBLIOGRAPHY	

INTRODUCTION

The primary purpose of this investigation is to produce a method whereby the cerebral cortex of man may be rendered temporarily nonfunctional in any focal area desired. It is felt that by such a method the effects of removal of an area may be determined in advance, and thus important areas such as hand and speech may be avoided, yet approached more closely with safety than is possible at present. It may also be possible to distinguish the true epileptic focus from a referred or transmitted epileptic pattern. Since such a method would cause temporary arrest of all activity and function in the given area, it would be useful in the prevention of full development to a generalized seizure when one has been initiated by cortical stimulation in man. Such initiated seizures almost invariably start as a localized involvement of one extremity, the face, or the like, and if this area of firing cortex could be rendered inactive, the activity could not spread to other areas and the subcortical areas. It may be useful in testing the effect of the temporary arrest of an area of cortex under different circumstances, such as mental arithmetic, writing, speaking, identifying objects, complex motor movements, etc., in other words, temporary ablation experiments in the human.

The requirements of a method to be used on humans are quite strict. First, of course, it must be safe; the function

of the area must return completely and permanently to its original state. It must be safe to repeat the application several times, if necessary, in the same area. Since time is a big factor in the routine operation for seizures in the human, the paralysis must be quick in onset (a matter of seconds) and there must be quick and complete return of function when the agent is removed (also in a matter of seconds). Not least in the requirements is that it must be consistent in its action or it would only be confusing to the surgeon. Again, because of the limited time during the operating procedure, it must be quickly and easily applied.

The two methods investigated are, first the flow of a constant current near the anode (anodal block) which will probably meet all the requirements; and secondly, localized pressure which produces a localized increase in threshold to electrical stimulation and suppression of electrical activity, but the return time is longer than desired and somewhat variable. There are also suggestions that the local pressure is not entirely free of damaging effects.

The fundamental points not investigated which apply mainly to the anodal arrest are the pH at the cortex, the temperature at the cortex-electrode junction, the presence of organic or inorganic substances at the cortical surface, and the rate of blood flow in pial vessels.

Likely methods not investigated are cold, which was not investigated because of insufficient time and because anodal arrest proved so successful, and local chemical anesthetics of which there is none known which has a duration as short as required.

PART I

ANODAL POLARIZATION

There were several very good reasons for trying the method of anodal polarization. Its effectiveness at producing local anesthesia of a segment of peripheral nerve (anodal block) has been established over a period of almost one hundred years. When the current is judiciously employed to cause nerve block it is harmless to the nerve and may be repeated many times without damage to the nerve. It meets all the other requirements for use: short duration, short period of induction, consistency, and ease of application, when used on peripheral nerve. There is a possibility that anodal polarization may be the method of production of physiological inhibition in the central nervous system. Thus knowledge gained from studies of anodal arrest of function may be applicable to physiological inhibition. The magnitude and duration of the agent can be controlled with the greatest of precision. Finally, there are certain similarities between the behavior of the motor cortex and peripheral nerve which lead one to believe that the same mechanism (anodal polarization) may be effective in both.

REVIEW OF THE LITERATURE

There are two lines of investigation which have bearing upon the problem of anesthesia by electricity, They are local anesthesia of a segment or exposed peripheral nerve (anodal block), and electronarcosis or general anesthesia of the intact animal. The former is thoroughly investigated and established as a readily reproducible, well controlled method of obtaining a reversible nerve block, which closely resembles chemical nerve block in many respects but has an extremely short recovery period. The latter is not completely accepted and has little resemblance to chemical anesthesia.

Anodal block or anelectrotonus was described as early as 1859 by Pfluger in his monograph Physiologie des Electrotonus, and he formulated laws of electrotonus which are essentially true today though much information about the process has been added. Pfluger found that the passage of a constant galvanic current through a segment of nerve caused temporary reversible changes in the nerve whether the nerve was fired or not. The changes at the anode were different from the changes at the cathode, in fact they were quite opposite in effect. A curve of these changes (Fig. 1) is contained in many textbooks.

The curve may be obtained experimentally by applying a constant current to a nerve by two electrodes placed in

Figure 1 A

Diagram showing the flow of current in and around a single nerve fiber (Bard, 1941).

Figure 1 B

Changes in threshold following application of direct current stimulus to a nerve. Cathodic current is started at A and stopped at B; anodic current is started at C and stopped at D. Threshold at any instant is measured as voltage of a brief test shock just adequate to cause excitation. Normal threshold is at N, and excitation takes place when threshold falls to zero. (Curtis and Cole, 1944).

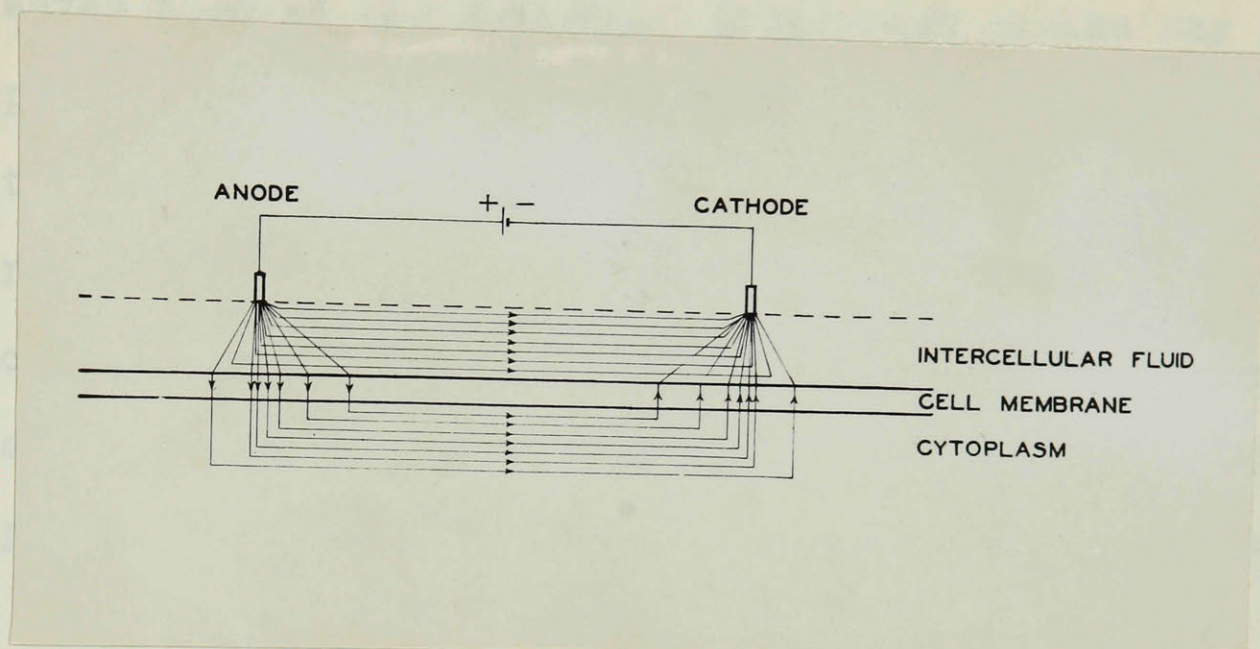


Figure 1 A

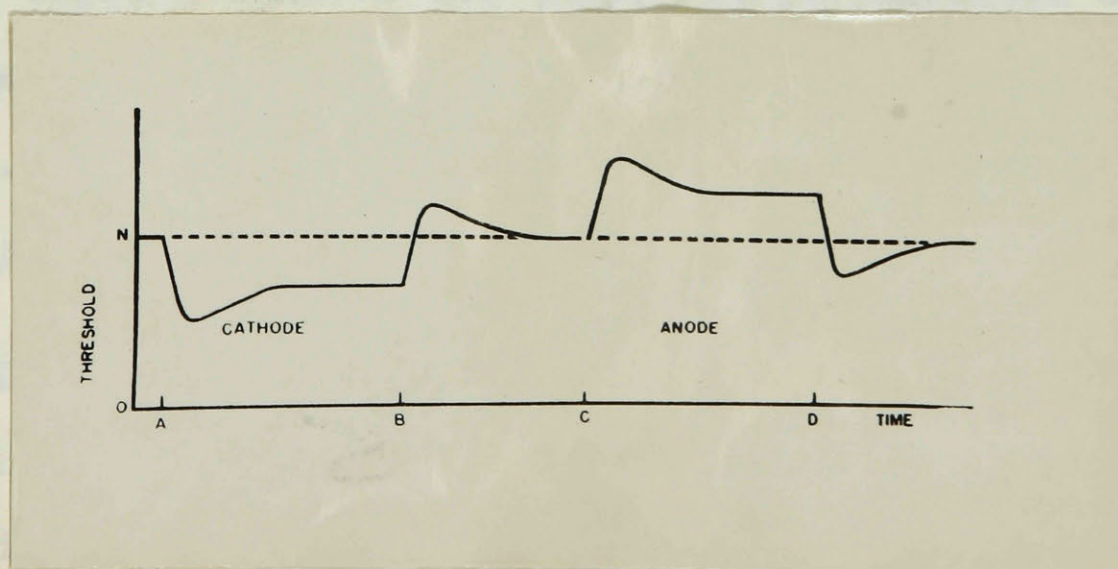


Figure 1 B

such a way that current enters the nerve fibers at the anode and leaves them at the cathode. Brief test shocks may then be applied by two additional electrodes, one of which is situated at the same point on the nerve as one of the other electrodes. The test shocks are applied at a certain time after application of the constant current, and the magnitude of the test shock just necessary to cause excitation is determined. This procedure is repeated as many times as desired, and from these data the threshold curve may be plotted.

One reason electrotonus has been so intensively studied is that some of the most important facts of electrical stimulation are represented by these curves and thus a better understanding of nerve function has been gained (Curtis and Cole, 1944).

1. Figure 1 shows that as long as a constant current passes through a nerve the threshold is decreased at the cathode (catelectrotonus) and increased at the anode (anelectrotonus). If the anodal current is made strong enough, it may block passage of a nerve impulse.

2. If the current in Figure 1 is made strong enough, the threshold will fall to zero (excitation) at the cathode following the start of the current ("make" excitation), and, if made still stronger, will fall to zero at the anode after the break of the current ("break" excitation).

3. At the cathode (Fig. 1) the threshold, after reaching a minimum, tends to return to its resting value. This phenomenon is known as the decay of electrotonus, or accommodation. If the current is increased gradually instead of being applied abruptly, accommodation, which acts relatively slowly, will tend to prevent the attainment of excitation. Thus, slowly increasing currents may be passed through a nerve and attain very high values without eliciting a response, provided the nerve exhibits sufficient accommodation.

An addition to Pfluger's laws of electrotonus (Bishop and Erlanger, 1926) is that there is a decrease of amplitude under the cathode, and an increase under the anode of the polarizing current if the current is not strong. Even with strong currents which reduce the amplitude under the anode the amplitude at either side of the anodal area may still be increased.

In the explanation of the above, the oversimplified membrane hypothesis of nerve transmission is resorted to. The nerve cell membrane is considered to behave like an electrical condenser, the charge being maintained by energy obtained from the chemical constituents of the protoplasm. This resting potential, with the positive charge on the outside, is about 50 millivolts. The diagrams in Figure 2 represent this situation. A stimulus applied to the nerve increases the permeability of the membrane at that point and the charge

Figure 2 A

Current flow in and around inactive end (left) and region of breakdown during propagation of an impulse in a single nerve fiber, according to membrane hypothesis. Shaded areas, regions of breakdown. Graph shows positive potential measured along outside of membrane, V , relative to that of cytoplasm, V_0 arrow indicates direction of propagation (From Bard, 1941).

Figure 2 B

Propagation of the nerve impulse by current flow from active to inactive nerve. The process is continuous once started for the potential difference remains but in a section of nerve farther away from the original point of stimulation. The protoplasm restores the resting potential again in a short time after the impulse has passed. During the short period of time the nerve is in the depolarized state the nerve is in the refractory state. (From Best and Taylor, 3rd ed.).

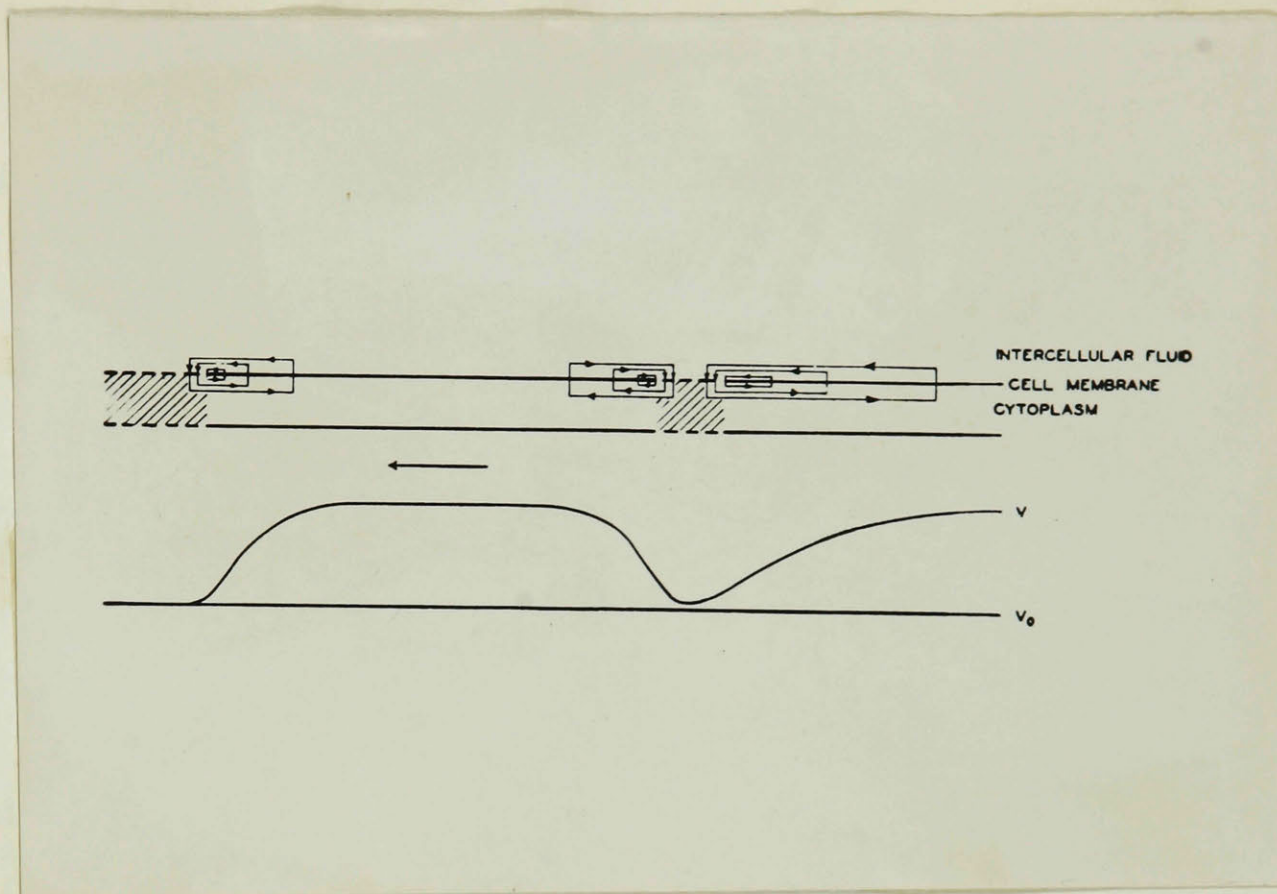


Figure 2 A

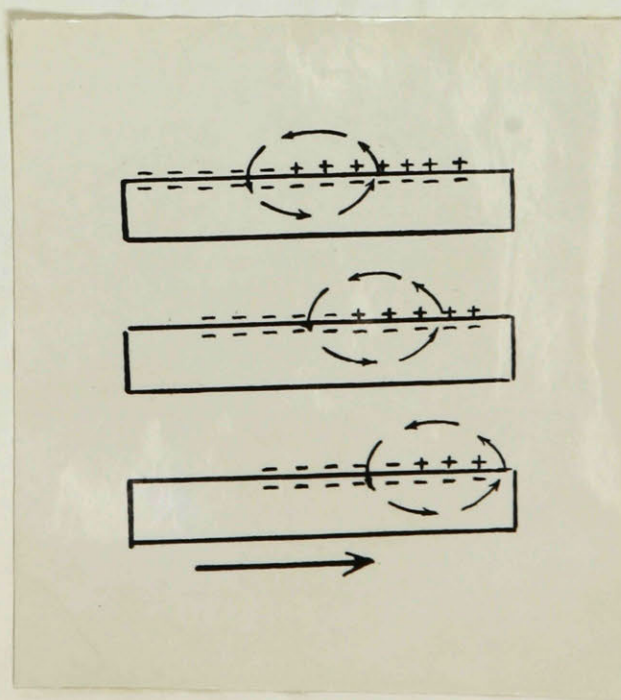


Figure 2 B

Figure 2 C

Circuit diagram of single nerve fiber. R_1 , external resistance; R_2 , internal resistance; R_3 , membrane resistance; C , membrane capacity; L , membrane inductance; E , membrane e.m.f. (From Curtis and Cole, 1944). E maintains a potential of about 50 microvolts. L equals 0.2 henrys per cm^2 . R_3 equals 1000 ohms per cm^2 . C equals 1 microfarad per cm^2 .

At rest, all the condensers are charged, but there is no current flow because all elements are at the same potential. If for any reason the membrane resistance and e.m.f. in element A are drastically reduced in magnitude, the condenser in this element will of course immediately discharge, and also the condenser in element B will discharge through the external (R_1) and internal (R_2) resistances and element A. The condenser in element C will also discharge, but not as rapidly because the resistances are greater. When the condenser in element B has discharged by some critical amount, then the resistance R_3 and e.m.f. E in this element will suddenly decrease. The condenser of element C can now discharge through element B, and thus discharge more vigorously and in turn break down. In this way a wave of breakdown is propagated along the nerve. Up to the instant of breakdown 95% of the membrane current flows through the capacity arm of the element; membrane e.m.f. is protected from sudden changes in current by the inductance.

collapses. This portion is relatively negative to the inactive portion which is still polarized and thus a current flows because of this potential difference, thus collapsing a new area. After the impulse has passed, the membrane is actively charged again by the protoplasm of the nerve and this a.s.f. is maintained until another impulse passes.

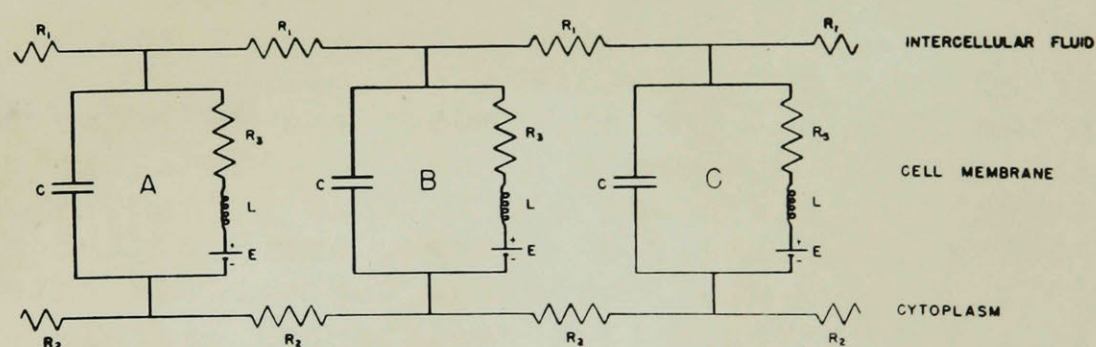


Figure 2 C

collapses. This portion is relatively negative to the inactive portion which is still polarized and thus a current flows because of this potential difference, thus collapsing a new area. After the impulse has passed, the membrane is actively charged again by the protoplasm of the nerve and this e.m.f. is maintained until another impulse passes.

Support for the membrane hypothesis is given by experiments of Lillie (1922) who prepared a metal model which behaves in a manner somewhat comparable to that of nerve. More important, the membrane potential, membrane resistance, and even the impedance, have all been measured in the giant squid axone (Curtis and Cole, 1940) (Fig. 2 C).

The following is an explanation, in more general terms, of the mechanisms concerned in nerve function and polarization in which Bishop and Erlanger (1926) caution against a too naive expression of the "membrane theory".

"By the concept of polarization used here, we mean to designate not merely the passive concentration of ions at an inert membrane, analogous to the concentrations of electrons in a condenser plate. Nerve is certainly not such a system. Rather we have in mind the altered state of reactivity induced, under a potential change, in active or potentially active substances which may be at or near a polarizable surface. Polarization of such a surface bounding a reactive medium whose ions carry the current will obviously result in an

altered equilibrium at the surface, or any reaction into which such ions may enter, due to concentration of the ions at the surface and to the potential drop there. Conversely, any reaction involving the ions producing a state of polarization will alter its potential. Since nerve maintains a potential by its own activity, at its own surface, any external alteration of this potential may be expected to alter the reactions of the nerve until a new state of equilibrium is attained. The nerve 'responds' to polarization perhaps in much the same way as it responds to stimulation, without a sudden change, however, that appears as an excitation.

"If the rise and the fall of potential as a response to stimulation are signs of distinct processes, which, however they may be related, may be affected differentially, then the resting or unexcited condition of nerve might be looked upon as a condition of equilibrium between them, which may be affected by operation of either process. The action potential would then be the external sign of the initiation, or perhaps the acceleration, of first one of these processes and then the other, while polarization may be looked upon as a more or less persistent shift in the equilibrium condition. The fact that nerve with excitation gives off an increased amount of CO_2 is consistent with the idea that excitation may be only an accentuation of some phase of its normal resting activity. The fact that it maintains its own polarization during rest may be an expression of the same function that causes restoration of potential after excitation, or after polarization.

"If we may further look upon the refractory state as the absence, relative or complete, of some material necessary for excitation, and stimulation as the initiation or acceleration of a reaction in this material when present, it will serve to correlate the different effects of polarization in the unexcited and in refractory nerve. We may assume for this argument that negative potential at the nerve surface tends to cause this reaction to take place, and might lower the threshold by summing its effect with a superposed stimulus. But it might also tend to hinder or prevent the return of irritability after excitation by maintaining a low rate of reaction in the nerve, as the reactive material was produced again. If the nerve were reacting at a low rate, but constantly, under a cathodal polarization, it would be able to react less violently when specifically stimulated. The external potential sign of this steady induced reaction would be masked by the applied negative potential itself. The lowered amplitude of cathodally polarized nerve would be due to the decreased amount of material available for the reaction, together with the cathodal effect on some process of potential restoration, possibly disposal of the first reaction products. The reverse of this hypothesis would apply to anodal effects."

Lorente de No' (1947) has conducted experiments in controlled atmosphere. In the presence of 95% O_2 and 5% CO_2 , "the catelectrotonus as well as the anelectrotonus exhibited two distinct components, a 'fast' component that appeared as

a discontinuity of the deflection at the make and at the break of the applied current and a 'slow' component that was established during the flow of the applied current and decayed after the end of the latter at an exceedingly low rate. The height of the electrotonic potential was not proportional to the applied current and in addition the heights of the catelectrotonus and the anelectrotonus were different. However, if consideration is given to the amplification at which the individual records were obtained, it is found that the fast components were practically equal to the total height of the electrotonic potential that had been produced previously by the same current. Therefore, the slow components represent an additional polarization potential that was produced by the current after the presence of CO₂ in the atmosphere and had resulted in a change in the properties of the nerve fibers. This additional component of the electrotonus is the slow electrotonus."

Lorente de Nó feels that he has established that the fast electrotonus is referable in part to the establishment by the applied current of a potential difference across a layer of poorly conducting material, and that this part of the fast electrotonus is not immediately related to the resting membrane potential.

