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THRESHOLD MOVEMENTS PRODUCED BY EXCITATION OF CEREBRAL CORTEX AND EFFERENT FIBERS WITH SOME PARAMETRIC REGIONS OF RECTANGULAR CURRENT PULSES (CATS AND MONKEYS).

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INTRODUCTION

SINCE THE EARLIER studies on mapping the motor cortex (24, 27, 32), there has developed an increasing awareness of the role of the stimulus parameters[1] (4, 5, 6, 7, 8, 9, 10, 20) and of anesthesia in the cortical maps obtained (16, 17, 26, 28). A map[2] determined with one set of parameters may be only one of a group of maps which vary with the parametric set[1] (and the parametric region[1]) and with the values employed on a given cortical region. It is well known that the responding parts and the type of movement change radically when the electric current is raised above its threshold value[3] (10, 18, 24, 27). It is also known that train duration[4] and train repetition frequency[4] can markedly alter the responses to stimulation (4, 5, 6, 7, 8, 9, 20). The influence of the frequency of the waveforms in the train is recognized (18, 34) and is being investigated for pulses (29); the

[1] A "parameter" is defined (as in the mathematical sense) as an independent, controllable variable whose values can be chosen to distinguish the various specific cases of a general functional form (which, here, is to be experimentally determined). A "parametric set" is defined as a given group of parameters whose ranges of values are to be chosen (for a given experiment). A "parametric region" is determined by the simultaneous choice of an upper and lower limit (range) for the values of each parameter of a given set. A "parametric point" is defined as the group of simultaneously assigned single values, one for each parameter, of a set. A "parametric line" is a set of parameters all of whose values are fixed except for one (say, peak current); in a "parametric area," two are not fixed; in a "parametric volume," three are not fixed. The parametric set chosen for the stimuli in this paper are pulse amplitude (I.), duration (P.D.), repetition frequency (P.R.F.), and train duration (T.D.); I. is held constant during each train. Train repetition frequency is held constant throughout at 1 per 60 seconds.

[2] A "map" is here defined as a set of data referred to (cortical) spatial coordinates, derived from measurements or observations of some function relating that (cortical) space to another space (such as the peripheral one). A family of maps, called "threshold maps," are here defined as those determined by threshold current values in different parametric regions.

[3] The "threshold current" is defined as the least peak current value on a parametric line eliciting a minimum observable movement irrespective of location in the periphery or type or timing of the movement.

[4] A stimulus "train" is a series of pulses of the same current waveform at a constant frequency and amplitude. "Train duration" (T.D.) is the time such a train passes through the animal. The rate at which such trains are repeated is called the "train repetition frequency" (T.R.F.).

effect on threshold in the case of sine waves has been studied (34, 35). Some studies on the importance of the waveform have been made (50). Adequate methods of waveform measurement applicable to most waveforms have been described (21, 22, 36, 39). Some studies of a few parametric points[1] of several parameters have been published (3, 4, 5, 6, 7, 8, 9, 18, 20, 29, 34, 41, 50). Results of stimulating unanesthetized man (23, 44, 45) and unanesthetized animals (14, 15, 16, 17) suggest that anesthesia is an important factor. Recent threshold maps (48, 49) have been done with a single parametric line.

In order to evaluate the importance of some regions of the known parameters of stimulation in their contribution to "threshold maps,"[2] we have investigated the threshold values[3] of current trains of one simple waveform, the unidirectional "rectangular" pulse, applied to the motor cortex of cats and monkeys (12). The current through the animal, of every stimulus train, was observed and measured with a cathode ray oscilloscope technique. Wide ranges of several parameters applied to a few cortical zones have been studied. To evaluate the role of narcosis, both anesthetized and conscious preparations were investigated.

We have found that the quantity of electricity in a train at threshold ("coulomb threshold") is less (despite a larger "current threshold") for shorter duration pulses than for longer duration pulses, in the range covered, at all repetition frequencies investigated. These observations suggest that long duration pulses may waste large quantities of electricity which transport ions not useful in the excitation processes, and which may lead to cellular injury in the cortex.

Our results suggest (1) that certain parametric regions[1] of this electric waveform stimulate mainly cortical efferent cells and/or fibers, (2) that other regions stimulate both cortical summating cell groups and the efferent systems, and (3) that long periods of stimulation by unidirectional rectangular pulses injure first the summating cell groups at the cortex, later the efferent system, and injure the summating cell groups more than the efferent system.

METHODS

1. *Choice of electrodes.* A single cortical electrode and a large body electrode (in contrast to 2 cortical electrodes) were chosen as a configuration producing a simple current flux pattern in cortex and underlying white matter. In order to keep the waveform of the rectangular pulses constant at all values of current amplitude (I.), pulse duration (P.D.), pulse repetition frequency (P.R.F.), and train duration (T.D.) used, we found that it was necessary to devise special cortical electrodes (Fig. 1) for use with the two available stimulators. With electrodes of the type usually employed for stimulating the cortex (1 mm. diameter, chlorided silver, or platinum balls), it was found that polarization capacitance and polarization resistance (37) distorted the pulse waveform in a way that usually changed during a train (Fig. 4). These variations were found to depend on the impedance of the pulse source (Fig. 3), and could be corrected by raising the source impedance to 10 to 100 times that of the electrode-animal circuit. However, this solution to the problem has the disadvantage that hydrogen, oxygen, chloride, and other electrolyte concentrations rapidly change in the vicinity of the metallic surface of the cortical electrode, with unidirectional waveforms (40). Also, if the current density at the metal-liquid interface is

high enough, the decomposition potentials (of water and other substances) are reached; at higher current densities gas bubbles form (25, 40).

In order to minimize these effects, and to remove the site of their action from the pia, the reversible (19) electrodes in Figure 1 were used. In each case the current density is kept low at the metal interface by using a large area of chlorided silver exposed to a volume of solution not directly in contact with the pia. The ionic current is conducted through this solution (in a cavity in lucite) and through a short (1 mm.), narrow (0.3 to 1.0 mm. diameter) "pore" to the pia or arachnoid. The current waveform through this form of electrode is undistorted over the ranges of pulse amplitude (I.), pulse duration (P.D.), pulse repetition frequency (P.R.F.), and train duration (T.D.) employed, for a period of days at a time (Figs. 3 and 4); a source impedance as low as 100 ohms does not effectively change the waveform.

The non-cortical electrode (the external cathode, in these experiments) was changed