In regard to the slow electrotonus, he states that the situation can be defined with greater precision. The slow electrotonus consists of a change in the value of the L fraction of the resting membrane potential. He defines the

L fraction "as that fraction of the membrane potential which is restored at a l w rate after the passage of the nerve impulse and consequently appears as negative after-potential when the nerve is caused to conduct a rhythmic train of impulses at frequenceis between 40 and 120 impulses per second". When a cathodal current is applied to the nerve the decrease of the L fraction of the membrane potential is recorded as slow catelectrotonus and similarly the increase of the L fraction that is brought about by an anodal current is recorded as slow anelectrotonus.

Finally, says Lorente de Nó, in the study of the slow component an important circumstance must be taken into account. If the applied currents are small, slow catelectrotonus and slow anelectrotonus are nearly mirror images of one another. However, if the applied currents are large, the slow anelectrotonus will become higher than the catelectrotonus because the anodal current has the ability to increase the L fraction of the membrane potential. In other words, with currents of moderate magnitude and duration the height of the slow catelectrotonus is limited by the circumstance that the electrotonic potential cannot exceed the value of the L fraction of the membrane potential; since no limit of this kind exists for the magnitude of slow anelectrotonus, the height of the slow anelectrotonus may become several times greater than that of the slow catelectrotonus.

Schmitz and Schaefer (1933) indicate that changes at the anode reach an equilibrium in about 0.5 seconds, but Erlanger and Blair (1940) found that as time progressed the voltage required decreased in a smooth curve. Eventually, however, the curve begins to run almost horizontally. Thus after two minutes, 75 per cent of the original voltage was needed, after 20 minutes 50 per cent, and after an hour only about 25 per cent was needed. These findings do not, of course, fit into the curve of the earlier workers.

The relief of anodal block by rhythmic activity of the nerve was reported by Erlanger and Blair (1940) and confirmed by Lorente de Nó (1947). If the anodal block is just adequate to block an impulse, a volley of impulses may break down the block and it will not be restored again until after the train of testing shocks has passed.

The anodal current produces irreversible damage to normal nerve only when it is very large and is maintained for a long period of time. Anodal currents that are barely sufficient to produce a block do not damage nerve even if maintained over an exceedingly long period, e.g., Lorente de Nó states that Bethe quotes observations made by Wedensky of the rapid restoration of excitability after the end of a current that had maintained an anodal block for several hours. This was near the turn of the century. In 1940 Erlanger and Blair report similar observations.

Ether enhances the ability of anodal current but also renders the nerve more susceptible to irreversible damage.

The lack of sodium ions in the tissue near the anode also enhances the block and also tends to make the block less reversible (Lorente de No', 1947).

During the flow of a constant current, Krusen (1941) states: "The sodium chloride in the tissues is broken up, the electropositive sodium ions migrate toward the negative pole, and the electronegative chlorine ions toward the positive pole. When these ions reach the poles, they lose their electric charges and become free atoms. The chlorine atoms react chemically with the water in the tissues to form hydrochloric acid at the positive pole. At the same time, during this chemical reaction, oxygen is liberated. In a similar manner, the sodium atoms react chemically with the water in the tissues, at the negative pole, to form an alkali, sodium hydroxide. Hydrogen is liberated during this chemical reaction."

Thus at the positive pole (Kovacs, 1945) there is an acid reaction and coagulation of albumen with a tendency to hardening of the tissues. At the negative pole there is an alkaline reaction, with liquefaction of albumen and a tendency to liquefy the tissues.

The control of anodal block is quite remarkable, as evidenced by the work of Kuffler and Gerard (1947) and Kuffler, Laporte and Ransmeier (1947). In the study of the small-nerve motor system to skeletal muscle, a current block was found to be most convenient, fully reversible, and could be maintained for about 10 minutes at a time and repeated at will. The

current was applied through Ag-AgCl wick-electrodes and regulated by a rheostat. Responses below the block were observed in any desired muscle and it was found that preparations obtained by block tend to become progressive, so that the current is best gradually diminished once the large nerve fibers are blocked leaving only the small nerve fibers firing. Not infrequently a graded increase of current blocks all nerve fibers practically simultaneously, when tested by stimulation above the block. In such cases, a satisfactory differential block was obtained by the following procedure, sometimes repeated several times. The current was reversed, maintained at blocking strength about one minute, reversed again and gradually increased until the large fibers only were blocked. The electrical activity supplied a good control of the progress and extent of the polarization block and aided the repetition of a given degree of block.

It is of interest that muscle also responds to anodal block. The frog's heart may be rendered locally incapable of contraction by the application of an anodal current (Lillie, 1913), being polarized in the same manner as nervous tissue.

There are similarities between brain and nerve such as the following. Dusser de Barenne and McCulloch (1939) in studying facilitation and extinction in the central nervous system found voltage drifts which resemble in many points those observed in peripheral nerve and in the spinal cord, but are usually much larger and more prolonged. "Points of

resemblance are: a) the sequence, i.e., negativity followed by positivity; b) the susceptibility to various conditions such as temperature, poor local blood supply or poor general circulation, partial asphyxia. In our experiments on the cortex the depth of Dial-narcosis has been shown to be also of great importance, though we are not in a position to exclude entirely some element of lesser ventilation, since the animal breathed spontaneously. Finally these voltage drifts are augmented with increase of the number of neurones discharged and with the number of times they are discharged. This resemblance is not surprising if one considers the great number of nerve fibers in the cortex.

"But irrespective of whether the processes underlying these voltage drifts are the same in the cortex, cord and nerve, their association with the changes in threshold to repetitive stimulation is always the same; negativity is associated with increased responsiveness, positivity with decreased responsiveness. It is of interest to point out that while the manner of picking up these voltage drifts on the cortex (without injury) is entirely different from that of picking up the after-potentials in an excised peripheral nerve (from longitudinal and cut surface) both are explicable in terms of the membrane theory, for in both, negativity is associated with a decrease, and positivity with an increase of the 'membrane potential' in cells of fibers that have been discharged; the essential condition being that one electrode is at the site of this

discharge, the other at an unaffected site, be it a remote focus in the cortex or the killed end of a peripheral nerve."

The slow voltage variations accompanying the spreading depression of activity (Leao, 1947) may be similar. Leao, however, measured the potential with one electrode on the cortex and one on the scalp, instead of both on the cortex as was done by Dusser de Barenne and McCulloch.

A constant current has been used locally in the brain with results which suggest that the brain responds to anodal and cathodal currents in much the same way as do muscle and nerve. Marinesco, Sager and Kreindler (1929) state that anodal polarization in the tubero-infundibular region facilitated sleep, and cathodal polarization caused excitement. Hess (1932) implanted micro-electrodes in the same region and produced sleep which he considered to be due to stimulation of the center. Harrison (1940) carried out a similar investigation with similar results as those obtained by Marinesco, Sager and Kreindler. A constant direct current and a non-stimulation current described by Hess (1932) were both effective. The nonstimulating current was an interrupted direct current with a slowly rising front. In Harrison's discussion, however, he states that somnolence is due to destruction and depression. In his experiments short applications of current caused transient somnolence and small lesions, longer caused more enduring somnolence and larger lesions. None of the cats treated with a stimulating current became somnolent.

One of the basic principles of the use of electrical currents for any purpose in the nervous system should be mentioned here. As brought out by Curtis and Cole (1944), Harrison, Magoun and Ranson (1938), and Silver and Gerard (1941), it is only that fraction of the current which flows through the nerve or nerve cell body which is effective in changing its threshold, and if the excitable tissue is buried deep in other tissue, the effective fraction of the current may be minute. Again if both electrodes are on the surface and the structures to be influenced are below the surface the effective portion of the current is very small. (An example of the latter is the influencing of the pial-ventricular potential by polarizing along the anteroposterior axis on the surface of the hemisphere, as will be mentioned below.) This principle is often overlooked when the effects of an anodal current upon peripheral nerve are compared with the effects of the same current upon the brain or spinal cord. Silver and Gerard (1941) have determined that, with one electrode of a constant current in the mouth of an animal, and the other in the rectum, 1.4 per cent of the current flowing through the animal flows through the cord.

Gerard and Libet (1940) using the isolated frog brain found that the olfactory bulb gives an electrical beat, at six per second, larger and more regular than before removal from the frog. The spontaneous potentials of the bulbs are depressed or abolished during the flow of a constant current

of as little as 0.06 milliamperes, when the cathode is on the bulb and the anode on the occipital pole. Immediately following interruption of the current, the bulb shows a greatly exaggerated rebound over-activity, and it is some minutes before the rhythm settles down to the normal. With the anode on the bulb the picture is reversed, potentials being greatly increased in amplitude and frequency while the current flows, and disappearing entirely when it is terminated.

With a similar preparation the same workers found that caffeine would start large waves which traveled at about 6 cm. per second mainly from the anterior to the posterior pole of the cerebral hemispheres. Here again with the cathode on the anterior pole, the amplitude, frequency, and rate of travel were inhibited. With the anode on the anterior pole there was an increase.

Libet and Gerard (1941) continued their investigations using the isolated frog brain and discovered a potential gradient between the pial surface and the ventricular surface which is on an average 2 millivolts. The pia is negative to the ventricular surface. A current of 0.05 milliamperes passed for ten seconds through the hemisphere wall from the ventricular surface to the pial surface will increase the gradient from the normal 2 millivolts up to 15 millivolts. This drops rapidly at first and then more slowly, but even after 6 to 10 minutes the potential is 3 to 5 millivolts and may not return to the original value of 2 millivolts in another half hour. After a similar polarization in the reverse

direction the immediate voltage may be great, the pial surface now positive to the ventricular, but the fall to 3 to 5 millivolts is achieved in 1 to 4 minutes and by 10 minutes the potential has passed through zero to 1 or more millivolts in the normal direction. This potential gradient could also be affected by polarizing along the anteroposterior axis but to a lesser degree, as the authors expected, for only that part of the current on its way to deeper tissue regions was effective perpendicular to the surface.

These investigators have developed an hypothesis which explains the propagation of electric waves along the brain in a manner analogous to the propagation of an impulse along a nerve fiber. The potential referred to above is considered equivalent to the membrane potential of nerve.

The ability to influence this potential that exists between the pial surface and the ventricular surface is considered the means of influencing the six per second spontaneous waves from the olfactory bulb and the travelling caffeine waves discussed above.

As a preliminary to this work on the hemisphere, Dubner and Gerard (1939) recorded impulses along the optic pathways, especially in the lateral geniculate, as a response to light flashes. The subject was the cat. By the use of a feeble constant current passed through the brain and concentrated toward a "different" needle electrode, placed just lateral

to the pick-up electrode, and enormously increased amplitude of potentials was noted. This increase was most marked when the anode was the different electrode, though in this case, the cathode also increased the amplitude but to a lesser extent. With a 30 second polarization the augmentation persisted for ten minutes.

Direct constant current has been used for over half a century as a physiotherapeutic aid, especially in Europe (Kovacs, 1945), and its dangers and methods of application have been discovered. First, never apply a metal pole, anode or cathode, in direct contact with the tissue. Always separate it by a thick layer of felt or some other material which is then saturated with normal saline. Secondly, see that there is even contact so that current density is not excessively high in one spot. Thirdly, again so that current density is not too high in one spot, the appropriate size of electrode must be used in keeping with the milliamperage to be passed. Fourthly, the cathode especially is uncomfortable to many patients, depending especially upon the part of the body to which it is applied and how large it is in relation to the milliamperage. It must always be moist enough to make a low resistance contact with the part to which it is applied.

Let us now go to the other line of investigation which has a bearing upon the problem of anesthesia by electricity. As was said earlier this comes under the head of electronarcosis or general anesthesia of the intact animal.

Leduc (1902) is cited by most investigators as one of the first persons to publish an attempt at electro-narcosis. He used interrupted direct current on animals and claimed fair results. It is of interest that he allowed it to be tried upon himself, but when he began to lose motor power the experiment was discontinued. He reported dimming of vision and decreased hearing.

For more history and references see Guallierotti, Martini and Marzorati (1942), Ross (1943), and Ivy and Barry (1932). Most investigators are not satisfied that the symptoms of electronarcosis have much in common with general anesthesia by chemical anesthetics.

As an example of the symptoms, the following is taken from Harreveld, Plesset, and Wiersma (1942). Von Harreveld and associates have done quite a complete investigation over a period of years and are in general agreement with Guallierotti, Martini and Marzorati, having repeated part of their work and added to it.

Symptoms of electronarcosis (en.) and usual method of production:

"The best way to produce en. is to apply a relatively strong current (eg. 60 cycle alternating of about 300 ma.) for about 30 sec. which is then decreased to a lower level. Immediately upon applying the strong current the animal falls to the ground, its legs in a flexed position. During the next few seconds, the extremities are almost toneless, but after 5 to 10 seconds a strong extensor spasm develops in the legs which are

stretched backward. There is complete respiratory arrest. This state then remains unchanged during the application of strong current. Often urination occurs and sometimes defecation.

"After 30 seconds the current is decreased to a lower level, the "narcosis level", at which sufficient respiration becomes possible; this level depends upon the type of current used (for 60 cycle ac it is 30 - 60 ma) on the individual reactions of the animals and probably upon the placement of the electrodes. The decrease of the current causes relaxation of the extensor spasm and appearance of clonic twitches. The first respiration will occur 50 to 70 sec. after the beginning of the experiment. If current is too strong the return of respiration is delayed and the current has to be diminished. After regular respiration has set in, the animal lies quietly and without tone although light clonic twitches may proceed for some minutes. The symptoms can subsequently develop in two directions, which will be described as the narcotic and the kinetic type of en.

"In the narcotic type, the animal remains quiet, with a slow and deep respiration, which is often labored because of the glottis contraction. The heart rate is slow, about one-half normal due to vagus stimulation. Except for respiratory movements and sometimes occasional clonic twitches,

the animal shows no spontaneous activity. Positive and negative supporting reactions are present when the legs are placed in the proper positions. However, when the animal is placed on its feet, the legs do not gain sufficient supporting tone and the animal falls down as in deep narcosis. The tail is without pronounced tone. In some dogs, tone in the abductor muscles of the thigh is observed. The head is extended dorsally and the eyes are closed tightly. The latter symptoms are probably caused by a direct stimulation of the muscles involved. Tendon reflexes like the knee jerk are not disturbed. No righting reflexes can be elicited. Punching or pricking the skin does not cause any reaction. Pressure on the eyeball through the closed eyelids is often without effect, but sometimes causes defecation or irregularities in the respiration. From time to time there is a bowel movement. The narcotic type of en. can be maintained for many hours.

"When the current is cut off during the narcotic type of en. the animal recovers in a few minutes, usually passing through a cataleptic state.

"The kinetic type of en. is of a much less quiet nature, and is characterized by frequent righting attempts which are usually unsuccessful and which can develop into violent and disordered hyperkinesis of head and extremities, often accompanied with yelling and whining. Between righting attempts the animal is quiet, but righting and hyperkinesis can be instigated by stimuli. The most effective is pressure

on the eyeball; also effective is moving the animal, thus stimulating the vestibular apparatus and perhaps other sensory systems. Some times skin stimuli are sufficient. The heart and respiration rate are higher than in the narcotic type, usually even higher than normal.

"Cutting the current during the kinetic type of en. is followed by immediate recovery without cataleptic symptoms. After awakening, the animal is often somewhat excited for a short time."

Sixty cycle alternating current was chosen after the following had been tried. Constant direct current with a 1.5 per cent ripple; unidirectional square wave pulses, with frequencies from 5 to 3000 per second and 0.08 to 2 milliseconds duration; and sinusoidal alternating current from 30 to 8000 cycles per second.

Up to 750 milliamperes was used to induce the dogs and the narcosis level was 30 to 125 milliamperes. With the direct current, 300 to 500 milliamperes was used for induction and then reduced to 150 to 200, but the same symptoms resulted and life was not endangered if the 500 milliamperage was continued throughout the narcosis. Above 500 milliamperes gives considerable heating power making it incompatible. The heat at 550 milliamperes is approximately 50 watts.

In all cases the electrodes were both on the head just behind the eyes.

Strength duration curves of electronarcosis produced with unidirectional square pulses showed that a duration of pulse from 0.5 to 3 milliseconds was equally effective, but as the pulse became shorter than 0.5 the milliamperage required increased very sharply from 150 milliamperes right up to 300 milliamperes. Strength frequency curves for alternating currents were about the same in a range from 50 to 500, and then sharply rose. Up to a frequency of 500, approximately 50 milliamperes were required, and at 8000 cycles per second, 400 milliamperes were required.

Globus, Harreveld and Wiersma (1943) studied the influence of electric current applications on the structures of the brain of the dog. Alternating current of frequencies from 45 to 10,000 was used. The dogs were induced with currents from 200 to 700 milliamperes for 30 seconds duration and then the current was reduced to 30 to 60 milliamperes, and continued for 15 to 75 minutes. Electrodes were padded and moistened with salt solution and electrode jelly on the skin. They were placed on the temples. The animals were sacrificed in different ways. In some cases, ether was injected into the lungs one or more days after the last electronarcosis. In others, death was caused by applying a very high current shortly after an electronarcosis (700 milliamperes up to 1000 milliamperes) for about 5 minutes. A careful gross and microscopic study of the brains of dogs subjected to electronarcosis disclosed no pathologic alterations.

Harreveld and Dendliker (1945), using rabbits, recorded blood pressure changes during electronarcosis. There was a sharp rise from around 90 mm.Hg. to 160 mm.Hg. during the 30 seconds of high milliamperage (150 milliamperes) and a fall to around 60 when the current was dropped to 30 milliamperes. After a period of about 2 minutes, the pressure had gone through another rise to around 150 and back to normal in a smooth curve, where it remained during the rest of the narcosis. Respiratory arrest or convulsions do not prevent the blood pressure changes. Curare does not alter the blood pressure changes. Crossed circulation experiments gave a slight rise in blood pressure in the other animal.

Harreveld, Tyler and Wiersma (1943) in a study of brain metabolism during electronarcosis concluded that electronarcosis does not cause large changes in brain metabolism and thus that electronarcosis differs greatly from chemical narcosis in its effect on O_2 consumption of the central nervous system.

Harreveld (1947) concluded that stimulation of inhibitory centers in the diencephalon is responsible for symptoms of electronarcosis. Excitatory centers below the diencephalon are also stimulated and thus there is a mixture of inhibition and excitation in the picture of electronarcosis as described above. In the narcotic type, the inhibition almost completely predominates. The cerebral hemispheres do not enter into the process actively. These conclusions were drawn from decerebrate, uni- and bi-lateral decorticate preparations, as well

as the intact animal. Observations on animals with one deafferented limb made it clear that in general no spinal reflex mechanism is involved in the production of the extensor contractions which are a part of the narcosis symptoms. He does not attempt to localize the inhibition in the diencephalon to one area as is done by Guallierotti, Martini and Marzorati (1942). This center, Guallierotti and his associates think, is probably identical with the center of Hess (1932). If this center alone were affected, the electronarcosis would show loss of muscle tone but no tonus or convulsion. These workers used a square wave of 280 pulses per second with a duration of half on and half off. They are undecided whether electronarcosis is due to stimulation or inhibition of the center, but favor stimulation, for they could record no electrical activity below the current flow. Also micro-electrodes, placed on a spot where the current went through, resulted in action potentials of large amplitude which diminished slowly and which were still present after twelve hours. The cerebellum when stimulated produces no electronarcosis, but the action potentials of the cerebellum were lost after stimulation of the diencephalon. Ivy and Barry⁽¹⁹³²⁾ consider a stimulation to exhaustion, likening it to the postictal (see Penfield and Erickson, 1941) period of a grand mal attack, as a possible mechanism. They state that a constant current will not induce anesthesia, and neither does it induce rigidity

to the same degree. These investigators used interrupted direct current with a pulse frequency of 6000 per second and from 0.8 on to 0.2 on. The pulse was not square. The fact that electrodes on the spinal cord (polarity not stated) will induce analgesia in some dogs, without rigidity, indicates that a block of the reflex pathway may be produced by the current. Ivy and Barry found that decerebrate rigidity was relaxed by the interrupted D.C., whereas, Harreveld reports enhancement of the rigidity with alternating 60 cycle current.

Silver (1939) and Silver and Gerard (1941) claim electro-narcosis from direct current (uninterrupted) with the cathode in the mouth and the anode in the rectum of the dog. They postulate a reflex block in the central nervous system.

Ivy and Barry report that fish align themselves to a constant current passing through the water with the head to the anode. This has been reported by several other earlier investigators.

Several investigators have applied their currents to man. Harreveld has done his investigation primarily with that intention in mind. Tielz, Thompson and Harreveld (1946) report electronarcosis as a treatment for schizophrenia in 47 cases. The electronarcosis periods lasted five minutes and there were 1400 treatments in all with no important complications.

Death from electric current itself (Barrera, 1944) is due either to cardiac failure or to respiratory failure. The

cardiac failure has been attributed to ventricular fibrillation when the current passes in sufficient density through the heart. In cases where this is not so the arrest of the heart is explained by assuming a direct stimulation of the vagus nerve or of its centers in the medulla oblongata. The respiratory arrest can be overcome in practically all instances by sufficiently prolonged artificial respiration.

A fundamental, though unconfirmed, research has been conducted by Burge, Petefish, Armitage and Saunders (1941), Burge (1945), and Burge (1948) showing a relationship between the polarity of the cortex and anesthesia. Burge, et al, found the brain cortex of the conscious animal to be electronegative, and the administration of anesthetics gradually to decrease this negative potential to zero. Upon further increase in the depth of anesthesia, a reversal in polarity occurred, and in deep surgical anesthesia the brain cortex became electropositive.

The mode of action of anesthetics in rendering the brain cortex electropositive is as follows: "The anterior and posterior roots of the spinal nerves in the lumbar region of the cord of etherized dogs were carefully exposed. When a platinum hook electrode was placed on a posterior root and another on an anterior root of a deeply anesthetized dog, with a galvanometer in the circuit, a current of 0.09 microamperes passed from the posterior to the anterior root. This showed the motor anterior root to be electronegative in

deep anesthesia. As the dog recovered from the ether the strength of this current gradually decreased to zero. With further recovery from the anesthetic there occurred a reversal in polarity. When the dog was only slightly anesthetized, and semiconscious, a current of 0.06 micro-amperes passed from the anterior to the posterior root showing the sensory posterior root to be electronegative in the semiconscious dog. Upon the death of the animal, the potential difference between the two roots disappeared. The preceding observation was repeated with sixteen dogs and it was found that while the strength of current between the two roots varied with different dogs used, the direction of the current was always the same, namely, from the anterior to the posterior root in the slightly anesthetized, semiconscious dog, and from the posterior to the anterior root in the deeply anesthetized dog.

"The electronegativity of the motor anterior roots of the deeply anesthetized dog is interpreted to indicate that more negative charges, or nerve impulses, were leaving the brain by motor anterior roots than were coming to the brain by sensory posterior roots, resulting in loss of negative charges thereby causing the brain cortex to become electro-positive in deep anesthesia.

"The electronegativity of the posterior roots of the lightly anesthetized, semiconscious dog is interpreted to

indicate that more negative charges were coming to the brain by sensory posterior roots than were leaving by motor anterior roots. This resulted in a gain of negative charges, causing the cerebral cortex to become electronegative in the conscious state.

"It is known that irritability is increased at the negative pole, or cathode, a condition known as catelectrotonus. Likewise, it is depressed at the positive pole, or anode, a condition of anelectrotonus. Moreover as long as an animal is alive, negative charges or nerve impulses pass to the brain by way of the sensory nerves, and away from the brain by motor nerves, and upon death these charges disappear. If the negative charges leaving the brain are in excess, the brain loses negative charges and becomes electropositive, with resulting decreased irritability, anelectrotonus, unconsciousness and anesthesia. If the negative charges coming to the brain are in excess, the brain cortex gains negative charges and becomes electronegative, with resulting increased irritability, catelectrotonus and consciousness.