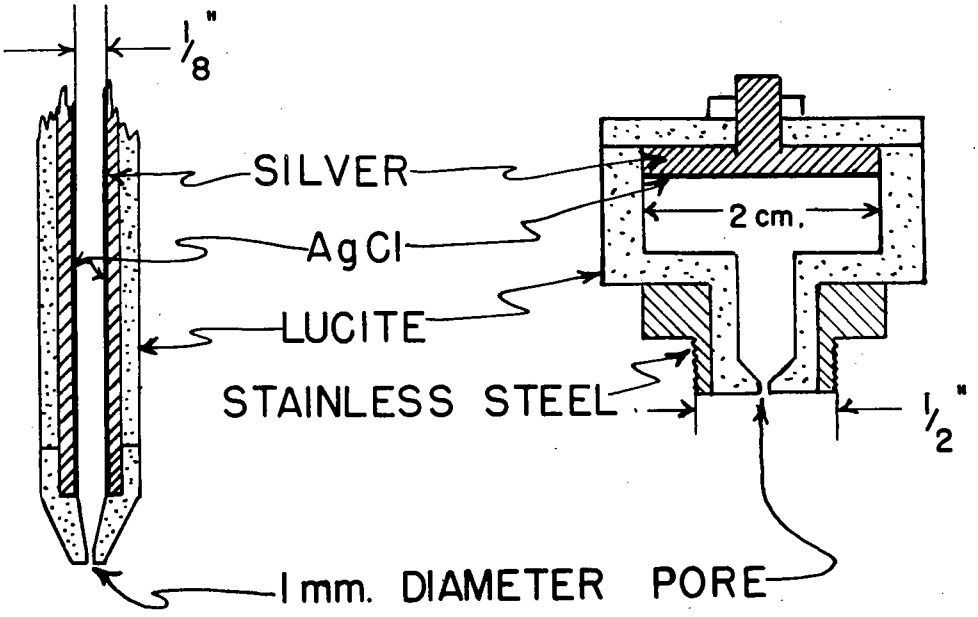

FIG. 1. *Reversible Electrodes for Cortical Stimulation.* Both electrodes have a large area of AgCl in contact with the electrolyte bridge to the pial surface. The one on the left (number 1) was built for and used with a Horsley-Clarke instrument for fixation. The one on the right (number 2) is designed for implantation in the skull. Another electrode similar to number 1 was used with a skull edge clamp, on one monkey (070949, see text). In use, the pore of number 1 is pressed against the pia until a slight indentation is seen around the edge of the lucite end piece; this assures close contact without an electrolyte shunt above the pial surface. Number 2 was constructed so that when the threaded ($\frac{1}{2}$ inch) stainless steel shell was screwed into a $\frac{1}{2}$ in. trephine hole in the skull of a young monkey, the polished lucite base pressed the pia inwards about $\frac{1}{2}$ to 1 mm. The current waveform through these electrodes is shown in Figures 3 and 4. In all cases, this electrode was the circuit anode; a large cathode was located elsewhere on the body (see text). Number 1 was used for the animals of Figures 5 through 13; number 2 was used for the monkey of Figures 15 through 18.

several times during the course of our work. A rectal chlorided silver bar was used and abandoned because of stimulation of peripheral nerves to the hind legs. When used as the cathode, the Horsley-Clarke frame was found to stimulate jaw and neck movements. The most satisfactory cathode was a chlorided silver band ($1'' \times 10'' \times \frac{1}{16}''$) wrapped in gauze, fitted snugly around the belly, and kept wet with saturated sodium chloride solution. This electrode reduced the current density below threshold in the nearby nerves and muscles quite satisfactorily. With small animals (a 3 kilogram monkey, for example) we sometimes had some neck responses (bilateral) at very low frequencies due to funneling of the current through the neck; by finding that these movements gave no after-discharge and had but slight "frequency sensitivity" (see below), we eliminated them as not originating at the cortex.

2. *Electrode fixation.* In the anesthetized animal with exposed cortices, the head and cortical electrode were fixed in a Horsley-Clarke frame in the usual manner.

A reversible, implanted electrode was used in one unanesthetized monkey (140949). The assembly is shown in Figure 1, its performance in Figures 3 and 4. We feel that this technique is the most satisfactory to date: we agree with previous investigators as to the advantages of implantation (16, 17). We found that this reversible type is easy to construct and use; it has the advantage over the previous non-reversible types (16, 17) of keeping the waveform constant over wide current, frequency, and train duration ranges.

3. *Pulse sources.* Two stimulators were available for our use, both designed by J. H. Busser. The first one has a pulse duration range from 0.05 to 500 milliseconds, a pulse repetition frequency range from $\frac{1}{3}$ to 490 pps., and peak current and voltage outputs at a maximum of 200 milliamperes and 210 volts. The second is basically like the first, with additional range of pulse duration (50 microseconds to 10 seconds) and of pulse repetition frequency (to 7500 pps.), and the addition of a train duration control (range 1 ms. to 4 sec.). The output resistance varied with the setting of the amplitude control from about 100 to about 1000 ohms; the variational output resistance is about 50 ohms, before reaching the output attenuator. The 5-second train duration and the 1-minute train repetition frequency were controlled by an electric clock motor, cam and microswitch assembly. The

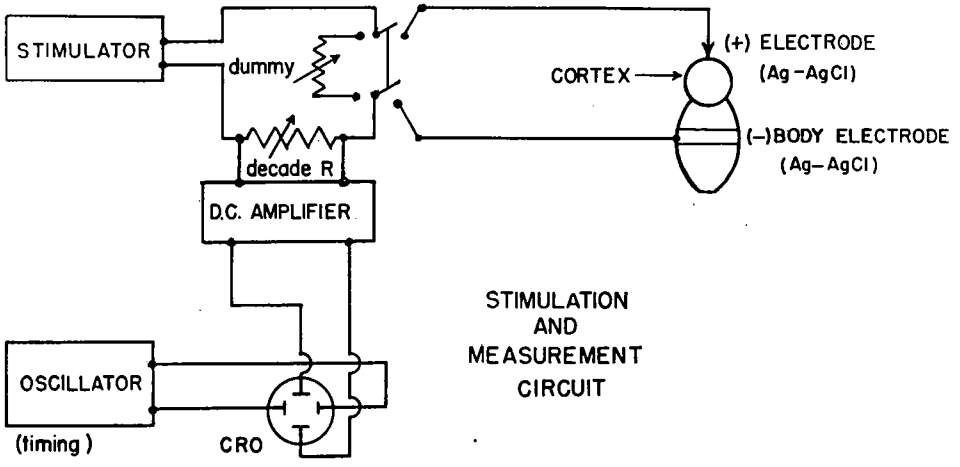

FIG. 2. *Circuit Used for Measuring and Adjusting Stimulating Current.* The current is measured by observing the peak voltage drop through a resistor ("decade R") in series with the minus (ground) lead from the stimulator. This voltage drop is amplified by a direct-coupled amplifier ("d.c. amplifier"), and observed as vertical deflections on a cathode ray oscilloscope ("CRO"). By means of a double pole, double throw switch, a 10 kilo-ohm variable resistor ("dummy" animal, whose value is chosen to equal that of the animal circuit) is substituted for the animal-electrodes circuit. The oscillator (or a sweep synchronized with 60 cps. line voltage) is used for setting the stimulator frequency to known values for each train. The stimulator ranges are described in the text.

positive pulse waveform has a rise time of 10 microseconds and a fall time of 8 microseconds through our electrodes (Fig. 3) at all pulse durations and pulse repetition frequencies used.

4. *Current measurement technique.* Every stimulus train passing through each of our animals was observed and measured on a cathode ray oscilloscope (39). This procedure assures avoidance of errors due to unforeseen variables (large swings of line voltage, contact or electrolyte changes, output potentiometer variations, changes in circuit components, drying of body electrode, etc.). In order to be sure that each train was a true parametric point,[1] the pulse waveform, amplitude, and frequency were measured for each train by one observer. The measurement circuit is shown in Figure 2.

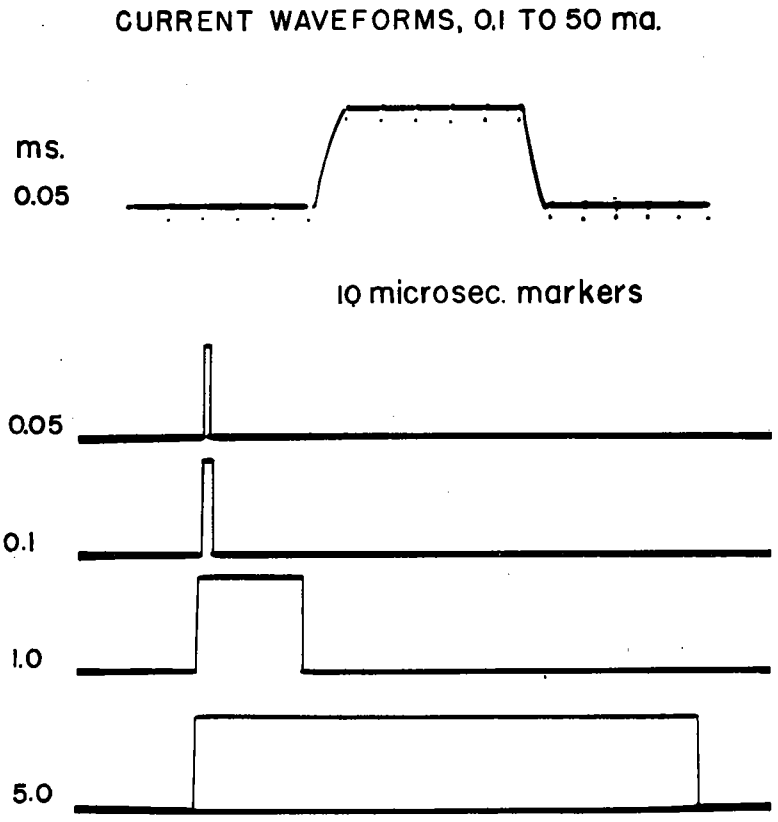

FIG. 3. *Current Pulse Waveforms Through the Electrodes.* The pulse durations are given, in milliseconds, on the left hand edge of the figure. The topmost record is on a fast sweep, the lower 4 on a slower sweep. In the top trace, it can be seen that the rise time is about 10 microseconds (dots and breaks in the trace at 10 microsecond intervals) and the fall time is about 8 microseconds. These values were found to be constant at all pulse durations used. The lower 4 traces show the rectangular current waveform up to pulse durations of 5.0 ms.; at pulse durations up to one second the rectangular form is maintained. The peak current limits shown on the figure are those over which records were taken; the forms were observed to be fairly constant up to at least 100 ma. peak values at all pulse durations up to 1 sec. The zero current line was recorded in the case of the 5 ms. pulse (lowermost trace). These waveforms were maintained over a range of output resistance (stimulator) from 100 ohms to 3 kilo-ohms. (The rise and fall traces were retouched for reproduction purposes.)

The "dummy animal" is a variable resistor (matched to the animal circuit) which is substituted for the electrode-animal circuit in order to set the value of current for the next stimulus train without stimulating the animal. This substitution allowed the threshold to be determined rapidly and to the desired degree of fineness.

The series resistor ("decade R") is a step-control decade wire-wound resistance box with a minimum value of 10 ohms and an accuracy of all values of resistance of plus and minus 0.5%. Values greater than 1000 ohms were not used in any of these experiments. The d.c. amplifier and cathode ray tube have a maximum sensitivity of 0.1 volt/inch; the pass band is wide enough to show a 100 kilocycle "square wave" as a reasonable approach to a rectangle. A battery-powered calibration unit was used to adjust the d.c. amplifier gain and to check the voltage values given to the measuring circuit.

Short, widely spaced leads were used to avoid errors due to shunt capacities between leads and between them and ground. The animal and supports were thoroughly insulated from ground to avoid unknown leaks of current.

5. *Operations.* In the first series of animals, dial (40 mgm./kilogram, ½ intramuscular and ½ intraperitoneal) was injected preoperatively, the scalp reflected, and the skull re-

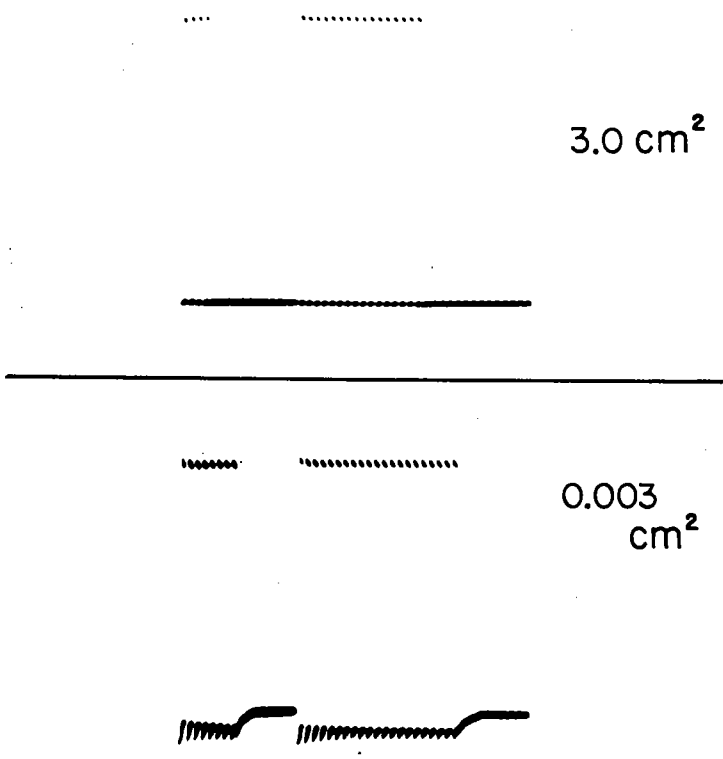

FIG. 4. *Effect of Area of Metal on Electrode Performance.* In each case the currents of 2 trains of 5 ms. pulses, 60 pps., and 1.0 milliamperes from a 500 ohm source are recorded. In each record, the fast rise and fall of the waveform does not show. The top record is through electrode number 2 (3.0 cm.² of AgCl surface) Figure 1, and shows the constancy of the waveform and peak current during a train. The lower record is through a small (0.003 cm.²) Ag electrode (AgCl surface) and shows that the waveform changes during each train. The peak value of current falls during each pulse ("electrode charging phase"), swings below zero after each pulse ("electrode discharging phase"), and, at the end of the train, slowly drifts up to zero current. By increasing the area of metal in contact with the electrolyte or by using a high source impedance these effects are attenuated (see text).

moved by trephine and rongeur. The dura was removed from the side to be stimulated. Hemostasis of bone was obtained with bone wax. No cautery was used. Procaine (1%) was used on fixation points to avoid pain. Each animal of this group was suspended from a horizontal bar, leaving all four limbs pendant under gravity.

In the case of the implanted electrode animal (macaca 140949) (nembutal, 26.4 mgm./kilogram), a 0.5 inch hole was cut in the scalp, which then freed up from the bone around the hole. A 0.5 inch trephine hole was cut through the skull. The dura was removed in the bottom of this hole, and the electrode assembly screwed into place immediately. The skin was pulled up against the electrode shell with a purse-string suture. Penicillin was used pre- and post-operatively.

In all animals, there were cerebro-spinal fluid leaks due to a punctured or torn arachnoid membrane.

Two monkeys (070949 and 140949) were operated upon and restrained during the stimulation period in a seat-table combination, previously designed by one of us (W. W. Chambers) for use in mapping motor cortex (11).

6. *Procedure in determining thresholds.* In the usual experiment there were three observers. One observer watched the cathode ray tube face, monitored the waveform, measured the peak current, and set the current for the next train. The second man watched the movements and recorded the data. The third man watched movements and plotted the data as each threshold was determined.

Two procedures for setting the current were used: the first, called "creeping up," consisted of starting at a very low current and increasing it by very small increments (5% or less) until the first faint movement was detected. In the second method, called "bracketing," the increments were larger and one went above and below threshold on alternate trains gradually narrowing the range until one had the smallest detectable movement. No striking difference was noted in the two thresholds determined by these methods. We used bracketing for the points where we could predict the threshold fairly well in advance from the plot of previous data, and used creeping up when in unknown regions.

In each case, the current was held at threshold for the next few trains to see the responding part and the type and the timing of the movement clearly enough for agreement among the observers.