"The question that arises in this connection is: How do general anesthetics produce a decrease in the negative charges coming to the brain by way of sensory nerves in deep anesthesia, thereby diminishing its negative potential? It is recognized that local anesthetics, when applied to the nerve trunk, block the negative charges and prevent them from passing to the brain. It is also known that local

anesthetics are more effective in blocking sensory than motor nerve fibers, so it is possible by selecting the proper strength of the local anesthetic to abolish sensation without impairing motor function. Do general anesthetics, like local anesthetics, block sensory fibers and thus prevent the passage of negative charges, or nerve impulses, to the brain while motor fibers are left unimpaired to conduct negative charges away from the brain? According to Forbes (1922), general anesthetics do block negative charges entering by way of sensory posterior roots of the spinal nerves at the first synapse in the cord and in this way prevent them from passing to the cerebral cortex. Hence it would seem that general anesthetics decrease the negative potential of the cerebral cortex by blocking the passage of negative charges coming in over sensory fibers to the brain, while the motor fibers are left free to conduct negative charges away from the brain, resulting in a loss of negative charges, thereby rendering the cerebral cortex electropositive in deep anesthesia." (Burge, Petefish, Armitage and Saunders, 1941)

"Scalp potential of dogs was studied in relation to brain potential, and the scalp was found to be positive to the underlying brain cortex. The positive potential of the scalp fluctuated with the negative potential of the underlying brain cortex, increasing with a rise and decreasing with a fall in cortical potential. Hence, scalp potential may be used as an index of cortical potential, thus affording a method for the

study of cortical potential without exposing the brain. An increase in the positive potential of the scalp as occurs during recovery from anesthesia indicates a rise in the negative potential of the underlying brain cortex; and a decrease in the positive potential of the scalp with an increase in depth of anesthesia indicates a fall in the negative potential of the underlying brain cortex in a 1 to 8 ratio. That is, a rise or fall of 1 millivolt in the positive potential of the scalp indicates a corresponding rise or fall of 8 millivolts in the negative potential of the underlying brain cortex." (Burge, 1945)

"The forehead was positive to the forearm in 1,680 subjects, principally university students and faculty members. Similarly, the forehead was found to be positive to the forearm in 174 hospital patients prior to anesthetization and operation. During anesthetization scalp potential was decreased to zero. In deep anesthesia (plane 3) polarity was reversed in most of the patients, that is, the scalp became negative to the forearm. Upon recovery from anesthesia the polarity was again reversed and the forehead became positive to the forearm." (Burge, 1948)

"In summary, these observations suggest that consciousness and unconsciousness may depend on electrical condition of the brain cortex, consciousness being associated with a gain of electrons and a negative condition, and unconsciousness with a loss of electrons and a positive, or less negative, brain cortex." (Burge, 1948)
 brain cortex." (See also, Ross, 1943)

A somewhat similar work, and also as yet unconfirmed, is that of Grenell (1948). He is said to have used a micro-voltmeter, which draws practically no current, and measured the potential difference between the head and the body of 150 schizophrenics. They averaged 65 microvolts. He is said to have found that 80 normals never had higher than 12 microvolts. As the schizophrenics improved their potential difference dropped. If they did not improve their potential remained high. What the relationship of this finding is to the work of Burge will be speculated upon later.

Also taken from the lay press is a report of an attempt by Grey Walter of the Burden Neurological Institute in Bristol, England, to produce sleep by a feedback of the sleep pattern generated by the brain. He reports a pleasant drowsiness when used upon himself. No scientific publication has yet appeared.

There are, then, those who contend that electronarcosis is due to the stimulating properties of the current and that the more stimulating the current the better the narcosis; and, on the other hand, there are those who contend that it is due to the depressant properties of the current. Curtis and Cole (1944), after considering that alternating current, as well as square wave pulses, and uninterrupted direct current, are all claimed to be effective in the production of electronarcosis, explain it all on the basis of anelectrotonus. They contend that in sending current through the central nervous system it is impossible to distinguish between anodic and cathodic

currents, and one could only hope that anodic or depressant effects would outweigh the cathodic or excitant effects. To include the alternating current they say that once inside the skin the current is probably rectified, producing a net result on the nerve cell of direct current pulses, which they state are more effective than continuous currents in producing and sustaining either excitation or depression. (See Figure 1, p. 8.)

METHODS *

Eleven dogs, one cat and six monkeys were used in the study of the effects of a constant current upon the cortex. The procedure has also been carried out in the course of a craniotomy for seizures in one human and for the removal of a glioblastoma of the occipital pole in another. Six cats and one dog were used in the study of cord and peripheral nerve block. Two rats and one cat were used in an attempted general anesthesia.

All methods were chosen with the idea of testing and perfecting a method of anodal arrest which would work safely and consistently in a matter of seconds when the current was flowing, and with complete return of function in a matter of seconds after the current flow had ceased.

Three essentials to the successful use of this method of local cortical anesthesia are to be stressed: 1) There must be some separation by a saline medium (1 to 2 cm. has been found to be adequate) between the metal polarizing plate and the cortex to prevent coagulation of blood in the pial vessels and surface destruction of the cortex. 2) Current density must be considered at all times. Thus a decrease in the contact surface of the anode with the cortex calls for a proportional decrease in the milliamperage. 3) Direct constant

* See details included in Results.

current must be increased slowly from zero to avoid a make shock and firing of the cortex, and the flow of current must not be suddenly interrupted or a break shock will result.

In the cortical studies, the general procedure was quite similar. The cortex was exposed (dura reflected), the motor area located by stimulation, and the anode pole of a direct constant current (galvanic) circuit placed over this area. The indifferent cathode pole was placed on the skin of the back, or in the rectum (Fig. 3). A wick of cotton saturated with normal saline was soon adopted as an anode (Figs. 4 and 5). Stimulating electrodes were built into the center of the anode (Fig. 4) and by means of a stimulus through these, a good movement of the contralateral fore- or hindlimb was obtained. When a test shock produced this movement consistently the constant current was gradually increased from zero and maintained at a given milliamperage. The test shock was then applied again. When the test shock was ineffective the current was decreased to zero and test shocks again applied to determine the earliest return of response.

All the dogs and cats were under nembutal anesthesia throughout the procedure. At the close of the experiment the animals operated on under non-sterile technique had a perfusion of formalin and gum acacia into the carotid artery with the opposite carotid ligated and the jugular vein cut. Microscopic sections were made and stained with

Figure 3

Circuit diagram as commonly used on monkeys and man. A milliammeter is included in the circuit (not shown, see Fig.10) and flow of current is gradually increased from 0 up to the usual 20 ma.

The anode is shown in more detail in Figures 4, 5 and 12. The power supply, with meters and control, is shown in Figure 11, and the wiring diagram of same in Figure 10. The cathode, represented by the cross-hatched area on the monkey's back, is a thick felt pad with copper screen on the back and insulated except on its front surface. The felt is saturated with saline. The pad is shown in Figure 11.

Stimulating electrodes in the anode are for testing effectiveness of the block and are not needed in man where effectiveness may be tested another way.

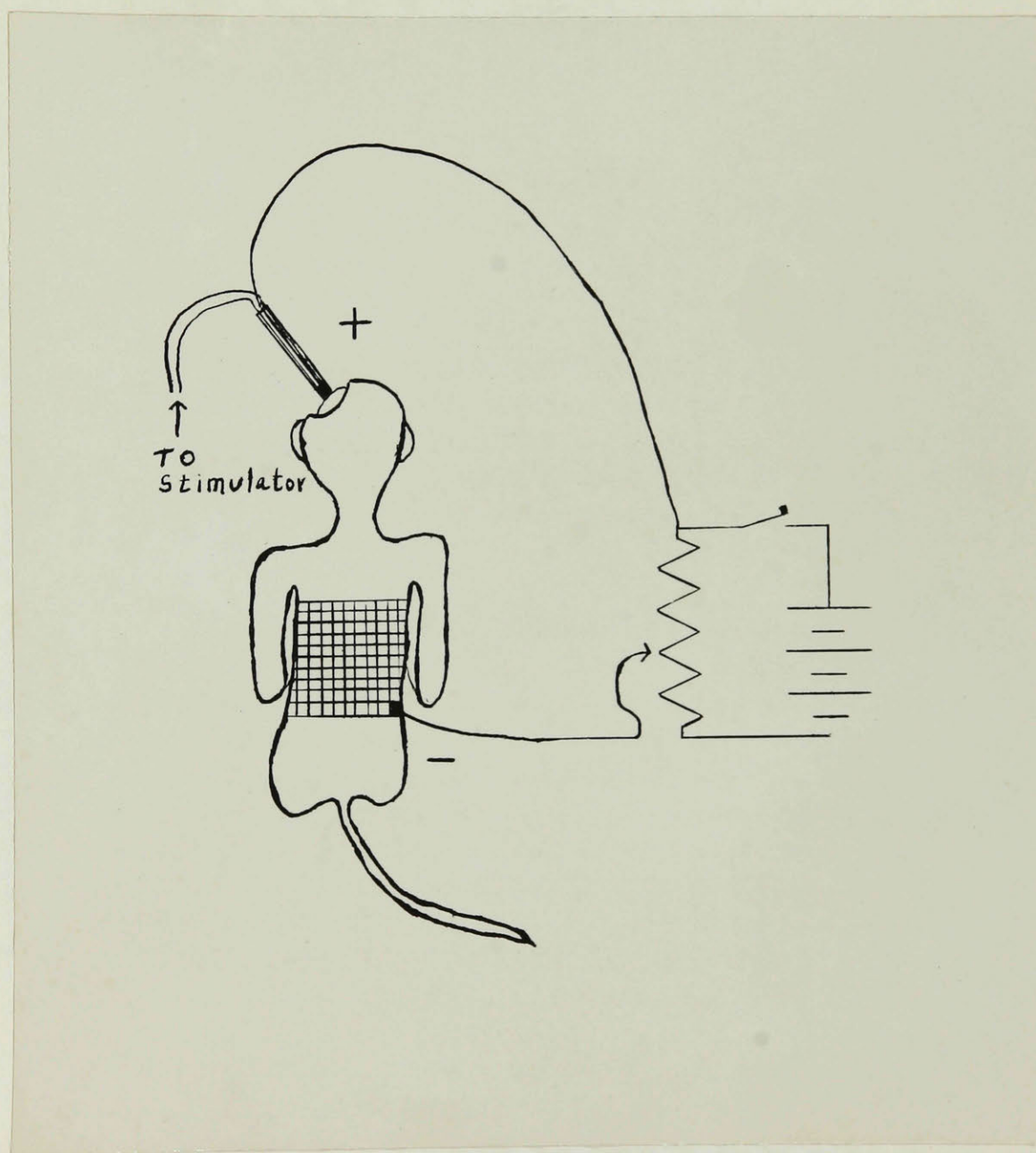


Figure 3

Figure 4

Diagram of anode showing the essential separation of metal from brain surface by normal saline medium (cotton saturated with saline). Above this point is nonessential and may be modified to suit the particular needs for application of the cotton to the brain. The diameter of the cotton-saline end (dental roll) is also important.

Formodifications see Figures 5 and 12.

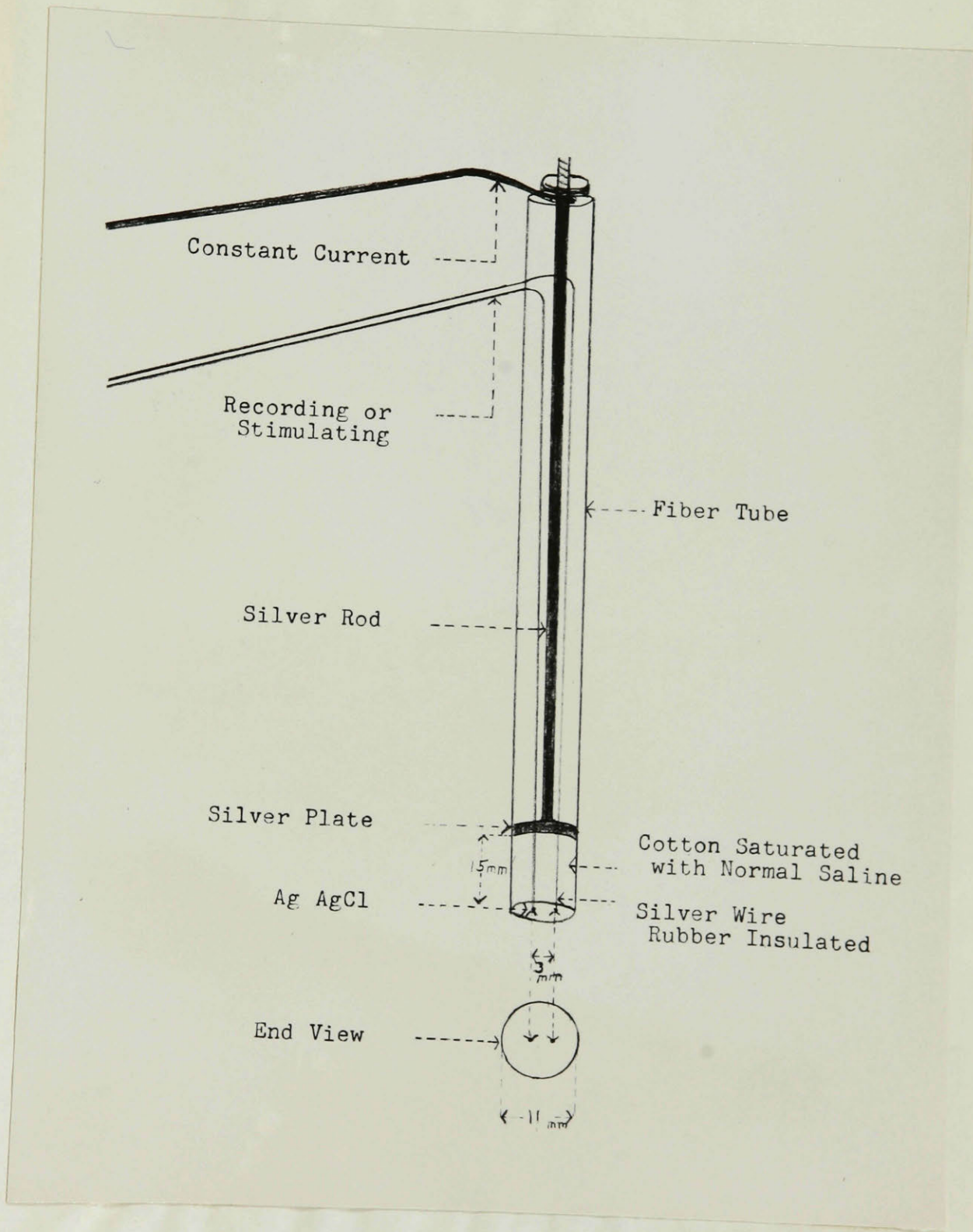


Figure 4

Figure 5

This is the anode instrument used on the human cortex. The diameter of the saline-cotton (dental roll) wick applied to the cortex is the same as in Figure 4. When the dental roll is changed after each patient, the silver plate should be scraped or resistance will be an unnecessarily high one next time the instrument is used. There are no stimulating electrodes in this instrument.

The insulated coil around the cotton is to hold it firmly against the silver plate anode. The coil spring mechanism above the silver plate allows gentle application of the cotton to the brain. There is also some lateral motion possible to allow free pulsation of the brain without damage.

Note the clamp for attachment to the edge of bone removal and adjustments to bring the anode into position. A part of the adjustment mechanism is a ball and socket joint.

This instrument is also shown in Figure 11.

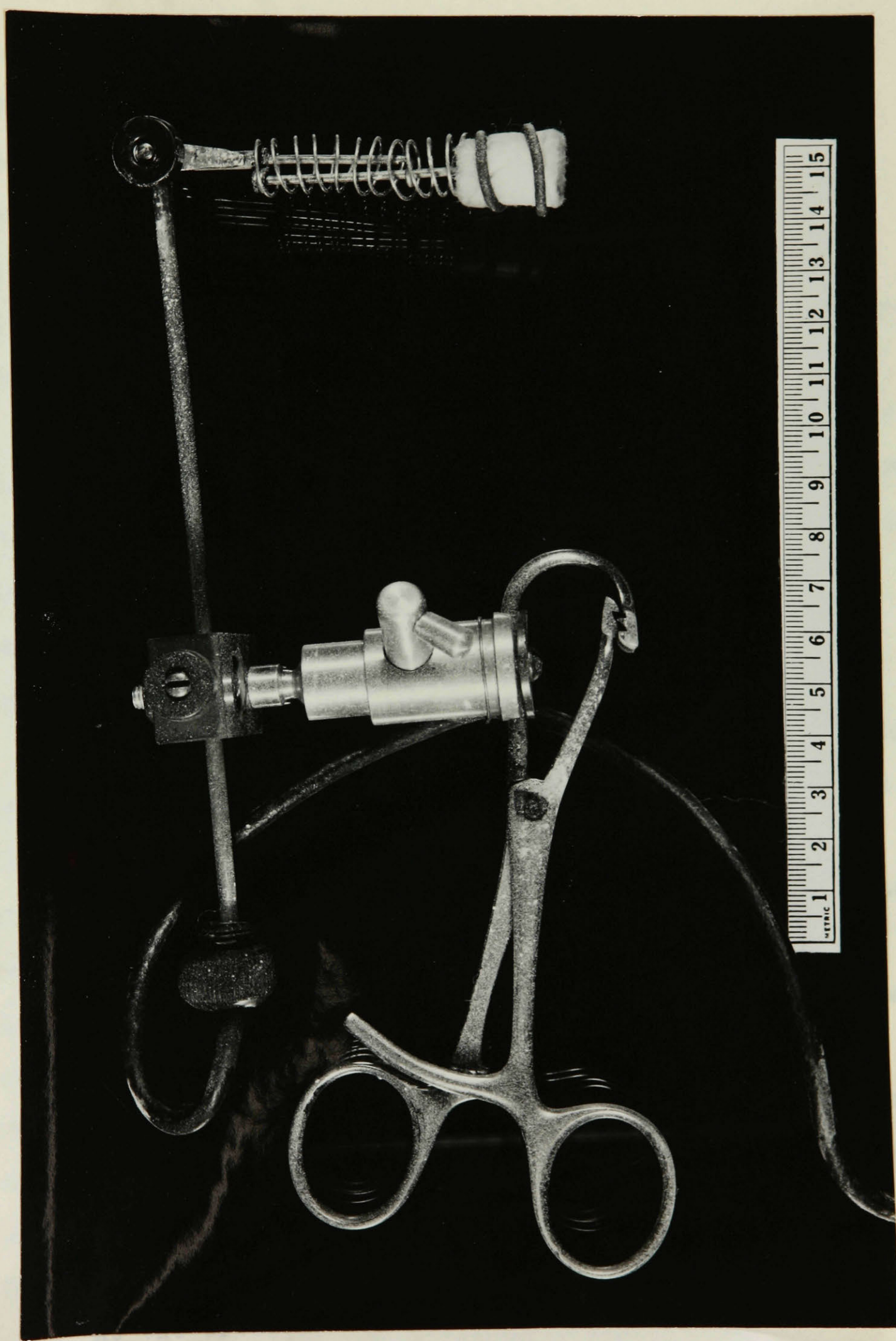


Figure 5

Nissl's and H.V.G. stains. The hemisphere which did not have current passed through it was used as a control for the one that did have current passed through it. In a series of sterile operations the dogs were allowed to live from several days to two and three weeks and observed for signs of damage to the cortical area which had been subjected to the constant current.

The question arose as to how marked would the signs of damage to the motor cortex be in the dog and in order to get first hand information a dog with no previous operations was prepared as a comparison. In this dog all the cortex of one hemisphere, which responded to stimulation by movement of the extremities, was ablated by suction.

In one experiment the cortex of a dog was exposed under sterile conditions, with nembutal as an anesthetic, but in this case both anode and cathode were on the cortex, the anode, as a blunt silver electrode one millimeter in diameter, in the center of a circular silver cathode, twelve millimeters in diameter (Fig. 6). The stimulating electrodes were on either side of the anode and halfway between the anode and the cathode. A response of a limb was elicited by means of the stimulator, and then when the constant current was flowing, the stimulus was again sent through the stimulating electrodes. This animal was observed for a period after this procedure.

At the close of the observation period for the dogs in the sterile series, the animals were given nembutal and the

Figure 6

Anode-cathode instrument. The essential part of this instrument is just above the 8 and 9 on the centimeter rule. The circle may be made either cathode or anode and the large pin in the center of this circle may likewise be made either anode or cathode.

Around the central pin can be seen four electrodes (all within the circle) used in diagonal pairs for recording and stimulating. The ring is supported and energized by the heavy wire running from its edge up to the fiber plate. Anode and cathode are silver; the other electrodes are silver silver-chloride

same procedure carried out on the animal as described above.

In one dog an electrode was implanted under sterile conditions and after recovery the constant current was passed.

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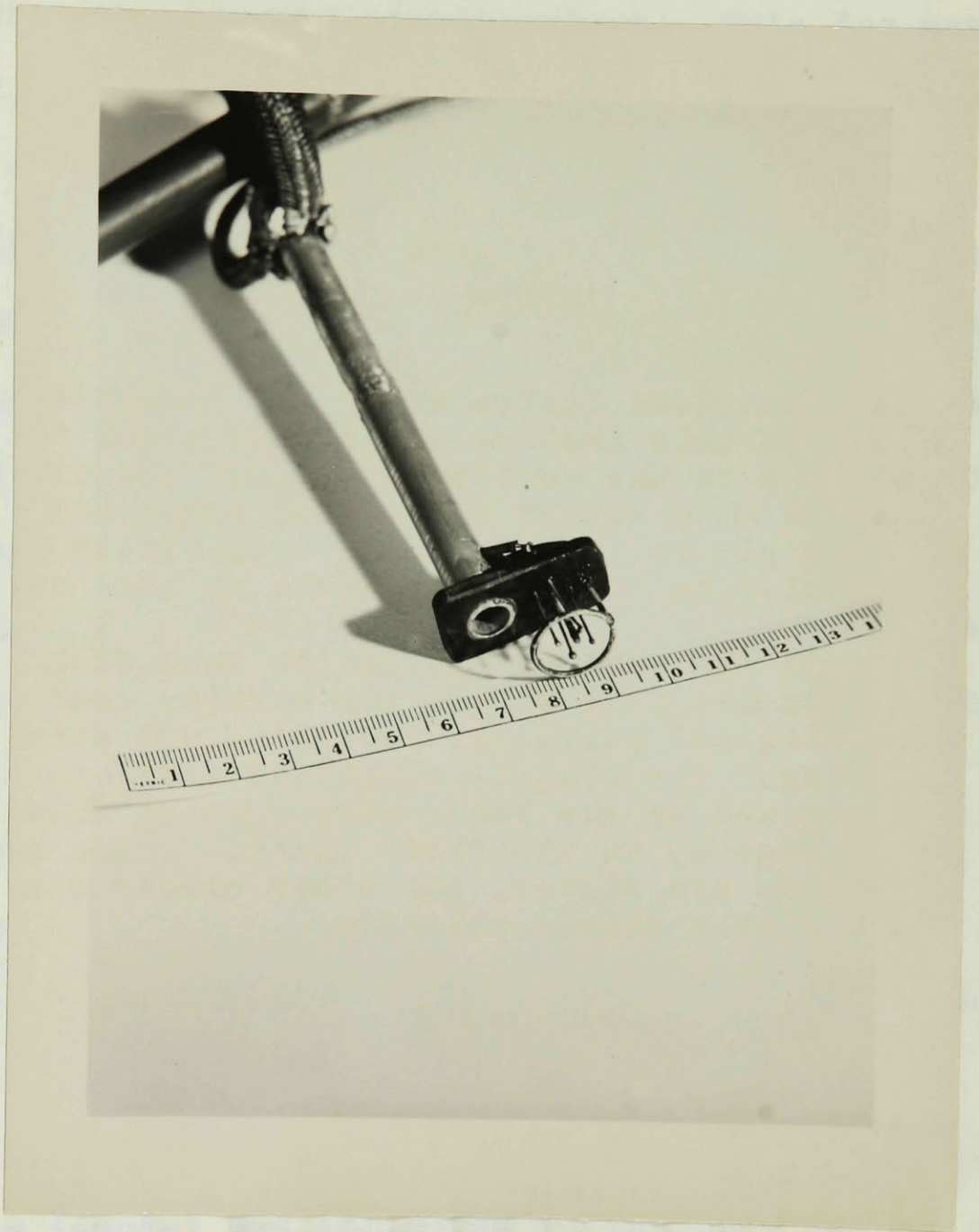


Figure 6

same procedure carried out on the brains as described above.