Plotting the results immediately (on log-log paper, 3×5 cycles) helped in avoiding overstimulation (prolonged after-discharges and seizures) and, after some experience, speeded up current selections for the next parametric point.

7. *Choice of the parametric set.* The rectangular waveform was chosen as one in which the shape could be maintained constant, while varying its amplitude, duration, and repetition frequency independently; in addition, due to its simplicity of form, this waveform shows quite obvious changes in its shape if the electrodes begin to polarize (cf. condenser discharges) thus giving an early warning of trouble; further, its theoretical treatment is the simplest of all the thoroughly investigated forms (38). Objections to this waveform on experimental grounds are given by A. V. Hill (33); as will be seen below, our experience with long pulses in cortex agrees with his in nerve; but to short, single pulses we do get responses from stimulation through cortex (probably white matter, see below).

The choice of the rectangular waveform fixed the choice of pulse amplitude, duration and repetition frequency (or interval) as members of the set of parameters.

The choice of current through the animal, rather than voltage drop, was made for the following reasons: there is a fixed geometry in each of our preparations, allowing a fixed current path without shunts of unknown values; and the voltage drops occur in elements (electrodes, electrolytes, and the animal) which may be non-linear (40) and out of easy reach (Fig. 1).

"Positive pulses" (anode on cortex) were used because they were found by experiment to give a lower current threshold than "negative pulses." Train duration was an arbitrary choice determined by convenience and available apparatus. (An alternative parameter is the number of pulses in the train.)

Train repetition frequency we fixed at a value of 1/minute on the basis of previous reports (17, 18). In our experience, values of train repetition frequency of less than this chosen value (down to 1/10 minutes) neither changed the threshold more than our experimental scatter (± 2 to $\pm 5\%$), nor created a definite trend in the data toward either an increase or a decrease of threshold.

RESULTS

Our quantitative results are presented in Figures 5 through 9, and 11 and 12. The choice of log-log co-ordinates was determined by the large ranges of our data—5 log units of frequency, for example. In addition, this type of plot shows the shapes of the different curves directly, in relative terms, independently of the absolute magnitudes of the variables (without calculating relative values as is usually done). Further, functions relating "y" to "x" by a simple power relation are straight lines on this plot, thus simplifying the interpretation of the data.

Some generalities from our qualitative results are given in Table 1, summarizing the type and the timing of the movements in various parametric regions. This table does not express the smooth transitions from one region

Table 1. Summary of dynamics of movements elicited by use of various parametric regions

Number	Parametric Region[1]				Movement		Responding Parts Best Seen	Movements for Supra Threshold Trains, Unanesthetized
	P.D. ms.	P.R.F. pps.	T.D. sec.	Threshold I., ma.	Timing	Type		
I[2]	>5–10	all	0.1–5	very low	onset of train	quick jerk	small	weak and variable during train
II[3]	<5–10	<10	0.1–20	very high, constant	with each pulse	quick jerk	small	some increasing spread, lack of after-discharge
III[4]	<5–10	10–200	5–20	falling with increase of P.R.F.	toward end of train	smooth contraction	small or large	spread, after-discharges, seizures
IV	<5	20 to 80% duty cycle	5	low	onset of train	quick jerk	small	weak and variable during train

[1] P.D., P.R.F., and T.D. signify pulse duration, pulse repetition frequency, and train duration, respectively. I. is the value of the stimulating current at threshold.

[2] Regions I and IV are very similar; I is the "classical rheobase" region; IV is practically "rheobasic" in the sense that the current is flowing a large fraction of the time.

[3] Region II is less affected by anesthesia than is region III (cf. Figs. 7 and 10).

[4] In region III as anesthesia deepens, from a completely conscious animal to surgical levels, the relative separation of the parametric points for threshold movement, spread, after-discharges, and for seizures become farther apart on a parametric line of current.

to another that occur in the animal, but does indicate the general regions involved. In summary, long pulses (greater than 10 ms.) and high duty cycles (pulse duration times pulse repetition frequency approaching 0.5 to 1.0) give only "on" responses at threshold. Very low frequencies, short-pulse durations, and short train durations give only single quick contractions with each pulse. In the region of falling threshold with increasing frequency, smooth small contractions occur at the end of the stimulus train (summation).

A more detailed discussion of these results (and others) can best be given by grouping our animals according to the technique used (see above). There are two main groups: (1) anesthetized (deep to light) with an exposed cortex; (2) unanesthetized with closed cranium (implanted electrode).

A. *Anesthetized animals, exposed cortex*

Examples of group 1 (6 cats and 3 monkeys) are given in Figures 5 through 9. In this group dial (or nembutal) was injected (I.M.) at intervals during the experiment to keep the anesthetic level as constant as was practicable (reflex withdrawal to pinch).

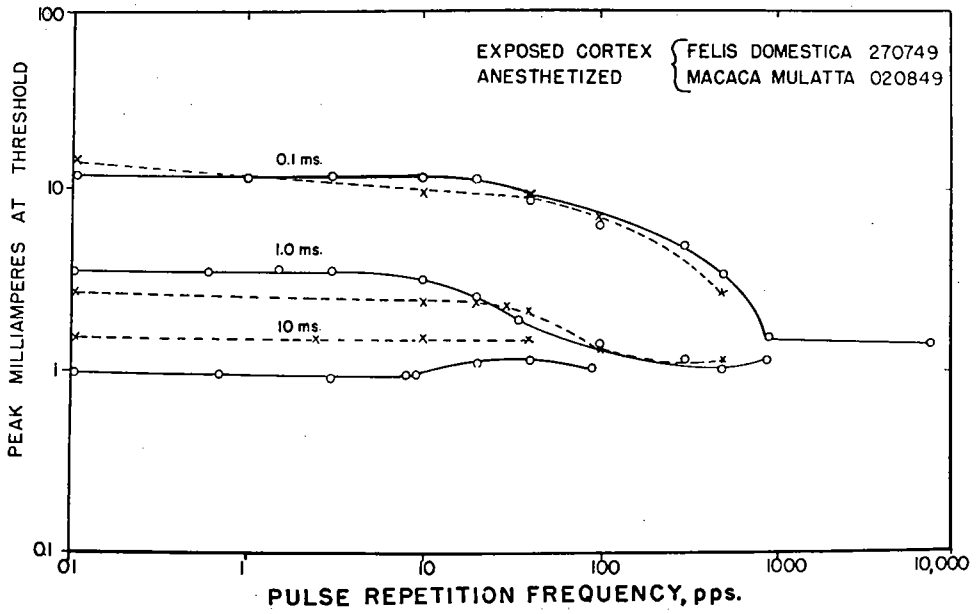

FIG. 5. *Anesthetized Cat and Monkey.* The train duration for this figure and all others unless otherwise noted is 5.0 seconds. For comparison, the threshold curves for an anesthetized cat and monkey are plotted on the same graph. The broken lines represent the threshold curves of the monkey. These curves were chosen for comparison because the 0.1 ms. curves are alike within ±5%. The 1.0 ms. curves can be seen to agree within about the same limits only in most of the frequency sensitive region. The 10 ms. curves show a much greater disparity. However, in other experiments there was a less satisfactory agreement between monkey and cat. Other variables than species differences may be more important—cortical locale, anesthesia (Fig. 7), and damage (Fig. 11), for example.