In one dog an electrode (anode) was implanted under sterile conditions and upon recovery a constant current was passed when the dog was walking about. This dog was also compared, when the current was flowing, to the dog which had had the ablation of the motor area.

All the monkeys but one were unanesthetized, except for local anesthesia used in exposing the cortex. The surgery and procedure were carried out in a chair designed and constructed by the investigator especially for the purpose (Fig.7).

Seizures, induced or spontaneous, starting in an extremity and progressing as a Jacksonian type march, were observed in the unanesthetized monkeys while the cortex was exposed. In several of these seizures, the anode was applied to the involved area and the constant current applied.

In one monkey the same procedure as described for sterile dog operations was carried out using the same anesthetic - nembutal.

In one of the monkeys, under local anesthesia, an electrode (anode) was implanted in the bone and in contact with the surface of the brain, so that current could be applied while the animal was moving about in the cage.

The monkeys were not sacrificed.

Some of the anode instruments had four silver electrodes built in them instead of two as shown in Fig. 4 (p. 49). The extra pair at diagonal corners of the square formed by the

Figure 7

Monkey chair. This chair designed to allow sterile or non-sterile operations to be performed on the unanesthetized monkey (local anesthetic used for exposing the cortex). With the adjustments shown, any size monkey may be accommodated and in any position desired: horizontal, vertical, lateral, prone or supine. The table may be lowered so that the operator may sit to work, or raised for the operator to stand. With the monkey in a horizontal-lateral position, i.e. the monkey lying down on his side, the cingulate gyrus is well exposed, for the hemisphere on the lower side falls readily whereas the septum supports the hemisphere on the upper side.

A rubber covered metal bar is placed through the appropriate holes in the head-piece and through the monkey's mouth as a bit. It was soon found that if this was not uncomfortably tight the monkey objected less and struggled less. It is often necessary to stop for a few seconds while the monkey struggles but it soon gives up and sits still for a considerable time. If the monkey struggles frequently look for the cause and correct it.

It can be seen in the figure that more than one adjustment may be used for the same movement. This is simply because the adjustment mechanism was originally designed for another purpose.



Figure 7

silver electrodes were used for recording the electrical activity of the cortex under the anode. (Electrode arrangement was similar to that in the pressure plate, Figure 16, p. 113.) In other experiments the stimulating electrodes were used for recording. All recording equipment was shielded. The corticogram was also recorded from just behind the anode, on the contralateral motor cortex, and from the more posterior areas, such as the lateral, suprasylvian and ectosylvian gyri. Offner push pull, condenser coupled amplifiers with Offner crystograph pens were used.

In an attempt to get artifact free recording from the cortex under the anode, a special instrument was built (Fig. 8). The silver-silver chloride anode* was separated from the cortex by a saline column of 6 cm. in length and the lower end of the

* Silver wire coil well cleaned with strong sulphuric acid and well washed. Remaining procedure in the dark: Coil in bath of saturated AgCN connected to negative terminal of $1\frac{1}{2}$ volt dry cell. Connect positive terminal to Pt. or Ag in the same bath for ten hours. This deposits colloidal Ag on the electrode. (Several can be done at once on the same battery.) Wash well with distilled water, agitating to remove excess material. Put coil in bath of 0.1 N HCl and connect to positive of the $1\frac{1}{2}$ volt cell. Connect negative to Pt. or Ag in the same bath for 10 hours. This chlorides the electrode.

Place in distilled water in a dark bottle to keep. (These electrodes have zero potential, remain non-polarizable and are believed to be better than the calomel electrode.) For d.c. potential work it is well to even out any potential difference by placing coils in normal saline and connecting their ends for 24 hours.

Coat the wire with tygon above and stick through bottle cork. Put in a glass tube with end drawn to small opening through which passes a bit of thread (or cotton). Fill with saline and keep in a tube of saline in the dark. (It would be well to use dark tubing or to paint it with shellac lamp black.)

Figure 8

This anodal instrument separates the silver silver-chloride anode from the surface of the cortex by a normal saline solum 10 cm. long. The recording and stimulating electrodes pass up the outside of the glass tube and the black strips between 7 and 10 on the centimeter rule are merely insulating material on these electrodes. The metal anode may be seen as a black coil between 1 and 3 on the centimeter scale. Between 10.5 and 13 on the scale is cotton to make contact with the cortex and to keep the saline in the glass tube.

The instrument on the other side of the centimeter rule shows the usual separation of metal anode from cortex by saline saturated cotton. The cotton has been removed from around the stimulating electrodes and the end of the metal anode may be seen protruding from the fiber tube. From 10.5 to 12 on the centimeter scale, i.e. 1.5 cm., is the usual length of the saline-cotton separation.

The long saline solum instrument was designed to reduce artifact as recorded at the surface of the cortex under the cotton. It did this but was much less effective in arresting the activity of the cortex when 20 ma. of constant current was flowing. The usual type, on the other side of the rule, was very effective in arresting the activity of the cortex but the artifact was great while the 20 ma. constant current was flowing.

tube was plugged with cotton (dental roll) saturated with

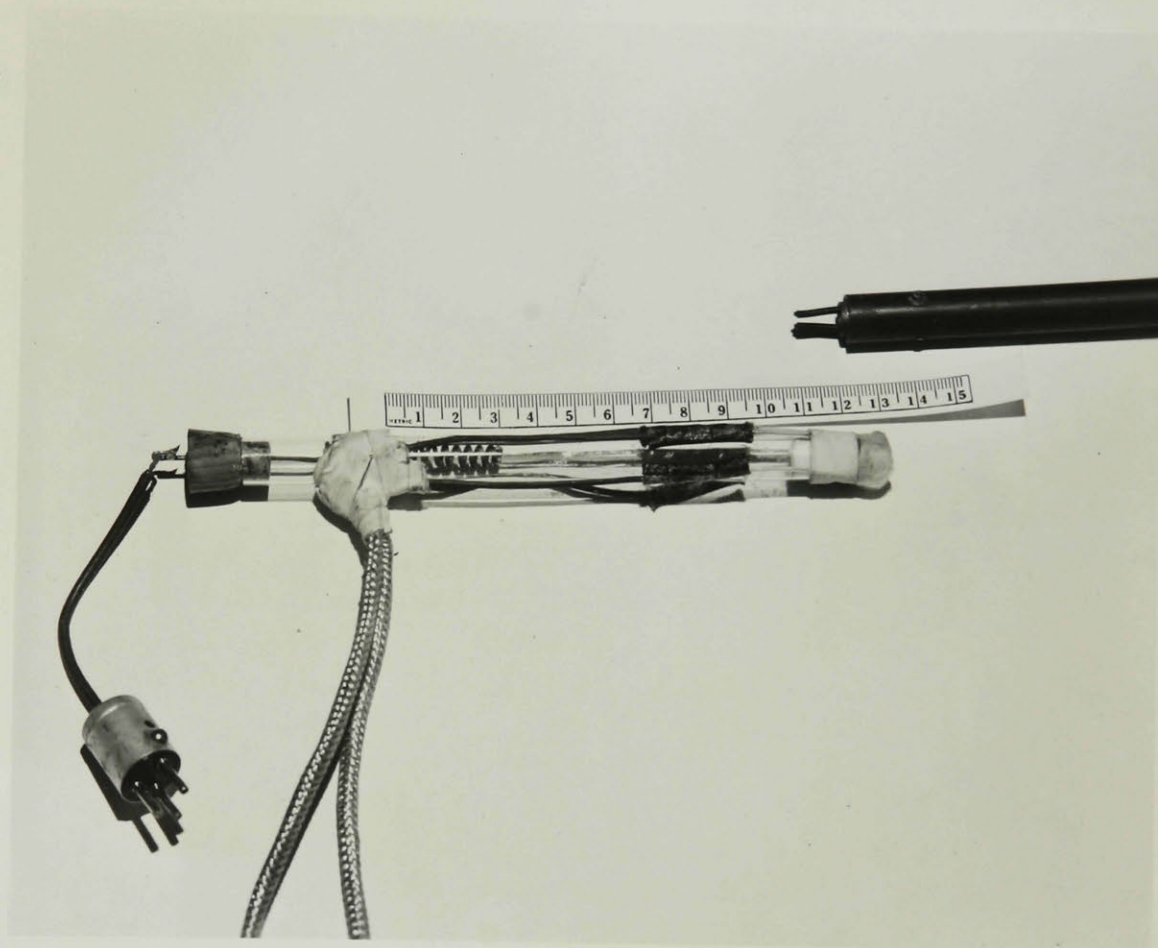


Figure 8

tube was plugged with cotton (dental roll) saturated with saline which made contact with the brain and contained the two recording and two stimulating electrodes.

An attempt was made to abolish electrical activity, as recorded by the electroencephalogram, with ice and ice-water, and with cocaine, so that a decision could be made as to the origin of electrical activity under the anode when the current was flowing.

Two experiments were conducted using dummy animals of cotton saturated with normal saline. The anode was placed at one end of the dummy and the cathode at the other end. Both electrodes were silver plates, 0.5 by 1.5 cm., and not chlorided. Spaced at intervals along the 30 centimeter length of cotton were electrodes in pairs all silver-silver chloride (Fig. 9). The recording electrodes were all in a straight line oriented with the direction of current flow.

A wiring diagram of the arrester is shown in Figure 10. Note the 1 microfarad condenser across the outlet. The condenser is intended to eliminate the tendency to surging of the current as the wiper in the potentiometer advances over the windings.

Figure 11 shows the equipment used in the procedure on the human. Figure 5 (p. 51) gives more detail of the anode instrument. Note that there are no stimulating electrodes built into the anode. The procedure in the human in the

Figure 9

Cotton saturated with normal saline was used in place of an animal so that cortical activity could be eliminated completely as a possible source of the high voltage activity which always developed at the anode. Note that when the 20 ma. is first flowing there is no electrical disturbance but with time for polarization effects to develop the disturbance occurs, primarily at the anode, less at the cathode, and least in the center of the interpolar distance. This disturbance develops gradually; first at the anode (electrodes 1 and 2), then at the cathode (electrodes 9 and 10), then at some distance from the anode (electrodes 3 and 4), and finally at some distance from the cathode (electrodes 7 and 8).

A saline bath is not satisfactory for this experiment because of surface waves, and vibrations which add additional artifact not related to the current.

RECORDING FROM NORMAL SALINE DURING PASSAGE OF A CONSTANT CURRENT

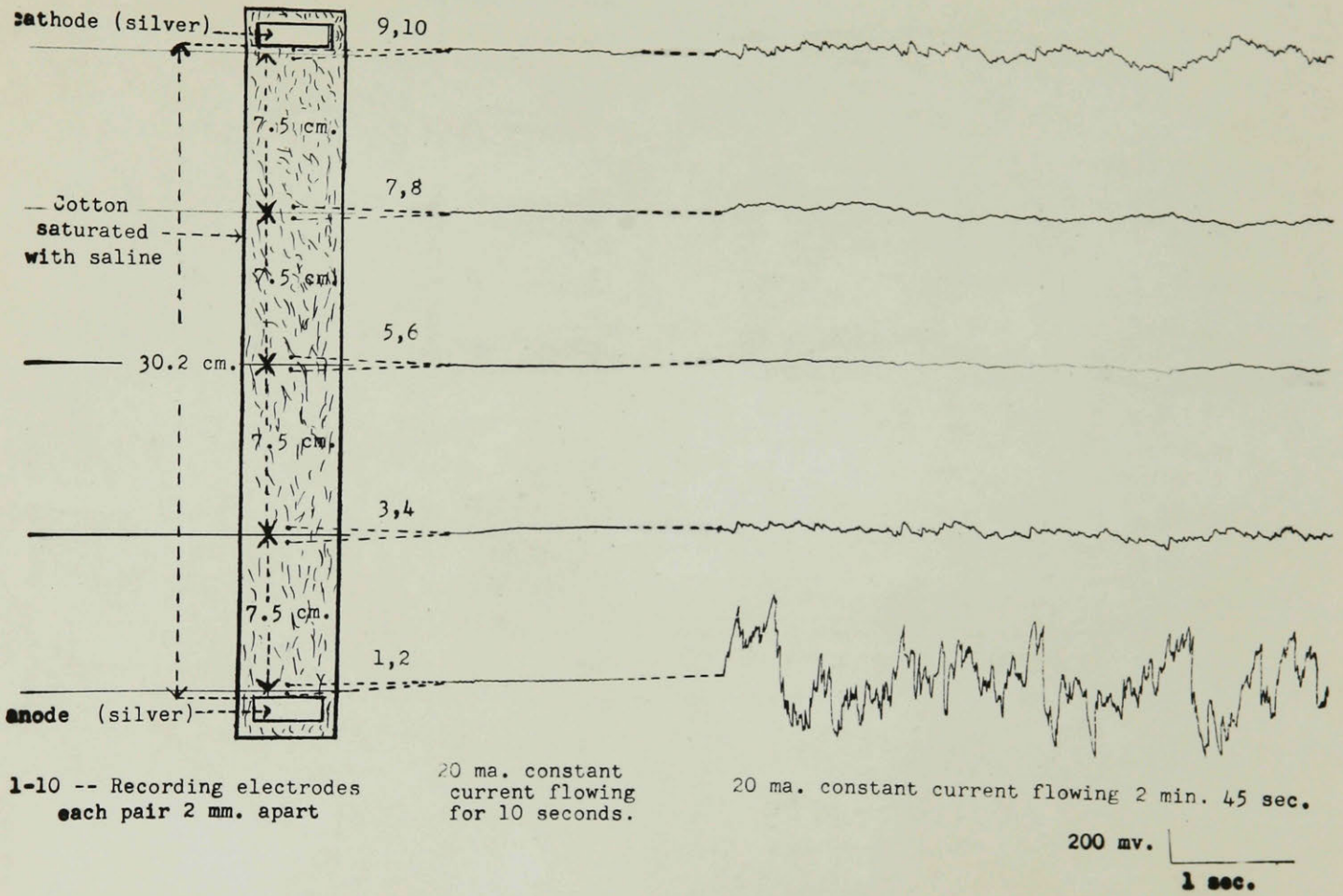
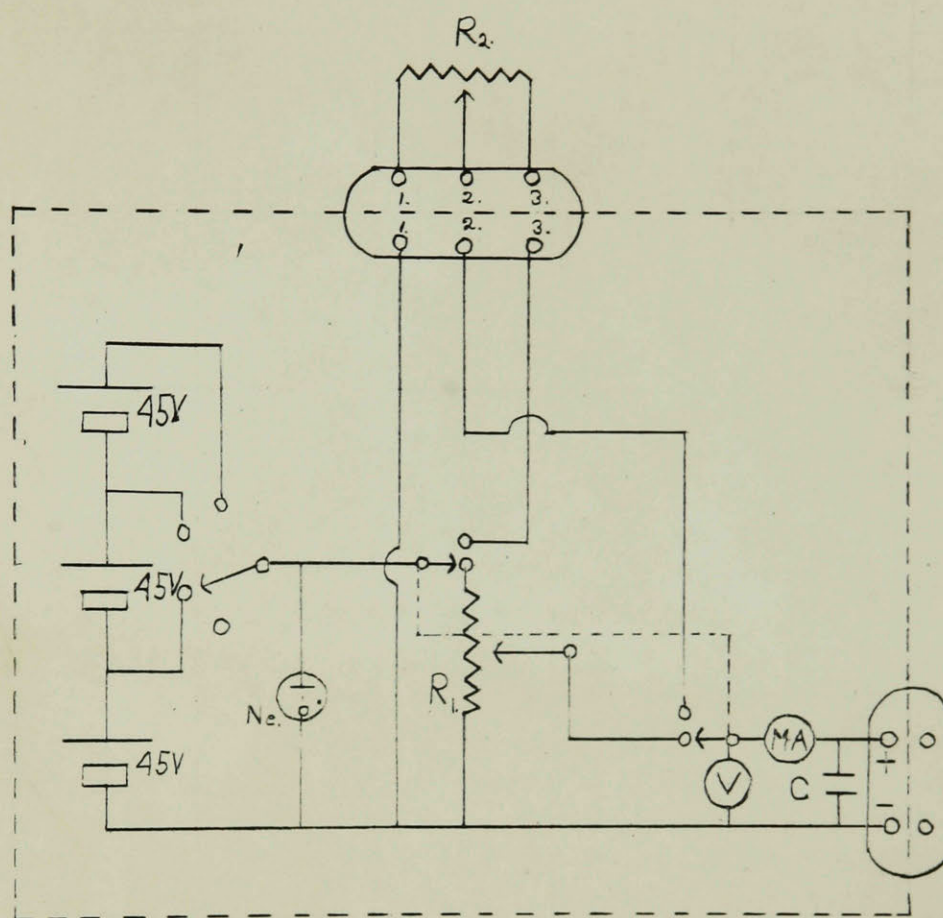


Figure 9

Figure 10

This is a wiring diagram of the arrester showing power supply with potentiometer control and meters for milliamperes and voltage. The large condenser allows a smoother rise from zero to 20 ma. for it eliminates the slight make and break effect created by the wiper travelling over the coils of the potentiometer. The milliammeter is set at 30 ma. full scale position and the voltmeter at 30 volts full scale position. The resistance in the circuit when used on man or monkey varies somewhat but is usually such that about 10 to 20 volts are needed to cause the 20 ma. flow (5,000 to 10,000 ohms). The arrester may be seen in Figure 11.

A remote control potentiometer is provided as shown in the wiring diagram and in Figure 11. The potentiometer may be autoclaved and should be hermetically sealed to prevent corrosion of the resistance wire. This attachment was not used during the procedure on humans.



$R_1 = 20000 \text{ ohms}$
 $R_2 = 20000 \text{ ohms}$ (remote control
 may be autoclaved)
 $V = 3, 10, 30, 300$
 $MA = 1, 3, 10, 30, 100$
 $C = 1 \text{ microfarad}$
 $Ne = \text{Neon Bulb (glows on } 90V, \text{ bright on } 135V)$

Figure 10

Figure 11

Arrester, cathode pad, and anode instrument are the essential parts of this picture. Also shown is a box containing an auxiliary power supply of three 45 bolt dry cells and the remote control potentiometer (round box with cable coiled around it).

The cathode pad is large enough to cover the back from the iliac crests almost to the axilla and around to about the nipple line. The rubber straps hold it in place.

All connections are different so that the anode cable could not be connected to the cathode pad, etc.

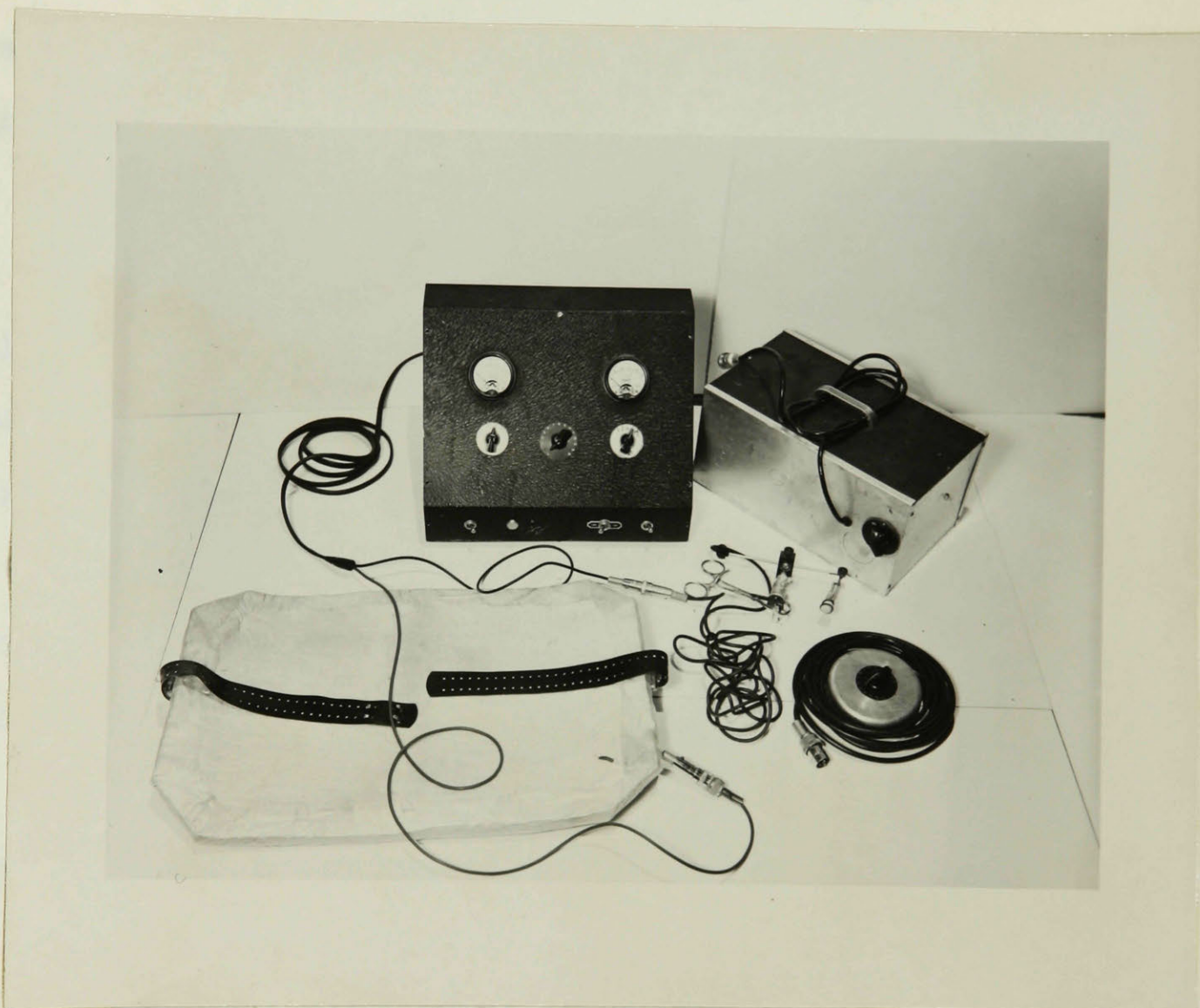


Figure 11

first trial was to locate an area of cortex which gave flexion of the fingers. The anode was placed on this area and after the current was flowing the patient was asked to grip. (Only local anesthetic is used in the craniotomy for seizures.) Again when the current was off the patient was asked to grip. Later, in the second patient, the angular gyrus was explored while the patient was reading. Still other areas are to be tried in the future, such as speech, primary and secondary, and areas that do not respond to stimulation. Note also that the anode instrument used on the human is built to lock to the edge of bone which surrounds the exposed cortex. With the instrument thus secured the circuit will not be broken if the patient moves.

Earlier instruments used on the monkey are shown in Figure 12. These were held in position by the operator while the constant current was flowing. It had the advantage of easy movement from point to point on the cortex, but there is danger of trauma to the cortex if the subject should move and there is also danger of breaking the contact with the cortex and thus breaking the circuit. This type of instrument without the stimulating electrode may be used later in humans after more is known of the reaction of the patient to the procedure, and after the operator becomes accustomed to the use of the instrument.

The cats and the dog used in the cord and peripheral nerve block were all done under nembutal anesthesia. In

Figure 12.

These instruments (all shown without their cotton) were designed to be held in the operator's hand applying the anode in a similar manner to the application of the usual bipolar stimulator. The main objection to this is that the contact with the cortex may be broken and the patient get a 20 volt shock which may be enough to precipitate a convulsion if the direct current has not been flowing long. If 20 ma. has been flowing for 30 to 60 seconds or more, the sudden removal of the anode from the cortex causes little or no disturbance because of the arrested function of the cortex. When the cotton is in place around the electrodes the surface for contact with the cortex is like that shown in Figure 4. At the bottom of each of the four cups shown is a silver plate which is the metal anode.

One of the instruments shown has three sizes of heads which allows a quick change from a small area of cortex covered to a large area covered, i.e., 1 cm.², 2.5 cm.² and 7 cm.² area. Only the 1 cm.² area was used. It was calculated that about 50ma. would be required for the 2.5 cm.² and 140 ma. for the 7 cm.² area. This is assuming that the larger electrodes would still require 2 ma. per sq.mm. in order to arrest function. Fifty and especially 140 ma. are not realizable from dry cells.

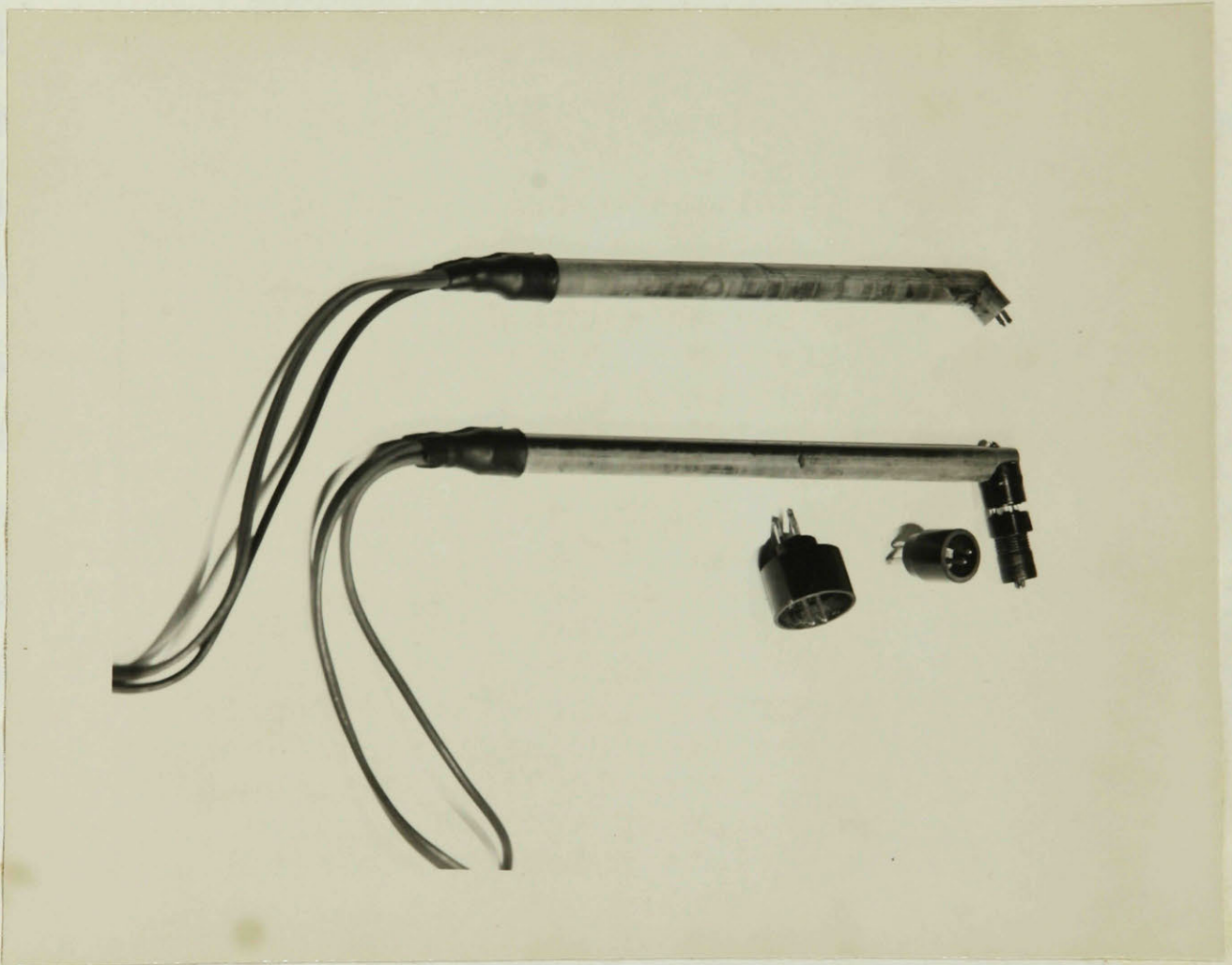


Figure 12

the acute experiments the cortex was exposed and the motor area located. In addition, the lower thoracic cord, and/or the brachial plexus, sciatic, and other smaller nerves, were isolated. Movement of an extremity was produced by stimulation of the motor cortex, and then an anodal constant current was applied to the cord or peripheral nerve in an attempt to block the impulse from cortical stimulation on its way to the effector organ. In all these experiments the cathode was in the rectum. Test of the block was also made by stimulation just above and just below the block on cord or nerve.

Other cats were operated on under sterile conditions in an attempt to implant an electrode (anode) around the thoracic cord in the hope that the block could be tested after the cat had recovered and was up and about. Nembutal was used for this procedure.

One cat was anesthetized with nembutal and under sterile conditions the brachial plexus was exposed in its entirety. An electrode (anode) of cotton saturated with saline was placed around the entire brachial plexus and insulated with rubber dam from the surrounding tissue. The cathode was in the rectum. Twenty milliamperes constant current was allowed to flow for ten minutes without interruption. The anode was then removed and the wound closed. The cat was observed for a month after. This was to test for possible damage to the nervous tissue by the flow of

current over a long period. Of the tests for possible damage by the constant current, the observation period after the procedure is considered most significant.

General anesthesia was attempted in two rats by passing a constant current through the animal with an electrode in the mouth and another in the rectum. The mouth electrode was made either positive or negative by means of a reversing switch in the circuit. Animals were not sacrificed.

General anesthesia was attempted in a cat by making the anode a silver cup which just fitted the globe of the eye inside the conjunctival sac. The cup was insulated on its outer surface. On its inner surface there was a layer of cotton, saturated with normal saline, which made contact with the cornea and sclera. By means of the reversing switch this cup was also made the cathode in one trial. This animal was not sacrificed.

Experimentation with the flow of 20 milliamperes current was carried out by the author on himself in order to determine how uncomfortable the cathode was. Various sizes of pads were applied to various areas of the body. All had a felt pad saturated with saline between the metal and the skin. Copper screen over felt 1.5 cm. thick and insulated so that only the front felt surface was exposed, was used as the cathode. The felt was well saturated with normal saline.

RESULTS

In the anesthetized animals (cats and dogs), using the anode which covered a 1 cm.² area, the threshold shock was rendered ineffective by the flow of a 20 milliampere current, for from 5 to 75 seconds (average 26 seconds). The current was increased from zero to 20 milliamperes in from 5 to 15 seconds (average nearer 5 seconds). If the 20 milliampere flow was maintained for a longer period of 90 to 120 seconds, the threshold could be increased to more than five times the threshold, when no current was flowing. The time necessary for return of the threshold to the precurrent level varied directly with the duration of the current flow and with the milliamperage used. The return time for long and short applications, taken together, varied from less than one second to 60 seconds (average 12.4). When the duration of current flow was less than 30 seconds, the return time was less than 5 seconds.

The unanesthetized monkeys responded in about the same manner. Twenty milliamperes consistently caused the test shock to be ineffective and in a shorter time (average of about 11 seconds). There was one monkey, however, in which 10 milliamperes consistently caused the test shock to be ineffective.

The brains of the dogs showed no gross damage immediately

after application of 20 milliamperes for as much as 20 minutes duration, and histological sections showed no significant change. Some dogs were allowed to live for two and three weeks after 20 milliampere current for 5 minutes and the only gross or microscopic change in these brains was a mild degree of dural adhesion where the latter had been sutured (Figs. 13 and 14).

Physiologically, two of the monkeys showed paresis of the extremity whose cortical representation had been the sight of anodal polarization. The paresis developed gradually near the end or soon after completion of the procedure and progressed to the second day, then regressed, so that on the fourth postoperative day, the extremity was used in a normal manner. In both of these monkeys, there was some cortical trauma inflicted inadvertently when they struggled.

In the monkey done under general anesthesia, thus eliminating trauma, there was no paresis of the extremities immediately after passage of the constant current nor in the weeks that followed.

The application of the constant anodal current to the cortical hand area of the human subject, at the time of craniotomy for seizures, was quite effective in preventing the patient from gripping when asked to do so. All the patient did was very slightly rotate the forearm in the attempt to close the hand. Immediately after (and in fact just before) the current reached zero, the patient could grip forcibly again. This was twice repeated. The grip

Figure 13

Twenty milliamperes direct current was passed through the motor area of the left side of this brain for a total of 32 minutes. Part of this flow was anodic and part cathodic current. The instrument used for contact with the cortex was similar to that shown in Figure 4.

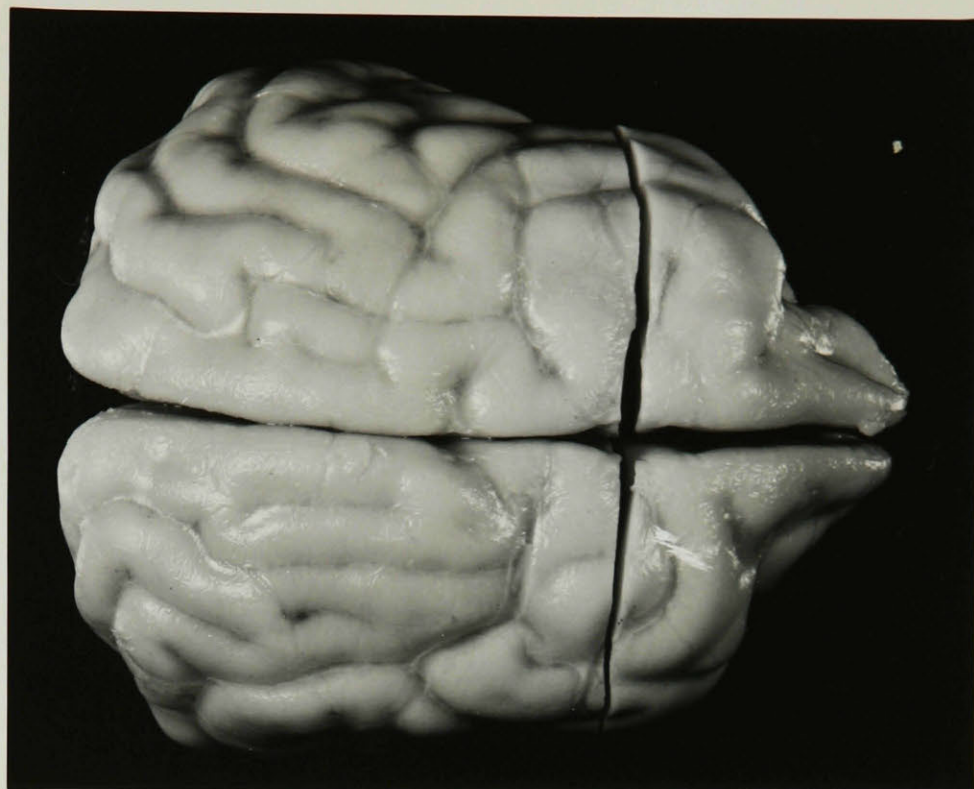


Figure 13 A

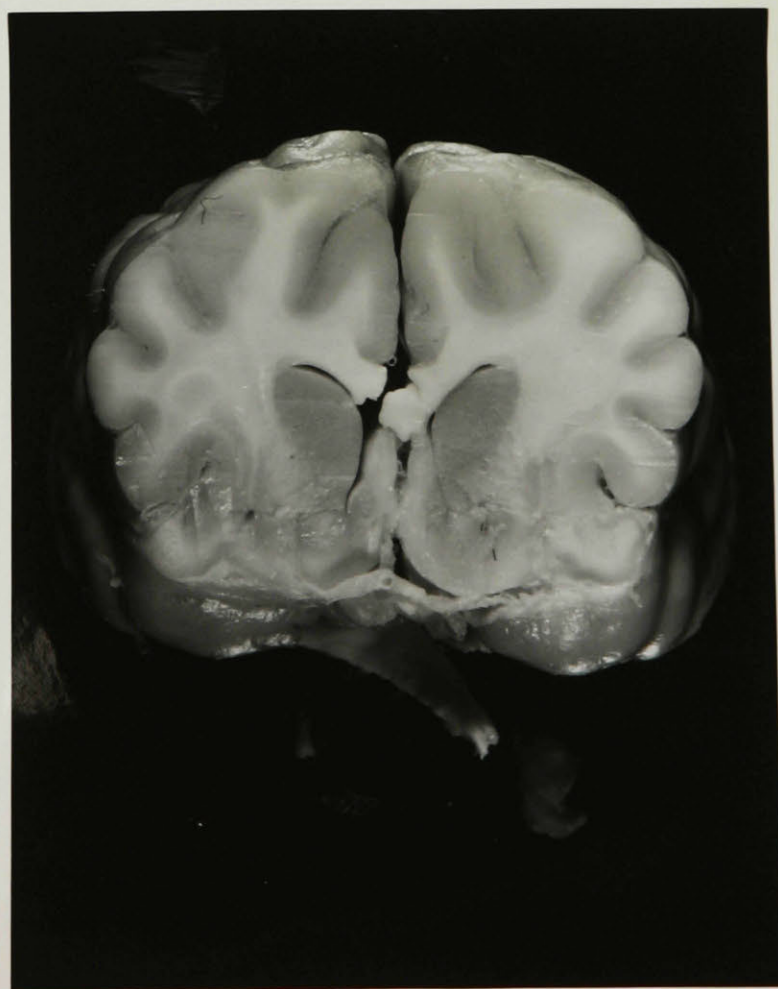


Figure 13 B

Figure 14

The section (Nissl X10) was taken through the center of the area covered by the anode through which had been passed 20 ma. constant current for 7 minutes. The dog was sacrificed 17 days after the current had been passed. It is obvious by the slight pial reaction through which hemisphere the current had been passed. The other hemisphere was not exposed at the time of operation. Higher power revealed no difference between the hemispheres other than at the pial surface.



Figure 14

was satisfactory the next day and remained so. Over two weeks after the procedure the grip is still as good as before the procedure.

In the second human case, two attempts to arrest the patient in his reading failed when the current was applied to the visual association area. Stimulation in the same area caused no change in the patient's reading and caused no symptoms. The entire left occipital pole was removed in this case including a glioblastoma for which the patient was operated on.

The flow of polarizing current at the anode is effective in stopping Jacksonian type convulsions which are arising from the area covered by the anode. Thus, in right-sided seizures, the anode was applied to the appropriate place on the left hemisphere. For example, in a seizure starting in the hand, progressing up the extremity to involve the face, the polarizing anode applied to the cortical area representing the hand stops the movement in the hand but the face may continue in clonus. A second application of the anode, this time on the cortical area representing the face will stop the face seizure. If the duration of the polarizing current flow is quite short, the seizure may begin again, but if the flow is longer, the seizure does not start again. These facts were demonstrated in monkeys

which had received no anesthetic or sedative, only local anesthetic in the scalp to allow exposure of the cortex. It was also found that if the anodal current had been flowing for a time and the monkey started to struggle voluntarily, the part the cortical representation of which was covered by the anode was not involved in the movement, e.g., if the anode was on the left hemisphere covering the hand area, the right hand would remain relaxed or paretic as long as the current was flowing. These facts are evidence that the area covered by the anode is truly functionless, while the current is flowing, and that the effect is limited to the area covered by the anode.

An example of the above, given in more detail as recorded during an experiment, follows:

"As was the case in the other Jacksonian seizures, the clonus of the hand and wrist was most marked, the elbow flexion with clonus was somewhat less marked and, if allowed to progress, the right face began to be involved in clonus. When direct current (anode) was turned on, the clonus of the right face and mouth continued but the clonus of the arm and hand immediately stopped and the elbow rather slowly extended and the hand came to rest on the arm rest. If the direct current was continued, the hand relaxed and fell from the arm rest, the extremity dangling at the side. When direct current was turned off the monkey put its hand back on the rest, but if the direct current had been on only a second

or two the convulsion started again as originally and progressed again. In this particular run, the fist remained clenched because the direct current was just turned up and then down and most of the movement was in the elbow. The forearm would come up quite quickly, then as the direct current was turned up the elbow would extend and the hand sink to the arm rest. When it just touched the rest, the direct current was turned down again and the elbow would flex again. A longer period of direct current caused complete relaxation of the extremity and in this case the slight, right-sided mouth clonus died out gradually. Nothing returned when the direct current was off, but the monkey replaced its hand on the arm rest."

An anodal instrument, consisting of a metal plate (silver or copper) separated from the cortex by cotton saturated with normal saline 1 to 2 cm. thick and 12 mm. in diameter gave consistent results without damage to the cortex, and was thus adopted as final.

Preliminary to this electrode an anode of silver 12 mm. in diameter and 1 mm. thick, covered with cotton cloth about 0.5 mm. thick and saturated with normal saline, was effective when 10 to 20 milliamperes was flowing but blood in a large pial vein under the anode was coagulated.

A carbon electrode, 12 mm. in diameter and 2 cm. thick, was effective but coagulated the cortex when the total flow

of constant current (several periods of 1 to 2 minutes) was continued for some time.

Signs of physiological damage after long periods of use with this carbon electrode were more severe in two dogs than they were in the control dog which had had its motor cortex sucked out. These dogs had difficulty in getting to their feet. The so-called control dog with the cortical ablation of the motor area of one hemisphere showed few and mild signs of deficiency or abnormality in walking or running, but he was occasionally a little awkward with the forelimb the cortical representation of which was absent. This forelimb, when the dog was standing, occasionally slipped forward from under the animal in a rigidly extended state. This sign could be brought out by the observer if the dog's forelimb was placed in an abnormal position and the dog then allowed to move the limb voluntarily back toward a normal position.

As mentioned under the section on Methods, one attempt at the production of local anesthesia of the cortex was made by applying both anode and cathode to the cortex at the same time. The instrument consisted of a central pole of silver about 1 mm. in diameter surrounded by a circle of silver 12 mm. in diameter (Fig. 6, p. 54). With the central pole as anode or as cathode, there was no change of threshold inside the circle, even with 20 milliamperes flowing. Also,

when the instrument was removed there were two coagulated points, one at the central pole and one on the circle where contact was made by the upright arm. This was obviously the point of highest current density. This animal had difficulty on slick floors the first day postoperatively, difficulty getting to its feet the second day, and on the third day postoperatively, he began to have seizures which were most frequently localized to the forelimb the cortical representation of which had been damaged, but others would spread as a Jacksonian march to become a generalized seizure. This progressed to a point where the dog had only 5 to 10 seconds between seizures. Phenobarbital, grains two intraperitoneally, was effective in relaxing the animal. Clonus began to reappear as the anesthesia passed off. The dog was kept free of clonus by repeated doses of phenobarbital which were given at longer intervals until on the fifth day postoperatively the dog was free of any tendency to clonus in the affected limb but had great difficulty getting to its feet. After a month of gradual improvement the dog was almost without signs, but when the dog was sacrificed, gross and microscopic sections of the cortex showed the entire thickness of the cortex to be involved in the necrotic process. These areas of cortex were vacuolated remnants of brain structure.

Attempts to record the electrical activity from under the anode while the current was flowing all met with failure. Recording was impossible due to the gross artifact which

developed when the current was flowing. At times this artifact resembled excitation of cortical activity with a period of build-up as the flow of current was continued. The instrument, mentioned under the section on Methods (Fig. 8, p.60), which removed the metal anode to about 6 cm. from the cortex was successful in reducing the artifact but was much less effective in suppressing the electrical excitability, i.e., the threshold of the cortex was not greatly increased by the flow of 20 milliamperes as it was when the metal electrode was near the cortex.

Similar experiments on the sciatic nerve of the dog showed that anodal block was much more easily produced when the metal anode was close to the nerve. The test of the block was made by stimulation of the nerve just central to the anode. A later experiment on a small motor nerve to the muscles of the scapula in a cat did not support this conclusion. With this nerve, which was about 1 mm. in diameter, a block could be produced with the metal anode separated by a saline cotton wick of 30 cm. in length.

The same results with the saline column instrument were obtained in two different animals and at the time it was quite conclusive that threshold was influenced to only a minor extent when 20 milliamperes were flowing.

In order to be more certain that the electrical activity recorded from the anode was artifact, the normal cortical activity of the motor cortex was abolished. The anode was then reapplied to this area and recording made while the current

was flowing. Ice and ice water were placed around two recording electrodes but the electrical activity continued unchanged. Cocaine 5 per cent was put on the motor cortex but the electrical activity continued though it was altered in character. Finally with a 25 gauge needle the cocaine was injected into the motor cortex and all electrical activity stopped. When the anode was applied to the area of cortex so treated the same fast high voltage activity was apparent.

As a last test a dummy animal was used as described under the section on Methods (Fig. 9, p. 63). The fast high voltage activity was present here and the build up could be easily observed as the current flowed. When the constant current electrodes were freshly cleaned the flow of 20 milliamperes caused no artifact and recordings from near the anode and cathode as well as those in between were iso-electric. After the current had been flowing awhile artifact began to appear at the anode and to progress in height to about one half its maximum. At about this time the artifact began to appear at the cathode as well. With a still longer period of current flow the electrodes several centimeters from the anode and from the cathode showed some activity but the one in the center showed the least or none at all even after long periods of current flow.

If the polarity were reversed everything started out in the reverse order.

This type of experiment was repeated several times and

each time the events were quite consistent. The artifact was so large that even on low gains the amplifiers were frequently blocked. If, however, the milliamperage was reduced by half, the artifact was reduced by about half. Five milliamperes gave little artifact, and 30 milliamperes gave little more than 20 milliamperes, probably because the amplifiers were usually blocked on 20 milliamperes. Gains were reduced to where the nature of the activity could be seen to be fast spikes with no great variation in its pattern. In all cases this artifact resembled somewhat the record taken from a patient having a generalized seizure (so-called grand mal pattern).

In the recording of activity from other areas of the cortex while the constant current was flowing through the motor cortex of one hemisphere, 2 to 3 mm. behind the anode unaltered cortical activity could be recorded. From a homologous area of the contralateral motor cortex, such as that covered by the anode, activity was undisturbed. From the suprasylvian, lateral and ectosylvian gyri the activity remained unchanged (Fig. 15). As a rule, the recording from other areas was undisturbed but there were exceptions. At times all the recording electrodes would be involved in the same fast high voltage artifact, similar to the way in which distant recording electrodes may be disturbed when the stimulator is used on any given area of cortex.

Figure 15

The corticogram, made with bipolar leads, shows the typical artifact under the anode and the lack of change of cortical activity from other parts of the brain.