(1) *Deep anesthesia*

Figure 5 shows typical results of stimulating a single cortical zone of animals at a depth of anesthesia in which a limb withdraws to very strong compression of a digit. At this level, little difference is seen between the curves of a cat and a monkey (Fig. 5). In parametric region III (Table 1) it can be seen that (for pulse durations of 1.0 and 0.1 ms.) the fall of threshold with increasing frequency is maximal in the frequency range from about 10 to about 500 pps.; this is called the "frequency sensitive region." In region I, there is no frequency sensitivity and the threshold is approximately the same as it is in region IV. For pulse durations greater than 10 milliseconds (10 to 500 ms.) (not shown), the threshold current value is about the same as that for 10 ms. In this group, we observed that using parametric

regions I and IV for long periods (15 minutes to ½ hour) caused inconstancy of movements and of threshold values; immediately after their application there were inconstant results with "test" trains (60 pps., 1.0 ms.). After about 6 to 8 hours of stimulation in this group we found a gradual rise in all thresholds.

Figure 6 shows the results, in a cat, of stimulating several zones in a line (7 mm. long) across the right anterior sigmoid gyrus, almost parallel

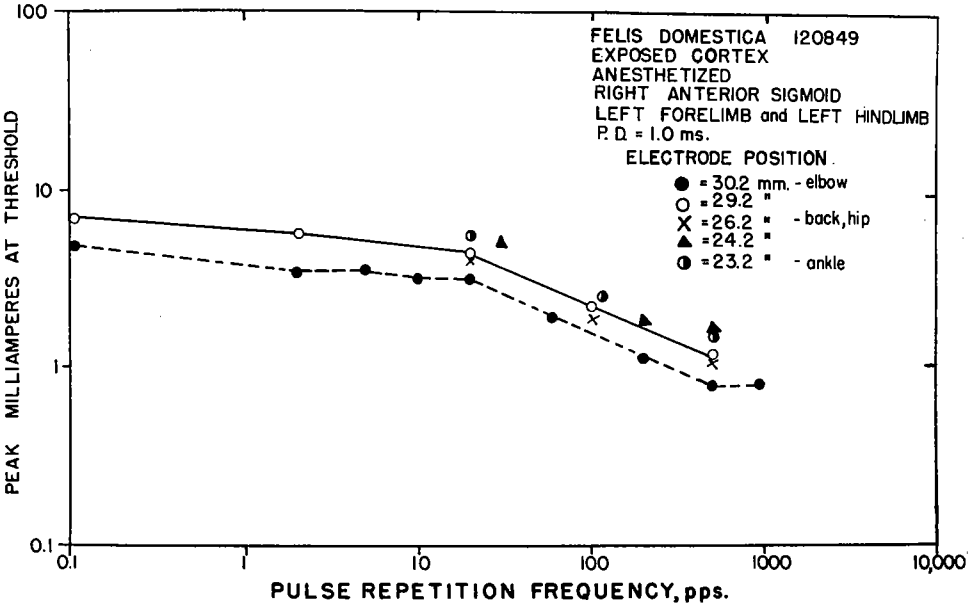

FIG. 6. *Five Cortical Zones of an Anesthetized Cat (2.24 kilograms).* The numbers to the right of the symbols refer to the scale readings on the Horsley-Clarke holder. The threshold movements and responding parts for each zone are as follows: 30.2 mm., flexion at elbow; 29.2 mm., flexion of elbow and abduction at shoulder; 26.2 mm., flexion hip, questionable turning of trunk to left; 24.2 mm., flexion knee and hip; 23.2 mm., flexion ankle and sometimes knee. The total time of stimulation was 7 hours and 23 minutes. The responding parts agree with the map of Ward and Clark (47) but not that of Garol (30).

to the cruciate sulcus. Despite the shift in the responding part with place on the cortex (hindlimb at 23.2 mm., forelimb at 30.2 mm.) the curves change but little in absolute threshold and even less in relative shape.

(2) *Very deep anesthesia*

In one animal (macaca 050849) extremely deep anesthesia raised the threshold beyond the maximum current available from the stimulator.

Figures 7, 8, and 9 show the results obtained on one cortical zone of a deeply anesthetized cat on which we determined some of the effects due to different train durations (T.D.). On this cat the thresholds of contralateral forelimb (solid circles) and the forelimb plus hindlimb movements (open

circles) were also determined (curves at a pulse duration of 0.1 ms., Fig. 7); this could be done only under very deep anesthesia without the production of interfering after-discharges.

Figure 7 shows the high thresholds (raising of whole curve) that may be due to deep anesthesia (no withdrawal reflexes to strong compression of paw) (cf. Fig. 5). The curve for hindlimb plus forelimb is approximately the same shape and relatively only slightly higher (region III) than that for forelimb alone. This difference depends, of course, on the cortical region stimulated (Fig. 6, and References 30 and 47). This animal was stimulated

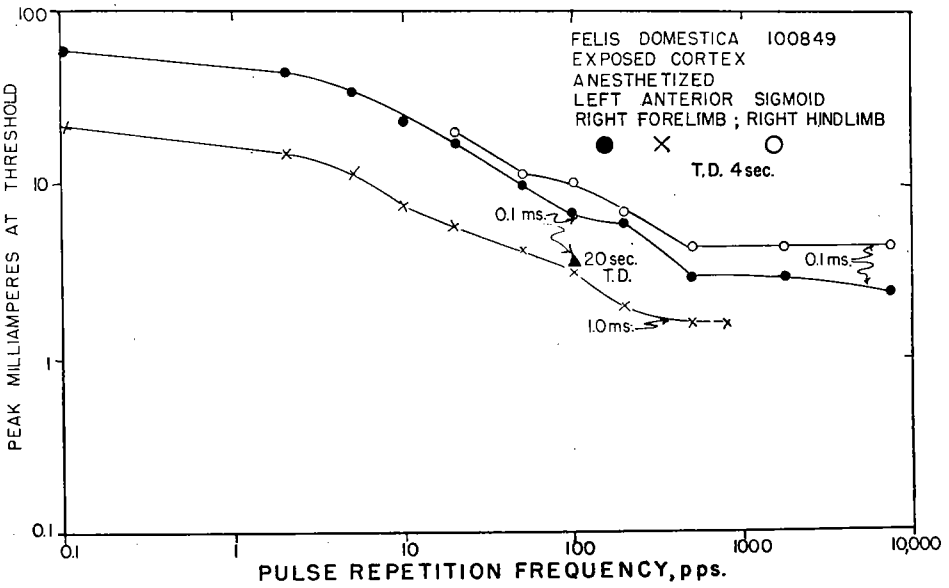

FIG. 7. *Deeply Anesthetized Cat (100849, 2.6 kilograms)*. The stimulated zone was 5 mm. to the left of the midplane and 1.0 mm. anterior to the cruciate sulcus. The threshold movement (crosses and filled circles) was flexion at the elbow; the suprathreshold movement (open circles) was this movement plus abduction of shoulder and of hip. The filled triangle is a point determined with a train duration of 20 sec. and a pulse duration of 0.1 ms. (see text). More data on this zone are given in Figures 8 and 9. The total time of stimulation was 9 hours and 30 minutes. By a series of doses of dial and, later, nembutal, this animal was maintained at a depth of anesthesia which just abolished the withdrawal reflex to very strong compression of a paw.

in a zone whose center at the pial surface was 5.0 mm. to left of the midplane and 1.0 mm. anterior to the cruciate sulcus. Assuming that the hindlimb region has a representative in cortex 2 to 4 mm. more medially (Fig. 6, and Reference 47), it can be seen that a zone stimulated by the current lines far from the electrode may respond in a fashion similar to the region near the electrode.

In Figure 7 there is one point (pulse duration of 0.1 ms., pulse repetition frequency of 100 pps.) of a long duration train (train duration of 20 sec.) eliciting only forelimb movement. This point is a single example of the change of threshold with train length, shown for a direct comparison with

the usual curves. More such data are shown for the same cortical zone (pulse duration of 0.1 ms.) in Figure 8.