ANODAL POLARIZATION OF MOTOR CORTEX

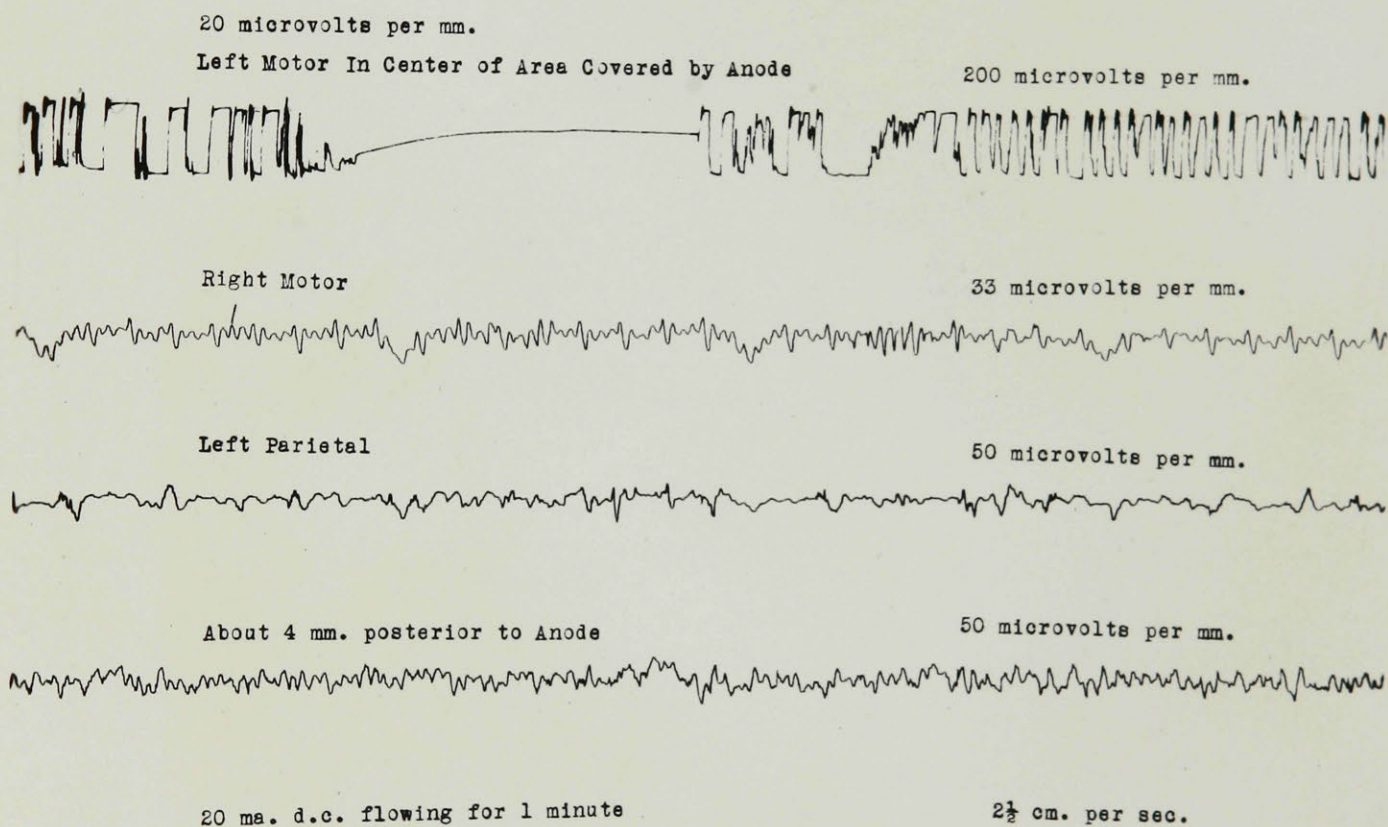


Figure 15

The threshold of the contralateral motor area was unaffected by constant current flow, i.e., with constant current flowing through one motor area and that area failing to respond to test shocks the contralateral motor area would respond to test shocks in the usual manner.

As mentioned in the section on Methods, a chronic preparation was made of one monkey by implanting a silver cup insulated except on its inside bottom surface and filled with cotton saturated with normal saline. Only the cotton touched the surface of the cortex on the motor area. A 45 volt hearing aid battery was strapped to the monkey's back in a box with a potentiometer. The cathode was in the rectum (as in Figure 3, p.47, but anode was implanted and cathode was in rectum). There were no stimulating electrodes in the anode. By predetermination with a milliammeter in the circuit the potentiometer was calibrated to allow 20 milliamperes to flow. When the current was off, the monkey could climb the cage. When the potentiometer was gradually turned up to 20 milliamperes and the monkey again released, it did not use the forelimb the cortical representation of which was covered by the anode, and it had difficulty with the hind leg on the same side. When the current was off the monkey again climbed the cage. This was repeated several times.

With the preparation just discussed, on one occasion only, the following square wave pulse frequencies were tried using the implanted electrode as one stimulating electrode and the rectal electrode as the other.

Electrodes on Left Motor Cortex and in RectumSquare Wave Pulse

Duration of Stimulus		Volts* (RMS)	Frequency	Effect
1	sec.	2.5	30	Forearm, fingers and toes respond on expected side.
1	min.	2.2	50,000	No observed effect.
30	sec.	2	50,000	" " "
15	sec.	4	50,000	" " "
30	sec.	4	20,000	" " "
1	min.	4	10,000	Initial jerk right arm.
1	min.	4	8,000	" " " "
30	sec.	4	6,000	" " " "
30	sec.	4	4,000	" " " "
1.5	min.	4	4,000	" " " "
3	min.	7	50,000	No observed effect.
15	sec.	0 to 7	4,000	Mild tonic state starting in right arm and spreading.
2	min.	0 to 7	4,000	Occasional twitches right arm.
1	min.	4	2,000	Nothing
2	min.	0 to 6	2,000	General depressed appearance and pained expression.
30	sec.	0 to 4	1,000	Monkey down on face in tonic state.
30	sec.	0 to 3	1,000	Same. Monkey tried to stand but seemed unable.
1	min.	0 to 2	1,000	No general effect.
15	sec.	0 to 6	1,000	Down and extremities flexed. Possibly unconscious 15 sec. after getting up. Normal, 30 sec. after.
15	sec.	2	2	Generalized clonic jerks at rate of stimulus.
15	sec.	2	60	On back in tonus.
3	min.	2 to 3	60	Fell on side but gradually regained some power of movement and tried to rise.
1	min.	3		Monkey fell back to the floor. Tonus not marked.
1	min.	2 to 2.2	60	Fell over on side in tonus.

*Where increased voltage is shown, the increase was very gradual, from zero up to the top voltage, during the period of time stated.

This chronic monkey with the electrode implanted over the left motor cortex eventually failed to respond to the constant current and instead went down on its face, as it did with the 60 cycle alternating, or 60 pulse square wave, in a tonic state. It was stimulated by the constant current. Also, in time the right arm became paretic. The electrode was removed 6 days later and it was found that the thin silver cup had broken down and the lead to it was making intermittent contact. The cotton was tightly adherent to the cortex and even a careful removal caused considerable trauma to the cortex. Obviously, cotton causes considerable reaction when in contact with the cortex over a long period of time. The paresis cleared up after about one month's time. The monkey was not sacrificed.

In an effort to get more proof that the constant current, even for fairly long periods, is not damaging to nervous tissue, and also because reports of the use of anodal block on nerves in the intact animal are few, the following experiments were performed.

Most pertinent to the thesis is a chronic cat which had 20 milliamperes constant current applied to the brachial plexus for 10 minutes continuously. Under sterile conditions, the plexus was exposed and a rope of cotton saturated with saline was passed around it and the cotton insulated from the surrounding tissue with a rubber dam. After the flow of current, the cotton was removed and the wound closed. After

about a five day recovery period, during which time the cat was disinclined to use the involved limb, it began to walk again in a normal manner. One month later, the cat is still walking about with no indication of nerve damage. The cat's rectum was, however, damaged by the cathode and was not entirely healed after a month's time.

All attempts to produce a chronic preparation with an anode around the spinal cord failed, for in each case the cat was paraplegic upon recovery from the anesthetic and for several weeks after, i.e., until sacrificed. Attempts were made with the dura removed from the cord and with the dura in place. It was hoped that a chronic preparation could be made in this way, and the constant current passed from cord to rectum while the cat was walking around.

In one of the paretic cats which had a cotton wick electrode around the cord with the dura removed, twelve milliamperes constant current anode, cathode in the rectum, caused the hind legs to become flaccid; however, there was still a withdrawal reflex as elicited by pinching the toes. When the current was off, tone returned. This was repeated many times on the one cat.

Acute experiments, however, with the cortex exposed, showed that with the anode on the dorsal cord and the cathode in the rectum, test shocks to the cortex would not result in movement of the hind limb while the current

was flowing (10 milliamperes, 30 seconds) but would while it was not flowing.

Peripheral nerve will block with less milliamperage as the diameter of the nerve decreases. Ten milliamperes blocked the entire brachial plexus or sciatic nerve. Two milliamperes blocked a small sensory motor nerve on the anterior surface of the forelimb of the cat and 1 milli-ampere consistently and almost instantly blocked a still smaller motor nerve to the muscles of the scapula. This applied to increased voltage of test shock by about five fold.

The flow of 20 milliamperes through the skin at the cathode is least disturbing with a large felt pad, 30 by 50 cm. over the back. As mentioned before, the felt of the pad is 1.5 cm. thick and over the back of the felt is a copper screen to which is soldered the lead to the current source. This screen and the felt, except the front surface, is insulated with pliofilm - a form of insulating waterproof sheeting (Fig. 11, p.67). During the one trial on the human with the anode on the cortex and this large pad well saturated with saline on the back, the patient was aware of a definite feeling of heat and some tingling of the back while the 20 milliamperes was flowing. The second patient did not mention it. It is doubtful, however, if the majority of patients would tolerate a smaller pad on the thigh, though this would be a little more convenient and perhaps should be tried.

DISCUSSION

One cannot escape the obvious conclusion that cerebral (motor) cortex is subject to slow electrotonus in the same manner as peripheral nerve.

This conclusion is obvious in view of the findings of this investigation: ^{There is} a rise in threshold of the cortex under the anode and a fall under the cathode, both in a completely reversible manner, with time parameters and current densities all comparable to those found for slow electrotonus in peripheral nerve. The similarities between the behavior of motor cortex and peripheral nerve also support this conclusion. Negativity associated with responsiveness and positivity associated with decreased responsiveness are found in both cortex and peripheral nerve and are explainable in both cases in terms of the membrane theory (Dusser de Barenne and McCulloch, 1939), in fact, the "membrane potential" corresponding to that of nerve has been described and measured in the cortex (Gerard and Libet, 1940; Libet and Gerard, 1941).

In the light of the knowledge of peripheral nerve anodal block, one can easily explain the failure of the experiment in which both anode and cathode were on the cortex, for the path of the current was not across the nerve cell membranes but primarily along the surface of the pia (Fig. 1, p. 8). A wider separation of anode from cathode on the surface of the cortex would probably be more effective.

The finding of Gerard and Libet (1940) that an anodal current increases and cathodal decreases the spontaneous six per second activity of the brain as well as the caffeine waves travelling over the cortex is probably due to the small polarizing currents used. It is in keeping with the addition to Pfluger's Laws of electrotonus, that very weak constant currents have the opposite effect of stronger constant currents upon nervous tissue (Bishop and Erlanger, 1926). Could they have used stronger currents, the usual anodal depression and cathodal excitation would have taken place.

To explain the functioning of anodal arrest of the cortex any farther is repeating the explanations given for anodal block of peripheral nerve. That the cortex responds to polarization in much the same way as it responds to stimulation, without the sudden change, however, that appears as an excitation (Bishop and Erlanger, 1926), is strongly suggested by the observations on the unanesthetized monkey while the anodal current was being advanced. A sudden advance of the current would result in a frank response; a more gradual increase would result in a situation on the borderline of response and no response; i.e., there would be an increased tone with or without a slow slight movement of the extremity the cortical representation of which was under the anode. Even with very gradual increase of current when the closest observation would reveal no movement, a test of the tone usually revealed a slight increase of tone before flaccidity set in. If the

current were made instantaneously a vigorous quick, tetanic movement resulted followed by a gradual relaxation to flaccidity. If the current were suddenly broken soon after the current had reached its maximum, a response with after-discharge began. This continued and progressed as a march involving more cortex until a generalized convulsion resulted. If the circuit were made again while the seizure was still localized, the abnormal discharge stopped and in a few seconds a state of flaccidity existed in the extremity the cortical representation of which was under the anode. This detail is given to show the close balance between factors which would result in a lowering of the threshold to the firing point and a rise of the threshold, after the current had been flowing 30 to 60 seconds, to the point where a break of the circuit caused no response (about 20 volts).

The fact that, with the anode on the cortex and the cathode in the rectum, a sudden make of the current resulted in firing of the cortex does not seem to be in keeping with the explanation of stimulation on the basis of the membrane theory and with the law of excitation which states that there is stimulation upon make only at the cathode. One would think from Figure 2 B that any increase in positive charge would only tend to prevent firing no matter how quickly applied.* Nevertheless peripheral nerve responded in the

*A possible explanation in terms of the condenser theory (Fig. 2 C, Curtis and Cole, 1944) would be that the sudden strong current temporarily broke down the condenser and discharged it thus firing the next, etc.

same manner as the cortex; a sudden make of the circuit stimulated the bracheal plexus when the anode was the only electrode on the plexus, the cathode being in the rectum, thus the weakness in the explanation goes back to a weakness in the membrane theory for peripheral nerve and only suggests more strongly that a more liberal interpretation such as is given by Bishop and Erlanger is necessary.

If one can consider the cortex, or nerve, in a state of equilibrium potential when at rest (Bishop and Erlanger, 1926; Dusser de Barenne and McCulloch, 1939) and that this equilibrium, when suddenly upset, results in firing of the cortex or nerve, one can then assume that the firing could be prevented by maintaining a potential either far above or far below this equilibrium. This stable state would be resistant even to strong stimuli. That this is the case is born out by the findings of Erlanger and Blair (1940) and by the monkey experiments described above, as well as by similar observations on peripheral nerve in the intact animal with only the anode on the nerve.

A gradual change of potential from the equilibrium potential does not result in firing in most cases, though cortex or nerve is more apt to fire spontaneously when the potential is being lowered. It is thus possible to reach these stable states without any spread of the process of

excitation which is taking place locally. Admittedly, how it is possible to reach a very negative potential without firing the nerve in the process is not explained.

The state of stability (high threshold) by strong negative polarization over long periods (Erlanger and Blair, 1940) was only suggested in our experiments, perhaps because the 20 milliamperes of cathodal current ~~were~~ not continued long enough.

Five minutes of 20 milliamperes current in one case caused a decrease in threshold followed by a return to normal threshold, but the threshold even here was not increased.

Referring again to Figure 2 (p.12), consider how effectively any impulse would be stopped, if, by an outside force, the polarity were held stable or increased, or even very gradually reduced in potential to a discharged state and the protoplasm of the nerve not allowed to recharge the membrane. It would be holding the nerve in the refractory state.

That it is possible to produce a lesion with anodal or cathodal current without signs of stimulation was demonstrated in the experiment with both anode and cathode on the cortex and has been demonstrated many times in the intentional production of lesions in the brain stem and elsewhere. All that is required to prevent stimulation is that the current be brought up gradually.

If Harrison (1940) could have reached a high enough current density in the tubero-infundibular region without destruction of tissue, in all probability sleep would have resulted from the depressant effect of the current alone and would have been as readily reversible as any anodal block. Destruction of tissue is a stumbling block in the use of anodal polarization with needle electrodes, especially within the brain, for heat is generated to the greatest extent at the metal-saline (or tissue) junction and it is here that the greatest HCl production takes place.

As has been said, the separation of the metal anode from the nervous tissue prevents damage by: 1) Making more uniform and lower resistance contact with the nervous tissue, which in turn means an even current density and less heat production; 2) dissipating of the heat that is produced even under ideal conditions; 3) diluting HCl produced at the anode; and 4) supplying sodium ions in abundance (Lorente de No', 1947). As yet these destructive factors have not been overcome with needle electrodes, so that when current gets to blocking strength, tissue destruction results and resistance becomes still higher and a vicious cycle is started.

General anesthesia cannot be realized. Firstly, because the currents are shunted around the brain and brain stem, and secondly, it is quite likely that there would be little selective action of the anodal current between inhibitory

centers and excitatory centers, and all functioning would stop about the same time. Against this latter argument, however, is the fact that large motor nerve fibers are blocked before small motor nerve fibers (Kuffler and Gerard, 1947; Kuffler, Laporte and Ransmeier, 1947). Much of the current which was not actually shunted around the brain by the dura and cerebrospinal fluid would be passing somewhat parallel to the surface of the cortex and thus would not be as effective in producing anodal arrest. Even though the current density was obtained to produce arrest of the cortical function, the effect would not be felt in the diencephalon for the polarization effects do not penetrate to any great depth as judged by the monkey experiments and the human trials in which only cortical function was lost. Had the effects of polarization not been localized to the cortex, there would have been more signs or symptoms of the current flow. The only function that was arrested was the function of the cortex directly under the anode.

Electronarcosis as described in the literature seems to depend upon stimulating every structure in the central nervous system and the product depends upon the individual balance of total inhibition over excitation. Of course, if the stimulating electrodes are placed directly in contact with the inhibitory centers, these centers will receive maximum stimulation while the excitatory centers will receive minimum stimulation and flaccid, atonic, "drug

like" anesthesia should result. Electronarcosis on this basis, however, and anodal arrest of function of the motor cortex, producing a flaccid extremity, have little in common. Even an attempt to stimulate the motor cortex to exhaustion failed to produce anything resembling anodal polarization of the motor cortex.

The work of Forbes (1922), Burge, Petefish, Armitage and Saunders (1941), Burge (1947), and Grenell (1948) may lead to a more basic understanding of the entire process and would lend support to the idea of an equilibrium of cortical potential when the cortex is at rest; i.e., it is in equilibrium when the cortex is negative with reference to the scalp. The more negative (within limits), the more active the cortex and the more positive (or less negative), the less active the cortex.

One would expect the refractive cortex, which Penfield and Erickson (1941) describe as sometimes being found in the epileptic at operation, even in the absence of a recent seizure, would be quite positive in reference to the scalp, or it might be so far above the normal negative potential that it would be in a refractory state. At least it may be worth investigating.

Even the fantastic sounding explanation of how the polarity change comes about with chemical anesthetics may be within reason from the point of view of electrical possibility. It is quite well established, however, that

the cortex alone is not responsible for consciousness and unconsciousness, so that one would have to assume these potential changes are not confined to the cortex during anesthesia but apply to the diencephalon as well.

Any theory of general anesthesia must in the end postulate the vulnerability of one center, or the resistance of another, in order that the subject might lose consciousness and yet continue to perform vital functions, such as respiration and the maintaining of circulation.

To restate what has been said above, there is no similarity between electronarcosis, which depends upon a stimulating current (i.e., a current which will cause nervous tissue to fire when applied), and the arrest of function of the motor cortex by the application of an anodal current. The production of sleep by the action of a constant current, or a nonstimulating current of Hess (1932), however, may be an identical process. This could be proven if a method of producing anodal arrest of the center could be perfected which would not at the same time destroy the center. Without destruction the anodal current would cause a state of sleep which would be completely reversible and could be repeated time and again.

CONCLUSIONS

Anodal polarization by direct constant current is capable of rendering any part of the nervous system incapable of functioning while the current is flowing, and the function will return if the nervous tissue is not destroyed by heat and acid action. An obvious exception to this statement would be if a vital center were rendered incapable of function until death resulted. If the current is applied to a center which is active in maintaining a given state of the body, the state will change. Thus stimulation may appear to result from anodal polarization because of a release phenomenon.

A method has been found which meets all the requirements for use in the routine operation for seizures. It was successful in actual test upon the human. A danger exists, however, not to life but to upsetting the routine in the operating room by a severe convulsion if the circuit is broken just as the 20 milliamperes flow of current has been reached. When this was done intentionally with monkeys, convulsions resulted.

This same instrument will stop seizures if applied before they have become generalized, and will probably be of value for this purpose when a seizure is started with the stimulator during investigation at operation.

PART II

LOCAL PRESSURE

Local pressure was the first method investigated because of its simplicity and proven effectiveness. Its effectiveness in arresting the function of a local area of cortex was shown in clinical cases of depressed fracture, and, in at least one instance, Dr. Wilder Penfield has arrested speech by judiciously applying pressure, with the finger tip, upon Broca's area.

REVIEW OF THE LITERATURE

Aphasia, as a result of pressure on Broca's area, was known as early as July 1865, only four months after Broca's article (1865) was published. Bateman (1868) quotes a case of Dr. Lesure (published in Gazette des Hopitaux, 1865) in which a depressed fracture over Broca's area was treated by a large bone removal. Some time after, it was observed that pressure on the hair and skin over this area caused the patient to become aphasic while the pressure was applied. The power of speech returned when the pressure was released. A similar effect was sometimes obtained in the days when open drainage and packing of wounds of the cranial vault was considered good technique. It was found that a tight pack would arrest function, causing loss of speech or paresis depending upon where the wound

was located, and the removal of the pack would allow function to return. Sorrel and Sorrel (1944) report a case of depressed fracture in which the bone itself caused the pressure, resulting in right hemiplegia and aphasia. The removal of the depressed bone allowed function to return.

Subdural hematoma and non-infiltrative tumor frequently cause an arrest of function which is reversible if the cause is removed soon enough.

Reference to studies identical to ours cannot be found but there are related experiments. Using rabbits, with the dura intact, Glaser and Sjaardema (1945) applied very gradual pressure with a rod 0.7 cm. in diameter through a burr hole posterior to the motor area. Since the dura was not opened, a generalized increase of intracranial pressure was produced. The rod was advanced by means of a micrometer screw, 0.079 cm. per turn. At one turn there was delta activity, recorded from electrodes in the rod, and at 3 turns rapid and delta activity; at 7 turns delta predominated and at 12 turns the electrogram was iso-electric. The amount of EEG change is directly proportional to the amount of pressure. Release of the pressure showed a return of activity with the delta phase present but to a lesser degree. In addition, as the pressure was increased seizure patterns were the rule, and this was true to a much lesser extent upon release of pressure. Clinically, symptoms accompanying the increase of pressure

were of two groups; one group became motionless for a few seconds; another group exhibited generalized seizures which were difficult to distinguish from voluntary struggling. These manifestations were frequently associated with characteristic EEG seizure patterns. Other changes were an increased rate of respiration, increased heart rate, jerking of the head, movements of the nostrils, loud cries, gnashing of the teeth, jaw movements, dilatation of pupils and loss of sphincter control. Ninety-five per cent of seizure patterns involved the pressure electrodes; 42.5 per cent were definitely localized to the pressure electrode; and 47.5 per cent involved other electrodes.

Zimmerman and Putnam (1947), using the cat as the experimental animal, studied the effects of a sudden force on the middle Sylvian gyrus. The cats were under nembutal anesthesia. A rod of about 1 sq.cm. area at its end was suddenly brought against the dura through a burr hole, the force being supplied by an electromagnet (solenoid). This sudden force could be continued as a steady pressure until the electromagnetic field was allowed to collapse. Electrographic changes were recorded which were directly proportional to the amount of force and duration of pressure. Slow waves were less prominent than in the case of the very slow application of pressure and were inversely proportional to the amount of force. The investigators felt that electroencephalographic

changes varied with the amount of cell damage in a critical range but below this critical range cortical cell changes occurred without corresponding EEG deviations. Localized cell damage produced localized EEG changes. Unilateral convulsive patterns were produced by force. As with the gradually increased pressure, a point was reached at which the electroencephalogram became iso-electric.

Anoxia and asphyxiation of the brain will cause a decrease, or complete obliteration of the spontaneous activity of the cortex, and if the anoxia is not prolonged, the activity returns when the anoxia is relieved. Van Harreveld (1947b) injected Ringer's solution at body temperature into the cerebellar fossa and maintained a pressure of 5 to 6 cm. of mercury above the blood pressure. In 10 to 15 seconds most or all the spontaneous cortical activity had disappeared. Sugar and Gerard (1938) ligated the vertebral arteries and clamped the carotid arteries causing the electroencephalographic pattern over the motor cortex to change as follows: High frequency waves increase in speed and amplitude in 1 to 10 seconds or more, disappearance of all fast waves by 12 seconds, disappearance of slower 1 to 3 per second waves by 20 seconds and a continuation of this iso-electric condition to the end of the 29-second anemia period. When the carotid arteries were released the activity returned as follows: Electrical activity is ushered in by irregular slow waves 5 seconds after restoration, 6 to 9 per second spindles starting at 9 seconds after release and

lasting to 18 seconds; fast waves appear, spindles diminish in amplitude and increase in rate to 10 to 12 per second, and after 4 to 6 minutes the EEG is back to normal.

Local pressure on a peripheral nerve has been used by many investigators to block conduction in the nerve, and local pressure clinically not infrequently blocks the nerve until the pressure is released. To give an even pressure on the nerve Weir Mitchell (1872) and later Denny-Brown and Brenner (1944) used a bag filled with mercury. The amount of pressure was measured in centimeters of mercury rise as the bag was lowered upon the nerve. Seventy-six centimeters caused impairment of conduction, beginning at 20 seconds and being almost complete at 2 minutes. Complete recovery occurred in 6 minutes. Using 122 centimeters, failure of conduction was complete, and 16 minutes after release, recovery was almost complete. Denny-Brown and Brenner ascribe the reversible paralysis to ischemia and not to a direct consequence of pressure on nerve fibers. Variations in rate and extent of impairment of conduction are caused by uneven pressure gradients in the nerve bundles, with consequent variation in the degree of ischemia due to the escape of some small vessels. The effects of pressure on conduction have been graded by these investigators into four degrees: nil, paralysis with rapid complete recovery on release of pressure, paralysis with delayed recovery without

degeneration (intermediate type of pressure lesion), and complete anatomic lesion with degenerative phenomena. The third degree represents a lesion lasting from 1 to 19 days, possibly longer, without signs of loss of excitability below the lesion and with preservation of gross sensation throughout.

METHODS

Thirteen adult cats were used in the experiments and the method was tried on one human subject. In the cats the following procedure was carried out. A pressure device was used with which electrocorticograms could be made from beneath the center of a pressure block and at the same time electrical stimulation could be applied at the center of the block (Fig. 16). The procedure was to expose the motor cortex and apply the pressure block, the dura having been removed, to the area of fore- or hindlimb representation. Without applying pressure, a contraction of the limb was elicited and a continuous corticogram started. Pressure was then applied while the electrogram continued and after 30 seconds (shorter times with the $\frac{1}{2}$ cm.² block) a stimulus was sent through the electrodes under the plate. Another stimulus was applied at the end of a minute and each minute thereafter until no response to the stimulus was observed. The electrogram was continuous except where interrupted by the stimulus. When no response was obtained with stimulus, the pressure was removed, but the contact with the brain was not disturbed so that the electroencephalographic recording continued. Stimulation was carried out each minute until a good response was obtained after the pressure was released.

Bipolar parietal leads were also used, one on the hemisphere under investigation and one on the opposite hemisphere.

Figure 16

This is the final model pressure device which was designed for use on the human subject during craniotomy for treatment of focal epilepsy. The insert is an enlarged end view of the pressure plate showing the recording and stimulating electrodes. Power is supplied by a coil spring within a cylinder. This mechanism is quite similar in construction to that of a tire gauge. Pressure in grams is read at the top of the piston to which the pressure plate is attached. To apply pressure and maintain it for one to three or four minutes, the clamp is attached to the edge of bone around the exposure and the cylinder is brought down until the desired pressure is obtained (read off the piston above the cylinder). At this point the cylinder is locked in place by the thumb screw. It is important that the pressure plate be flat on the cortex so there is a ball and socket adjustment on the clamp. The piston, cylinder, and holder are aluminum.

The instrument was standardized by placing the pressure plate on a balance and lowering the cylinder until the desired weight was balanced. The weight of the piston and pressure plate are thus included and introduce no error as long as the instrument is used in a vertical position. Some error comes in when the instrument is used at a slant.

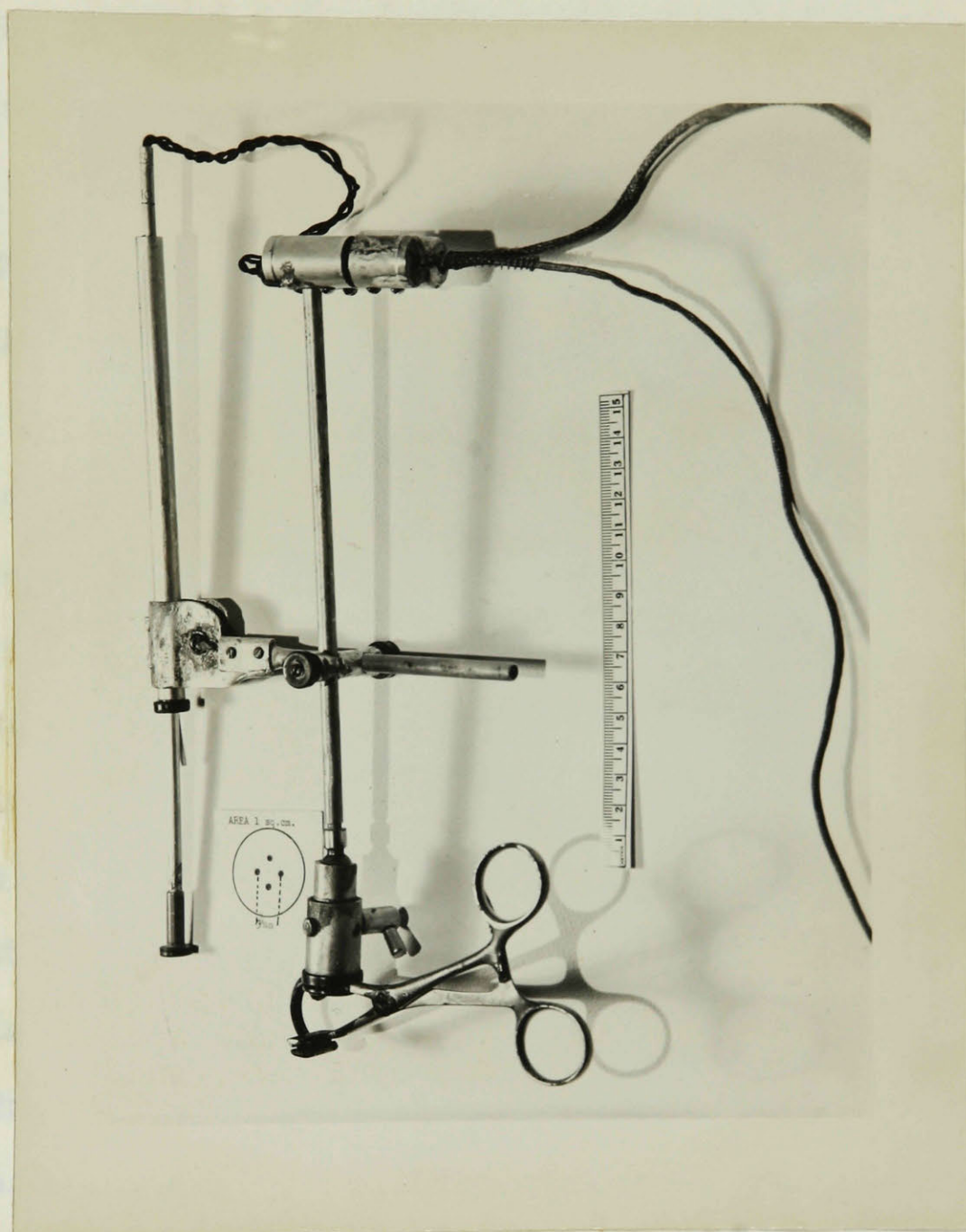


Figure 16

With these leads the extent of spread of the pressure effects could be observed.

In most of the experiments a 1 cm.² area circular plate was used for the application of pressure so that pressure reads in grams per cm.²

In the preliminary experiments a $\frac{1}{2}$ cm.² plate which was square and a 2 cm.² circular plate were used. In the $\frac{1}{2}$ cm.² plate the electrodes were at the four corners. In the 1 and 2 cm.² discs the electrodes were at the corners of a square, 3 mm. apart. This square was in the center of the disc.

Nembutal anesthesia was used. An attempt was made to have the animals in the same depth of anesthesia, but as usual this proved difficult.

At the close of each experiment the brain was fixed in formalin and sections were stained with H.V.G. and Nissl's stains. The sections included the anterior portion of both hemispheres so that in most cases one hemisphere acted as a control, since pressure was applied to only one hemisphere.

In one series of six cases only two applications of pressure were made to the left motor cortex. In the first, 50 Gm. and then 60 Gm. were used and in the second 60 Gm. and then 50 Gm. were used and so on, alternating through the 6 cases. The alternation was carried out to determine whether a second application of pressure was more effective than a first.

In the same series, at the end of 24 hours, two cats were again anesthetized with the same amount of nembutal as the first time and electrocorticograms were taken, the brain perfused and sections made. The same was repeated with two more except that they were observed for 4 days, and the last two observed for 8 days. This was done in an attempt to find any possible maximum of demonstrable damage from the pressure. Pressure was applied rather gradually in all cases.

The Rahm stimulator set to deliver the sharp saw tooth wave 60 cycles per second was used in most experiments. Two or 3 volts were used in most cases. In one experiment a square wave of 3.2 milliseconds duration and 60 pulses per second was used.

To function properly the instrument shown in Figure 16 must be as free of friction as possible and the piston must be as light as possible. Even the wires for recording which come out the top of the piston must be very light and free of spring effect. When the instrument is applied the pressure plate must be flat on the surface of the cortex (see legend of figure 17). Meeting these requirements presented technical difficulties which were gradually overcome by clamping the instrument in place, by using aluminum to reduce light weight, and wire for the same reason. Friction was minimized by using a few drops of sterile oil on the piston and giving the

bearings in the cylinder ample clearance. When the instrument pictured in Figure 16 was used on cats the cylinder was held by a dissecting microscope stand. The base of the microscope stand rested on the table and had ample adjustments to bring always the pressure plate down flat on the cortex. A rack and pinion moved the cylinder up and down. In the one trial on a human cortex the holder shown in Figure 16 was used. The clamp was applied to bone at the edge of the exposure and the pressure plate brought down flat on the cortex, then the cylinder was slipped down and locked with the set screw.

Figure 17.

The evolution of the final instrument is shown to some extent in this photograph. The instrument near the 1 on the centimeter scale had the advantage of being friction free but it was almost impossible to keep the pressure plate flat on the cortex. It was also found that stimulation electrodes must be led off to the stimulator by flexible wire, for touching the pressure block contacts moved the block. The dial type gauge at the 15 end of the centimeter scale proved to have so much friction that it could not be used. The piston type, whose pressure plate is between 4 and 5 on the scale, had the recording electrodes too near the edge of the block and apparently picked up electrical activity from cortex surrounding the pressurized area. Between 9 and 12 on the scale is an instrument which has a stronger spring and higher calibrations, built to apply the same grams per cm.² as the smaller plates. Shown on this piston is the cylinder which contains the spring. The two remaining pistons with their plates are just alike except that the one near 13 on the scale has rubber insulation over the solder joint between silver electrodes and hearing-aid wire. The insulation broke down after repeated autoclaving in the instrument near 5 on the centimeter scale.

Not shown in the picture is a dissecting microscope stand which for the cat experiments was attached to the cylinder and the latter brought down by a rack and pinion and locked in place. The stand had ample adjustment to allow for any angle of application.

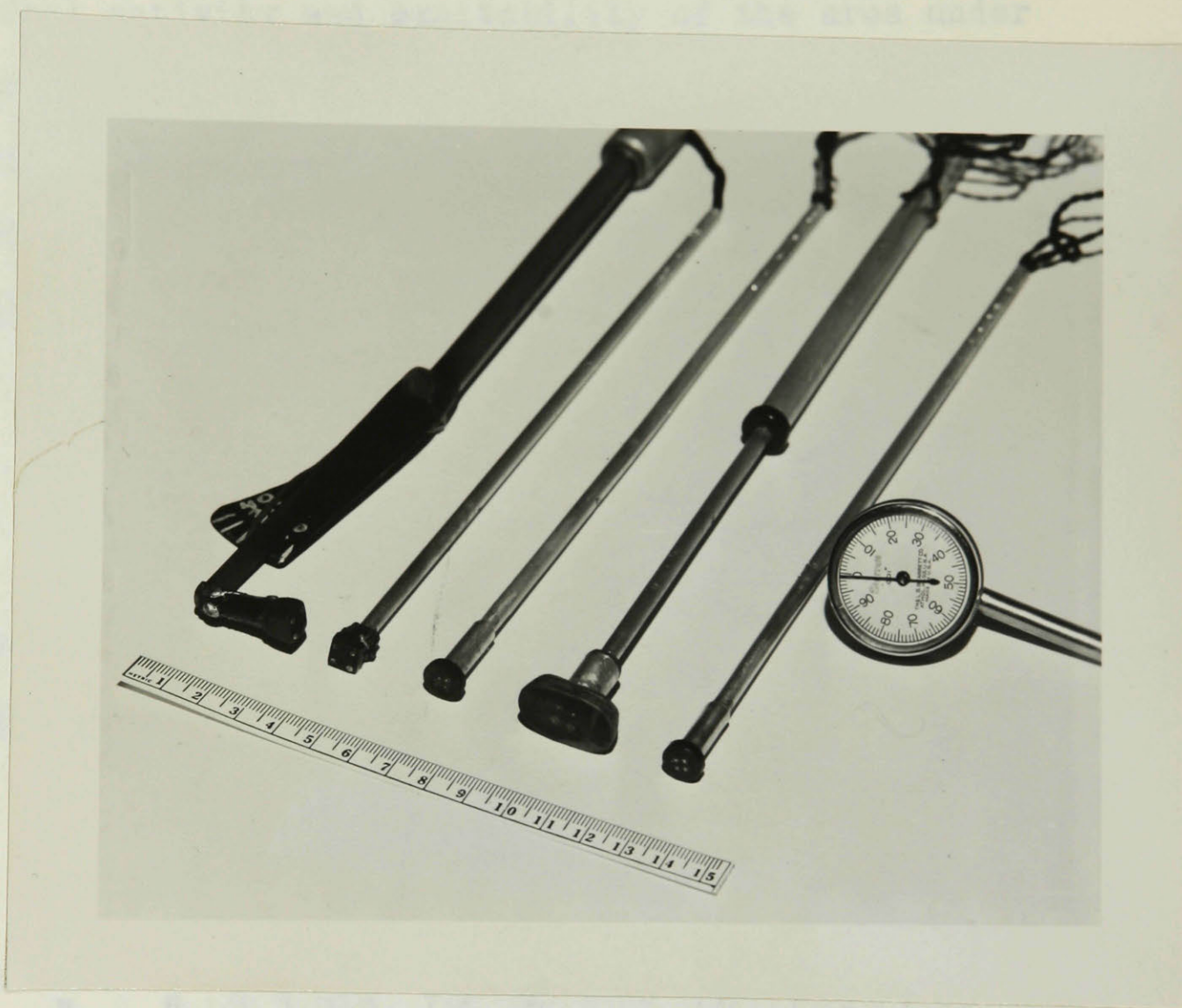


Figure 17

RESULTS

Local pressure on the motor cortex arrested the electrical activity and excitability of the area under pressure and the function of the area so subjected returned when the pressure was released. It took longer to accomplish this with pressure than with anodal polarization and the reversibility was less dependable, less complete, and much slower than was found for the electrical method.

Analysis of Results

50, 60, and 70 Gm./cm.² (36 runs)

Marked suppression of response 100%

70 Gm.	60 Gm.	50 Gm.
2.8 Min.	4.2 Min.	3 Min.

Average of 3.7 min. for the 36 runs.

"	"	3.3 min. for 34 runs (omitting experiment 12)
"	"	3 min. for 33 runs (omitting experiment 12 and another high run)

Complete return of response 72%

70 Gm.	60 Gm.	50 Gm.
3.2 min.	7 min.	2.7 min.
44%	70%	93%

Average time for the 72% to return was 3 minutes.

Partial return of response 22%

70 Gm.	60 Gm.
6.7 min.	9 min.
44%	30%

Average time for the 22% to return partially 8 minutes.

No return of response 6%

(Failure to return at all in two cases was probably due to a shift of the pressure plate, as EEG returned promptly.)

70 Gm.	50 Gm.
18 min.	1½ hr.
11%	7%

Marked suppression of electrical activity 91%

70 Gm.	60 Gm.	50 Gm.
2.6 min.	2.7 min.	3.2 min.
100%	82%	93%

Average time for marked suppression 2.8 minutes.
(In 2 cases EEG recording was unsatisfactory, i.e. 5.6% so the percentages are based on 34 runs instead of 36.)

Moderate suppression of electrical activity 6%

60 Gm.
3.5 min.

Little or no suppression of electrical activity 3%

50 Gm.
2 min.
7%

Complete return of electrical activity 80%

70 Gm.	60 Gm.	50 Gm.
7.2 min.	9.1 min.	5.5 min.
78%	69%	93%

Average time for the 80% to return 7 minutes.

Moderate return of electrical activity 14%

70 Gm.	60 Gm.
9 min.	17 min.
22%	8%

Average time for the 14% to return 13 minutes.

Slight return of electrical activity 2.8%

50 Gm.
3 min.
7%

Using $\frac{1}{2}$ cm.² block.

Marked suppression of response 100%

30 Gm.
1 min.

Leaving out one high of 6 min. the average is 0.6 min.

Return of response 63%

30 Gm.
4.2 min.
63%

Note: The 16 runs of the small block were not given time

to return in most cases so that the poor percentage of return shown is not accurate. Given as much time as in the controlled later experiments probably most would have returned. Also, the EEG was unaffected, probably because the electrodes were too near the edge of the block.

Using the 2 cm.² disc.

Neither response to stimulation nor electrical activity was depressed after 5 minutes at 50 Gm. and 70 Gm. (only one run at each pressure).

(More pressure or longer duration, or both, would almost certainly have given comparable results with the above.)

Progressive electroencephalographic changes with local pressure are shown in Figure 18 and the accompanying rise of threshold is noted. As the electrical activity decreases, the threshold to electrical stimulation rises; and, again, after release of pressure, as the electrical activity returns, the excitability returns. This parallelism between electrical activity and excitability of the cortex was not absolute, for at times one had disappeared before the other. There was only one example, however, in which, when the electrogram was iso-electric, a good response could be obtained and in this case there had been a spontaneous decrease in amplitude of the electrical activity between pressure applications which later involved other leads and suggested a spreading depression (Leao, 1944).

123.

Figure 18

Note that excitability and electrical activity disappear at about the same time and reappear after pressure release in about the same relationship. This relationship is not absolute, though if the electrogram is iso-electric the excitability is greatly reduced or there is no response at all.

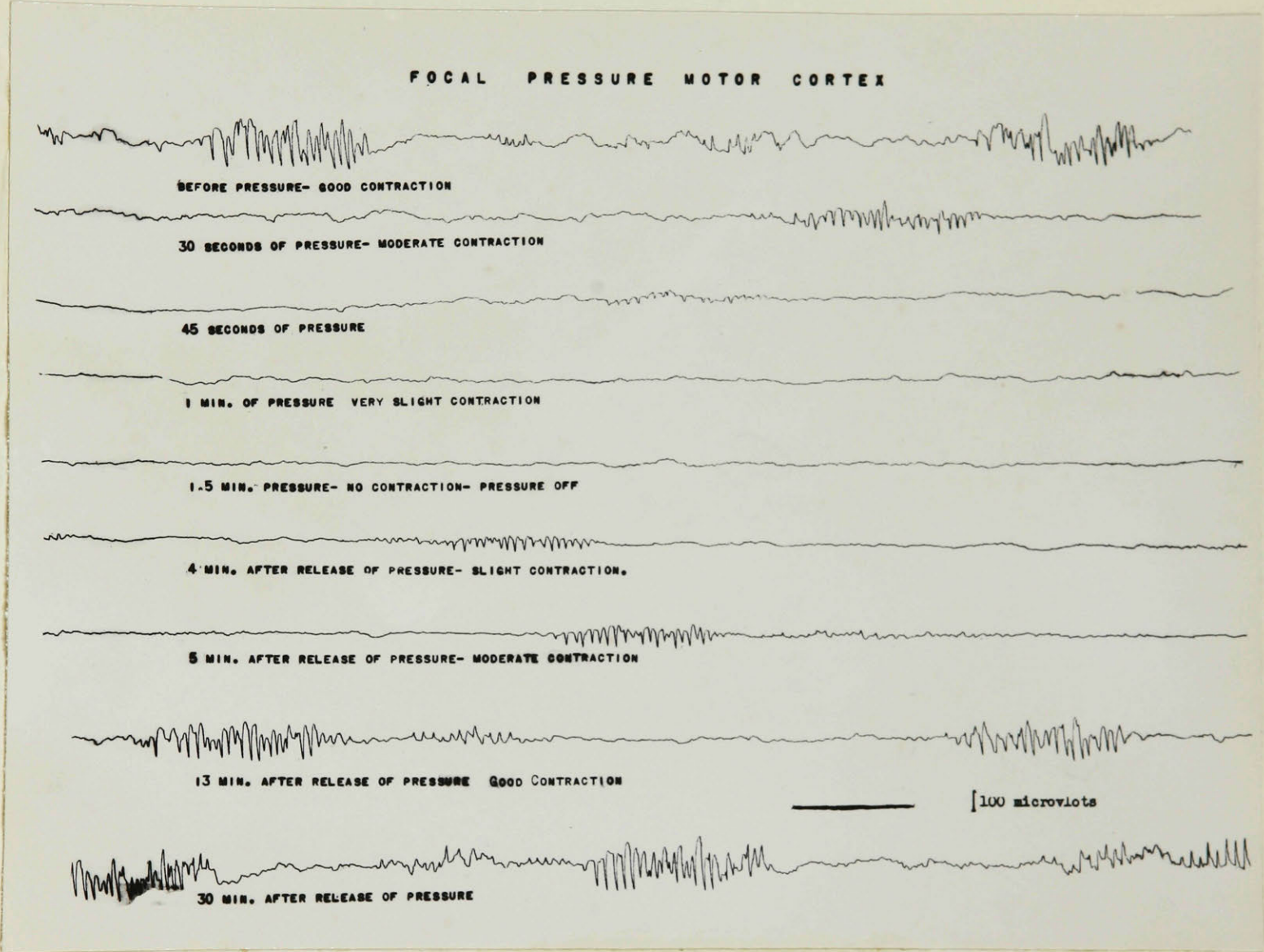


Figure 18

The effect of pressure was strictly limited to the area of the pressure block (Fig. 19). Bipolar recording electrodes one centimeter posterior to the pressure block were unaffected, with one exception, and bipolar electrodes on the contralateral motor cortex were also unchanged. The limitation of the effect was emphasized by finding that EEG recording electrodes at the edge of the pressure block picked up electrical activity from the surrounding area not under pressure, but the excitability under the block was depressed.

There was some suggestion that second or third applications of pressure to the same area were more effective than first applications so the following series was carried out. In a series of six cases only two applications of pressure were made to the left motor cortex. In 3 of the cases, 50 Gm. were first used and then 60 Gm.; and in the other 3, 60 Gm. were used first and then 50 Gm.

Figure 19.