Figure 8 shows the change of threshold (forelimb movement) (at a number of frequencies) with train duration. Within the range of train duration used, there is a uniform fall in threshold with increasing train duration (0.1 to 4 sec. and 20 sec. in one case). The horizontal curve for frequencies greater than 400 pps. is a reflection of the fact that the threshold response at these frequencies is only an "on" response (quick jerk, Table 1). The quantity of electricity in each train is calculated: current (in amperes), times pulse

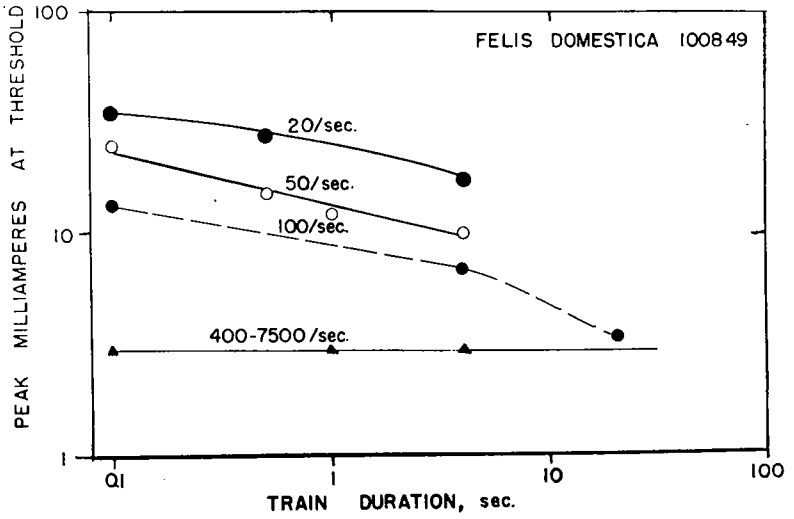

FIG. 8. *Effect of Train Duration on Current Threshold (Cat 100849).* These are additional results on the zone of Figure 7, for a pulse duration of 0.1 ms. only. The train durations were controlled by an electronic circuit in the stimulator, except for the 20-second one which was controlled with a stop watch. This figure is discussed in the text, and is to be compared with Figure 7.

duration (in seconds), times pulse repetition frequency (pps.), times train duration (seconds). The results are plotted in Figure 9.

Figure 9 shows that, at a given frequency, the quantity of electricity in a threshold train increases rapidly and uniformly with increasing train duration. At any given train duration, the quantity increases with increasing frequency (cf. Fig. 12 on another animal), but there is only a variation of about a factor of 2 times from 20 pps. to 100 pps. Comparing Figure 8 with 9 shows that, despite a falling current threshold, there is a rising coulomb threshold with increasing train duration. The importance of these results will be discussed below with those on an unanesthetized animal (macaca 140949).

B. *Unanesthetized animals*

There are 2 monkeys reported here, one with an exposed cortex and one with an implanted electrode.

(1) *Exposed cortex*

The curves of this monkey (070949) resembled those of an anesthetized monkey (020849, Fig. 5). We cannot be sure that these curves were not determined mainly by injury. The thresholds were not as stable as in the anesthetized series, and showed a slow increase detectable over periods as short as one hour. There was definite swelling of the brain with excitement

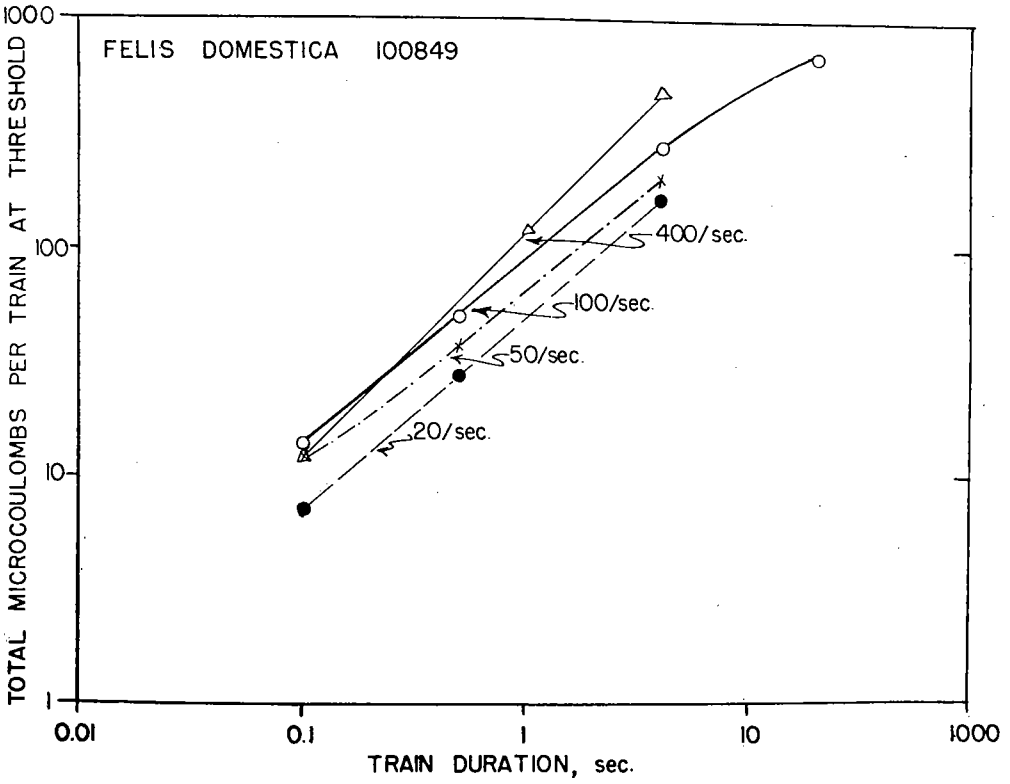

FIG. 9. *Effect of Train Duration on Coulomb Thresholds (Cat 100849).* These data were calculated from those shown in Figure 8. In addition to the points covered in the text, it can be seen that at a train duration of 4 seconds, there is a relatively small change in coulomb threshold with frequency from 20 pps. to 100 pps. This result is to be compared with those on an unanesthetized monkey (140949) in Figure 12, showing a similar effect.

and muscular effort. The brain did not dry out on the pial surface; the room atmosphere was continually saturated with water vapor at about body temperature throughout the experiment.

To avoid injury we changed our technique to the implanted electrode method. The curves on the monkey (140949) with an implanted electrode (Fig. 11) have only a gross resemblance to the ones on this monkey (070949) and then only after 10 or so hours of stimulation (see below).

(2) *Closed cranium*

Figures 11 and 12 show some curves obtained on this monkey (140949), whose brain is shown in Figure 10. The thresholds were obtained by determining the threshold current for those times when the animal was relaxed (even dozing) and rejecting all determinations which occurred just after or during voluntary movement.[5] It was found that slight noises or other unintentional stimuli by the observers caused the monkey to resist the movement and thus increase the threshold values by a factor of at least 2 and sometimes more. Voluntary movements just preceding a train sometimes lowered the threshold. Despite these disturbing factors, we found that we could determine thresholds in the conscious animal reproducibly within $\pm 5\%$.