Only the electrical activity under the pressure plate is influenced by pressure. Even when leads were placed a few millimeters posterior to the pressure plate the electrogram was not disturbed and electrodes on the contralateral hemisphere were also undisturbed.

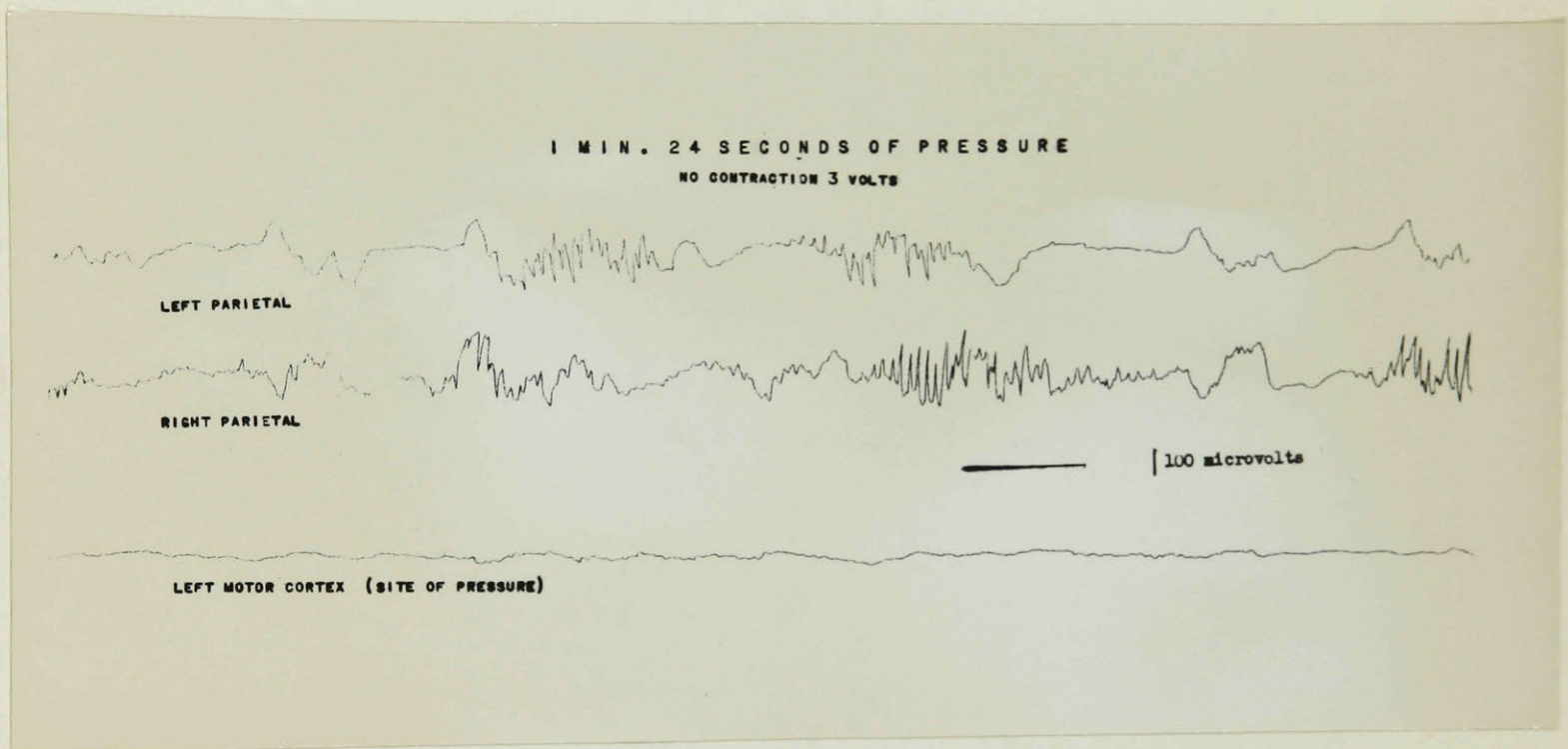


Figure 19

Analysis of First Applications vs. Second Applications.

	<u>Average time for 50 Gm.</u>	<u>Average time for 60 Gm.</u>
	<u>both 1st & 2nd</u>	
Suppression of response	4.6 min.	4 min.
" " EEG	4.2 "	3.3 "
Return of response	4.2 "	10 "
" " EEG	6 "	12.8 "
	<u>1st.</u>	<u>2nd.</u>
Suppression of response	3.8 min.	4.7 min.
" " EEG	3.7 "	3.8 "
Return of response	8.2 "	6 "
" " EEG	9 "	9.8 "

The above series shows that there is little difference between first and second applications of pressure.

In the chronic experiments the cats were clinically unaffected the following day, and for as long as eight days after pressure, (All experiments were terminated at eight days or less.) The one exception was a cat which had a slight paresis of the limb the cortical representation of

which had been under pressure, 16 hours after pressure, but the weakness had disappeared by 24 hours.

Microscopic Nissl and H.V.G. sections included, on the same slide, both the hemisphere which had been subjected to pressure and the hemisphere which had not, so that the latter acted as a control. The only difference detectable between the two hemispheres, under high or low power, was a little more reaction at the pial surface where the dural adhesion was a little more dense on the side of the pressure (Fig.20). Preliminary experiments, in which 8 to 12 applications of pressure were made on the same area of cortex, showed considerable petechial hemorrhage in the stained section.

The corticograms taken after pressure were unaffected in the one day, 4 day, and 8 day cats. One cat, not in the series, showed spikes in the EEG on the sixth day after pressure (Fig.21). There were some dural adhesions when the cortex was re-exposed for the electrocorticogram and the spikes may have been the direct result of freeing these adhesions.

In the trial of the pressure method on man, the 1 cm.² pressure plate was applied for 60 seconds to an area of cortex on or near the motor hand area. The depression of the cortical surface was so great and the procedure so time-consuming that the method was abandoned without further trial. There was no depression of the electrical activity

Figure 20.

Cross section (Nissl's stain X10) of motor cortex in cat. 50 grams pressure for 10 minutes and 60 grams pressure for 4 minutes were applied to the same area on the left motor cortex. The pressure plate was 1 cm.² in area.



Figure 20

Figure 21.

The electrogram was made from the cortex after the dura had been removed. There was some dural adhesion so that the spikes may be the direct result of injury to the cortex in separating the adhesions.

During this period of application and the patient continued to move his fingers voluntarily while the pressure was on.

Though this pressure method will probably never be used as an aid in the localization of any kind of abnormality in the motor cortex, it may have some application in experimental work with animals. An example

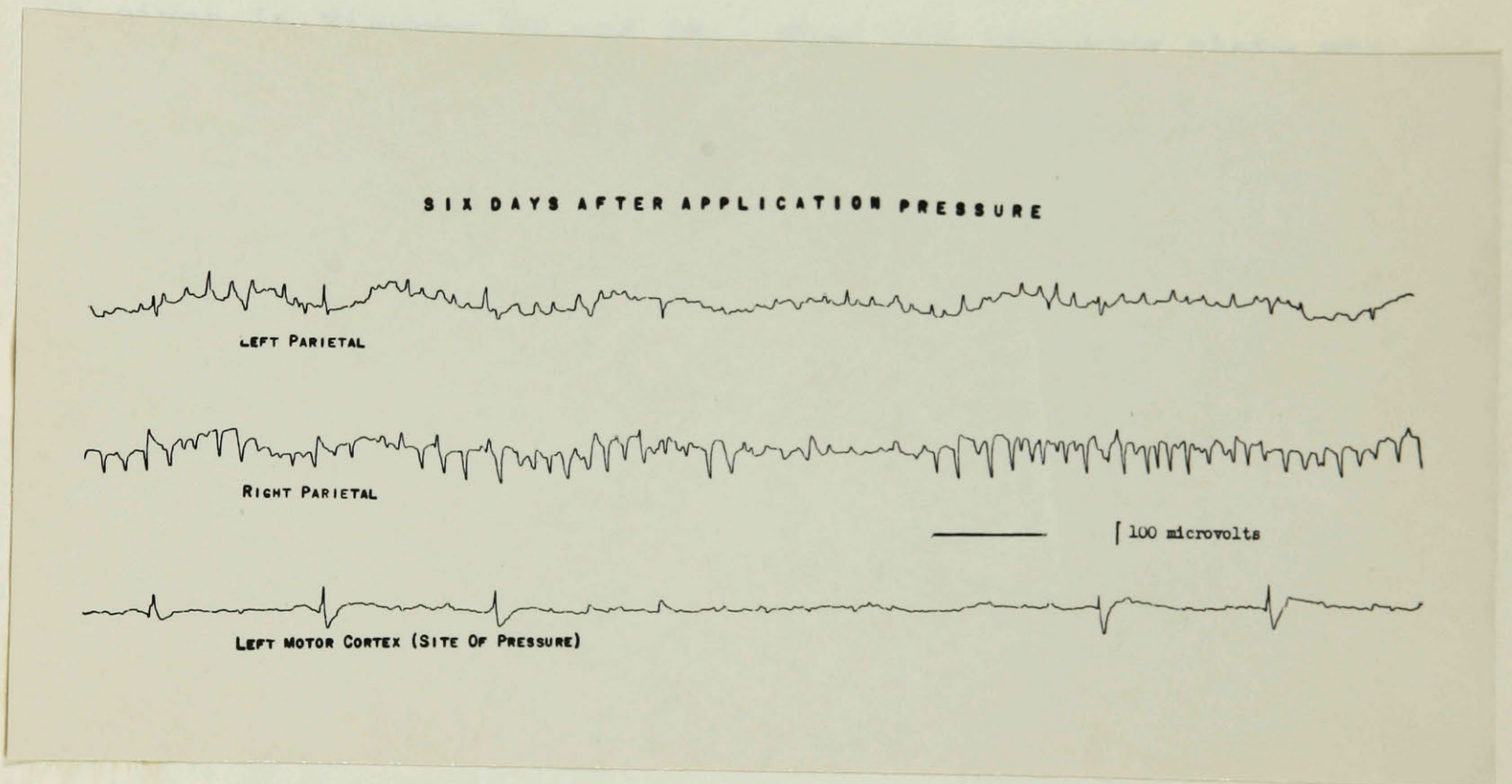


Figure 21

during this period of application and the patient continued to move his fingers voluntarily while the pressure was on.

Though the pressure method will probably never be used on man as an aid to cortical localization it may find some application in experimental work with animals. An example is given in Figures 22 and 23. When the pressure plate was applied to an area of cortex from which conducted strychnine spikes were being recorded, these spikes were abolished, but the spikes from the strychninized area of the contralateral hemisphere continued. Of course the spontaneous activity under the pressure plate was abolished also (Fig.22). When the pressure plate was applied to the strychninized area all the spikes disappeared from both hemispheres. In this case the spontaneous activity on the non-strychninized side continued (Fig.23).

Figure 22.

In the figure only the conducted strychnine spikes are abolished by pressure on the homologous area of the contralateral hemisphere from where the strychnine was applied. This would correspond to applying pressure to a false focus of epileptic discharge with the true focus still firing.

This preparation was made by applying strychnine to an area of cortex. In a short time spikes could be recorded both from the local area and from a homologous area on the contralateral hemisphere.

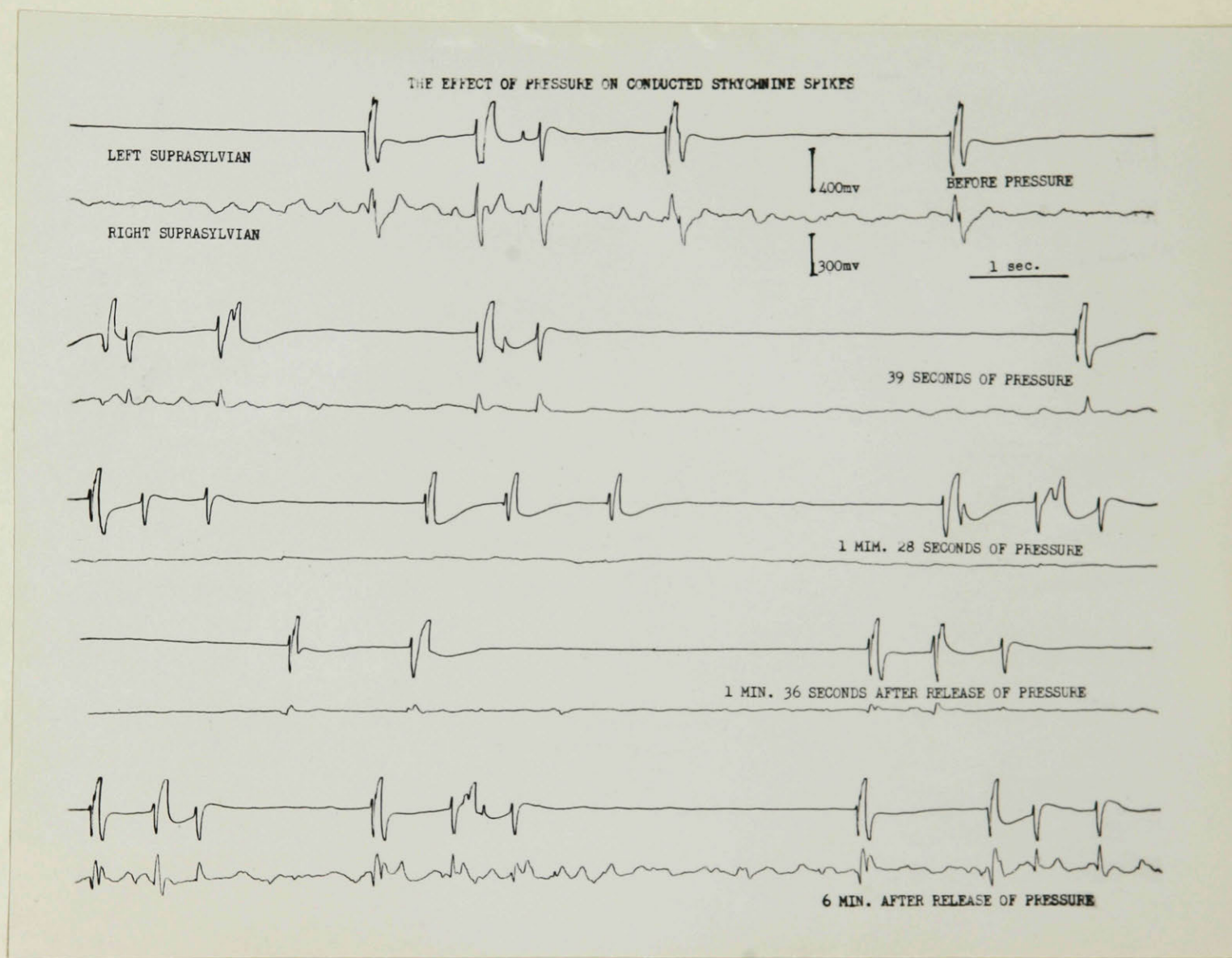


Figure 22

Figure 23.

Here the pressure was applied to the strychninized area and all strychnine spikes were abolished, i.e. those from the strychninized area and from the homologous area on the contralateral hemisphere. This would be similar to applying pressure to the true epileptogenic focus and abolishing the abnormal discharge from that focus as well as abolishing the conducted abnormal discharge.

Note that spontaneous activity from the non-strychninized contralateral area continues.

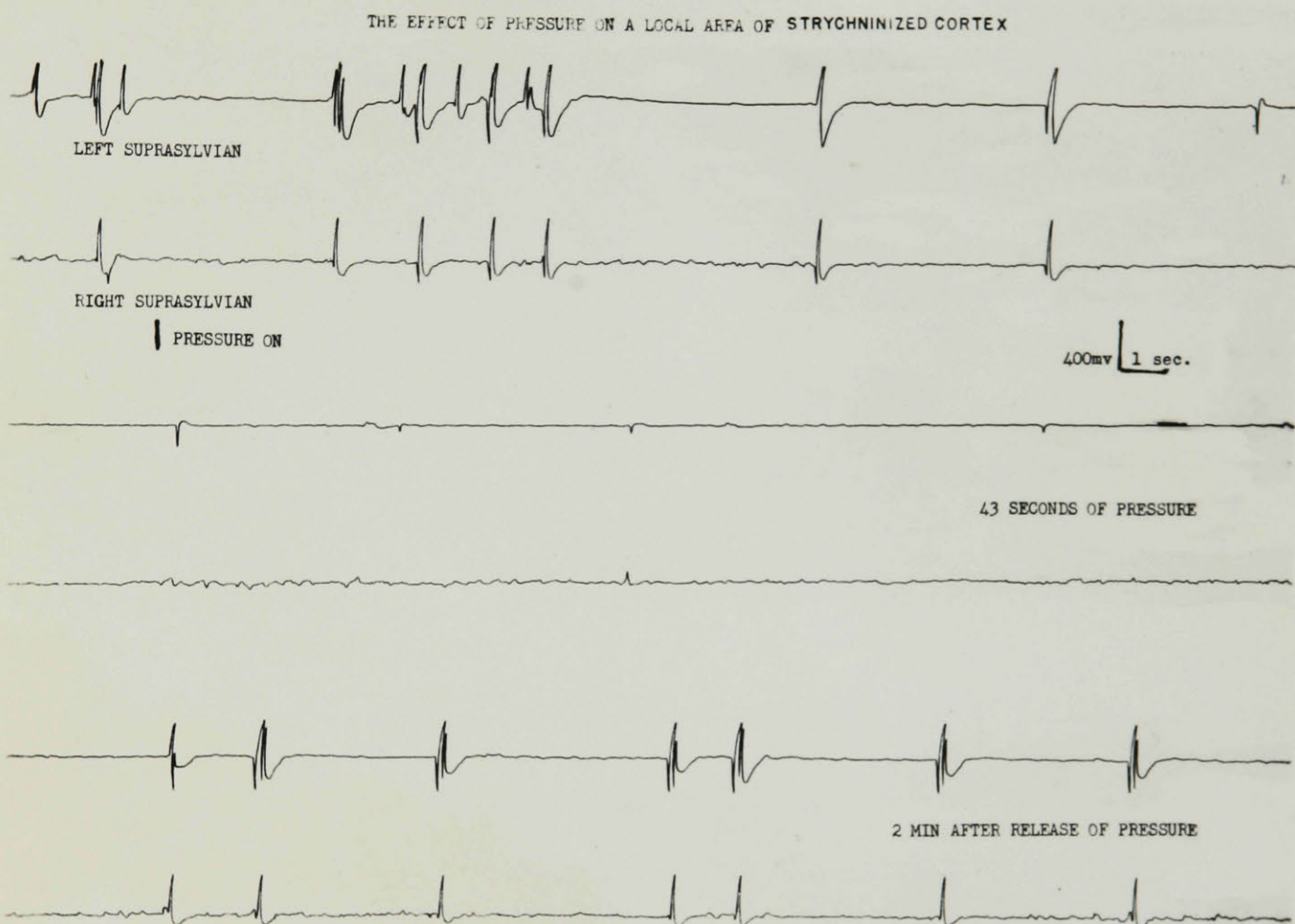


Figure 23

DISCUSSION

Depressed fracture (Sorrel and Sorrel, 1944), subdural hematoma, drainage packs, non-infiltrating tumor, and pressure on the skin over a large bone defect of the cranial vault (Bateman, 1868), all may cause a temporary reversible arrest of function. Pressure applied very slowly (Glaser and Sjaardema, 1945), less slowly (as in this investigation), or as a sudden force with continued pressure (Zimmerman and Putnam, 1947) also causes an arrest of the cortical activity at the site of pressure and in a critical range this is also a reversible process. Finally, an interference with the blood supply to the brain as a whole, ligation of the vertebral, and clamping of the carotid arteries (Sugar and Gerard, 1938), increasing the pressure in the cerebellar fossa and thus compressing the great vessels of the brain (Van Harreveld, 1947b), will also cause an arrest of cortical function which may be temporary and reversible if it is not continued too long.

The mechanism of arrest of function by local pressure is the same as a general arrest of cortical function after ligation of the great vessels to the brain. In both cases ischemia is responsible for the arrest of function. The arrest may be brought about by ischemia without damage to the cortical cells, but the same degree of ischemia if

continued long enough will result in a less reversible cell damage with slower recovery. If continued still longer, permanent damage may result from which there is no recovery. Added to this effect of ischemia may be the effect of trauma. The trauma may be due to a sudden displacement of the cortical tissue locally deranging it, without actual laceration, as in the case of the depressed fracture and the sudden force of the rod in the Zimmerman and Putnam (1947) experiment.

The later authors regard all electroencephalographic changes as due to trauma of the blow and do not consider ischemia as a factor. They show that a sudden blow, unsustained as pressure, is not as effective in causing arrest of function as when there is time enough for ischemia to have its effect. The fact that time is important is not emphasized in their discussion, and only the effect of trauma of the cortex is considered important in arrest of function.

Ischemia is the most important factor in the production of arrest of function, and there is a critical time-pressure relationship at which arrest of activity can be accomplished without harmful distortion of the nerve cell bodies and without asphyxiation of the cells by too prolonged ischemia. Given two pressures which will cause arrest of function of an area of cortex, the greater pressure will have the slower recovery time when other factors are equal, such as size of pressure plate, and duration of application. This suggests

that trauma to the nerve cells is greater in the higher pressures and accounts for the slower return of function. It is possible that it is merely due to a more complete ischemia in the higher pressure, but the former is more likely and is supported by the work of Denny-Brown and Brenner (1944).

The fact that second applications of pressure are no more effective than first applications is good evidence that return of function is complete between applications of pressure.

Fast activity followed by delta and sometimes seizure patterns is more apt to occur when the ischemia is not complete enough to cause arrest of function but just enough to cause an abnormal state and excitation. The stimulation effect may also occur as the result of a blow to the cortex when the pressure is applied suddenly.

Glaser and Sjaardema (1945) describe clinical symptoms which, in very lightly anesthetized animals, must be a pain reaction and not true seizures. The pain was probably due to the stretch put on the dura by the pressure bar. This reaction is well known to the neurosurgeon who finds it hard to manipulate the dura in the unanesthetized patient because of the rich sensory nerve supply.

CONCLUSIONS

Local pressure, though effective in arresting function of the cerebral cortex, by rendering the cells ischemic, is not as effective as anodal polarization. There is a longer and less definite recovery period and a more indefinite depression of excitability. The critical range of pressure between a reversible paralysis, and permanent cell damage with incomplete return of function, is not as great as is desirable.

The effect of local pressure is strictly limited to the pressure plate and because electrographic recordings can be made while pressure is applied, it may prove useful as an aid in experimental procedures on animals but will probably never be used as an aid in the localization of an epileptogenic focus in man.

GENERAL SUMMARY

A completely reversible paralysis of a discrete area of cerebral cortex, whereby the surgeon can determine in advance what the effect of removal of that area would be, has been accomplished by a method of anodal polarization. Paralysis is induced in a matter of seconds, may be continued as long as the constant current is flowing and function returns a few seconds after the current is reduced to zero. A gradual increase of galvanic current from zero to 20 milliamperes, with the anode a saline-cotton wick on the cortex, and the cathode a large saline-felt pad on the back, causes paralysis of the 1 cm.² area of cortex without stimulation in about 30 seconds. When the current is reduced to zero gradually, function returns completely, immediately or in a few seconds. The method has been used on unanesthetized monkeys and one trial has successfully been made on man. A caution is necessary, for if the current were suddenly broken with 20 milliamperes flowing, a 10 to 20 volt shock would be delivered to the cortex and a convulsion would likely ensue. Local seizures, of the Jacksonian march type, can be quickly and completely checked by applying the anode to the appropriate area of cortex and gradually increasing the current to 20 milliamperes.

A second method, local pressure, is described but is less effective. Sixty grams on a 1 cm.² disc for about 3 minutes will suppress electrical activity and excitability and function returns a few minutes after release of pressure. This method is not as reliable as anodal polarization.

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