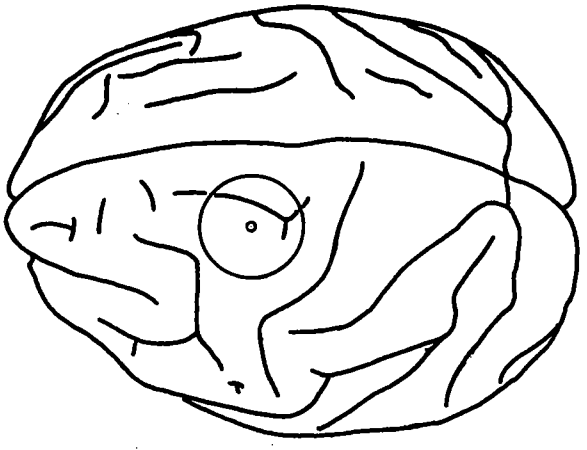

FIG. 10. *Brain of a Monkey (140949)*. The circle (12 mm. in diameter) shows the location of the trephine hole cut to hold the implanted electrode. The 1 mm. diameter pore was at the locus represented by the center of this circle. This brain was fixed *in situ* by perfusion of the animal (under anesthetic) with normal saline and 10% formalin through the aorta. During the hardening process a stainless steel plug was in the trephine hole, indenting the brain to leave a slightly depressed (about 1 mm.) region. The circle on this drawing is a lucite disc (2 mm. thick, 12 mm. diameter) resting in the depression. With this method the center of the zone formerly occupied by the electrode pore (Fig. 1) is re-determined with fair accuracy. The curves determined on this zone are shown in Figures 11 and 12. Histological sections were cut through this region and are described in the text. The total time of observation on this monkey was 8 days.

Figure 11 shows the change in shape of the curves with time. Our original data were taken by a more or less random choice of parametric lines, with repetitions of determinations over several hours. These points were then plotted as threshold current against time, and the curve of variation with time of each parametric line drawn in. The curves of this figure are the values for a definite clock time taken from this plot.

As can be seen from the figure, the curves become flattened at 23 hours, *i.e.*, there is a great loss of the original "frequency sensitivity" (region III, Table 1) which was present at "zero" hours. At 23 hours, the electrode was unscrewed,[6] the cortex under it was cut out, a clot allowed to form and the

[5] For a time we used a warning tone (5 seconds before the train was due) to alert the observers. This tone had to be abandoned when it was found that the monkey learned to use the warning to set his muscles to resist the movement.

[6] Directly under the 1 mm. hole in the lucite (Fig. 1), the pial vessels were constricted enough to give a white appearance to an area 1 to 2 mm. in diameter.

electrode screwed back to the same level as before. Other sets of curves were then run. The curves from 23 hours through 72 hours are alike within $\pm 15\%$ of the absolute threshold (at 3 pulse durations (5, 1, and 0.1 ms.)). Histological sections taken through this region show a reduction of intact fibers in the white matter and some growth of blood vessels at the former

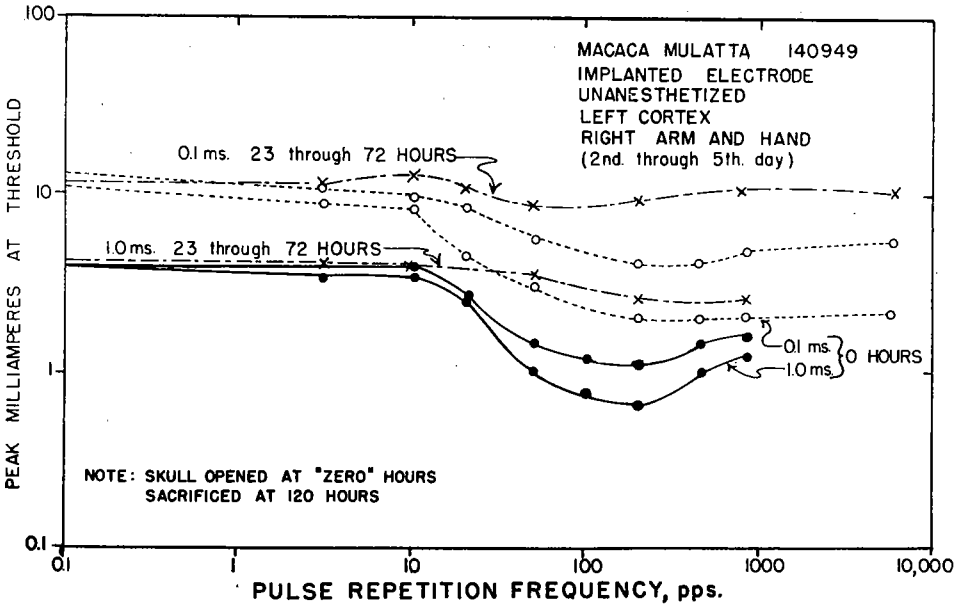

FIG. 11. *Current Thresholds of Unanesthetized Monkey.* The train duration used was 5 seconds for all curves. For each pulse duration (1.0 and 0.1 ms.) 3 curves are shown, one of each at zero (circles), 8 (circles, and unlabeled) and 23 through 72 hours (crosses). The thresholds for single pulses at long intervals (one per 3 seconds or longer) are placed at a pulse repetition frequency of 0.1 pps. and are shown here as intersections of the curves with the ordinate, rather than as coded points. The method of determining these curves and their interpretation are given in the text. The electrode used is the right-hand one in Figure 1. The location of the zone stimulated is shown in Figure 10. The threshold movement is flexion of the thumb and index finger; with currents slightly above threshold, extension of fingers, dorsiflexion of wrist, and flexion of the elbow occurred in various parametric regions (Table 1). The stimulation periods were 14 hours, 7 hours, and 4 hours, respectively, for the 3 successive days represented by these curves; in the first day (14 hours), there were about 840 trains passed through the animal, totaling about 420,000 micro-coulombs of electricity (Fig. 12 and text).

site of cortical cell layers with complete absence of nerve cells in the region subjacent to the pore of the electrode.

By comparing the curves at zero hours and those at 23 through 72 hours, it can be seen that (at 0.1 ms. pulse duration, for instance) the threshold current for frequencies lower than about 10/second is relatively unchanged with time. For higher frequencies there is a large increase in threshold current ($5\times$ for 200 pps. at 1.0 ms., for example) with time.

During the first 23 hours, the movements changed from definite smooth and reproducible ones (pulse durations of 0.1 and 1.0 ms.) to hesitant, fluttering, and intermittent ones. The latter movements were usually weak; at low values of pulse repetition frequency they occurred at every pulse but with different amplitudes to the pulses in the train; in the 10 pps. region, they changed from a definite small movement at the end of the train to inconstant, fluttering weak movements during the train; at the higher frequencies, there was the usual "on" response—a quick jerk of the respond-

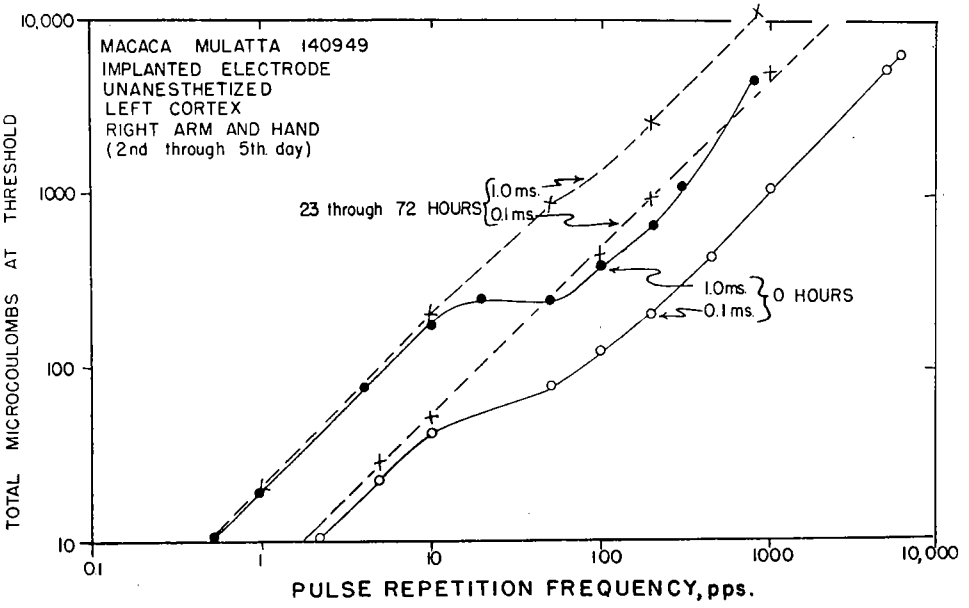

FIG. 12. *Coulomb Thresholds for Unanesthetized Monkey.* The data for Figure 11 were used to calculate the total coulombs in each train. (For rectangular pulses the coulombs in a train are the product of the current (in amperes), the pulse duration (in seconds), the frequency (in pps.), and the train duration (in seconds).) Only the 4 extreme curves of the 6 in Figure 11 are shown here: 2 at "zero" hours (0.1 and 1.0 ms.) and 2 at 23 through 72 hours (0.1 and 1.0 ms.). The "addition" region (see text) is seen here as a flattening of the two "zero" hours curves from about 10 to 70 pps.

ing part at the beginning of the train—and, sometimes, a few weak fluttering movements during the train.

These results suggest that for short pulses (1) at low frequencies only efferent fibers in the white matter are stimulated, (2) at higher frequencies, cortex and white matter are being stimulated, and that (3) some factor is destroying the cortex over the first 23 hours.

Despite the changes in these curves, this monkey could pull, with his thumb and index finger (responding parts), the lead out of an automatic pencil during the time of these experiments and up to the time of sacrifice (cf. Reference 31).

Figure 12 shows the results of calculating the quantity of electricity in

each stimulating train for 4 curves of Figure 11: zero and 23 hours for pulse durations of 0.1 ms. and 1.0 ms. As can be seen in the figure for the "zero" hour curves the quantity (in micro-coulombs) rises steeply with an increase of frequency in all regions except that from 10 to about 70 pps. for both the 0.1 ms. and the 1.0 ms. curves. Thus, this region of frequency is presumably the region of most efficient "addition" of pulses by cortex. After 23 hours, most of this "addition" effect has disappeared.

An important result in this figure is the lower "*coulomb* threshold" for the 0.1 ms. pulses than for the 1.0 ms. pulses at each frequency, despite a higher *current* threshold for the shorter pulses (cf. Fig. 9). Apparently, with 0.1 ms. pulses, there is a more effective excitation of the cortical and fiber elements, *i.e.*, as the pulse duration decreases, a greater fraction of the ions which are moved among the active elements is used in the excitation of the elements. This may mean that the extra quantity flowing through the tissue in the case of the longer pulses can be contributing to cortical damage by some set of processes[7] (vessel constriction (25), electrophoresis, electrodialysis, electro-osmosis, etc.), not yet investigated in this system.

DISCUSSION

Our results suggest that threshold maps due to *cortical* stimuli do not vary greatly with the parametric region of the electrical stimuli, nor with the depth of anesthesia; however, due to stimulation of white matter, variations in maps are to be expected for low pulse frequencies. The responding part is relatively fixed to a zone on cortex in a practically anatomical fashion (13) even in the unanesthetized animal (cf. Ref. 15).

However, the dynamics of the threshold response vary greatly with the stimulus parameters (Table 1), as do the threshold currents (Figs. 5 through 12). Single short pulses at long intervals give quick single twitches for every pulse (as in Ref. 41). As the intervals shorten, the twitches drop out, and smooth action at the end of the train appears. As the intervals shorten further, only a brief twitch at the onset of the train occurs. These are the dynamics of responses in animals at all anesthetic levels from the conscious to the deeply anesthetized one.

We wish to emphasize that this is a threshold picture, a particular threshold—that of movements just seen by the observers. With stimuli which are a small amount above threshold the picture changes rapidly (3), (especially in the unanesthetized animal) (17). If one does not critically control waveform, frequency, current, amplitude, train duration, and train repetition frequency, a controlled, small, threshold movement easily becomes an uncontrolled, large, suprathreshold movement involving other parts represented in an overlapping zone or in nearby cortex (13). This is found most dramatically in our parametric region III (Table 1).

[7] Heating of the pia is apparently not one of these processes. For a pulse duration of 1.0 ms., a pulse repetition frequency of 100 pps., a train duration of 5 seconds, a current of 1.0 ma., the rise in temperature (assuming all the electrical energy is dissipated in an electrolyte cylinder 1 mm. in diameter and 3 mm. long) is only 0.044°C.

In one animal (macaca 140949, Figs. 11 and 12) our results suggest that one can differentiate between stimulation of efferent fibers (and/or cells) and that of the efferent system plus cortical cells by a proper choice of the parametric region. The threshold for short pulses (1.0 ms. and less) at long intervals (greater than about 3 seconds) (parametric region II) does not change (for at least 3 days) with known damage to the cortical cell strata. The threshold for short pulses in 5-second trains (of frequencies between about 10 pps. and about 200 pps.) changes by a large amount with cortical damage and rises to almost that of the short, widely spaced pulses (region III, Table 1, and Figs. 11 and 12).

Tower's results (46) on the extrapyramidal systems (in animals with the pyramids cut) suggest that these systems have a higher threshold than the pyramidal one when stimulated at cortex; that the lowest threshold effect is inhibition of tone, and that the higher threshold motor responses are complex and involve several muscle groups at once. Since Graham Brown was using strong stimuli in repeated trains for long periods his "facilitation" by stimulation of white matter ((7), page 138) may have been due to extrapyramidal stimulation and intersegmental summation in the cord (43). These findings suggest that our results are due more to direct pyramidal system stimulation than to stimulation of the extrapyramidal systems. However, the electromyographic results of Bosma and Gellhorn (3) suggest that inhibition plays an important role, and that the mechanisms are more complex than we could see with our method of observation.

The pyramidal cortical mechanism (in cats, monkeys and rabbits) itself has been investigated by Adrian and Moruzzi (2). They found that pyramidal fibers can be driven by cortex (aroused by drugs) to deliver high-frequency volleys of impulses (in single units) up to frequencies of 500 to 1000 per second. A train of subthreshold single shocks (at 30/sec., Fig. 35, p. 188) causes a given unit to fire (after 4 sec.) giving first 1 impulse per shock and 4 seconds later an increasing number (3–4) per shock, at which time perceptible movement begins. By increasing the shock strength (at lower pulse frequency) each shock caused multiple, high frequency impulses and movement began earlier.

To explain our results in these terms, assume that the subcortical (cord) mechanism (42) requires, from each necessary pyramidal fiber, a certain number (n) of impulses within a certain time interval (t) in order to fire the anterior horn cells frequently enough (1, 18) to produce a perceivable movement. At low pulse repetition frequencies (less than 10 pps. at a pulse duration of 0.1 ms., Fig. 11) the pyramidal fibers are fired by each pulse to give the critical number (n) in the critical time (t). At higher frequencies (10 to 100 pps.) the unanesthetized cortex summates the stimulus pulses linearly (Fig. 12) until, at the end of the train, the pyramidal cells reach a firing frequency high enough, in volleys long enough, to give the critical impulse number in the necessary time interval. At higher pulse frequencies (greater than 100 pps. at a pulse duration of 0.1 ms., Fig. 11), cortex is firing the pyramidal fibers at their maximum frequency; any increase in

stimulus frequency does not raise the impulse frequency in the fibers, and the threshold levels off (Fig. 11, P.D. of 0.1 ms. at "zero" hours). At very high pulse frequencies, the cortical summation occurs in the first brief time interval after the onset of the train, and the critical firing is reached rapidly causing the quick jerk (of Table 1) near the onset of the train. This hypothesis suggests certain experimental tests of its validity.

Part of the mechanism of cortical injury seen in monkey 140949 may have been constriction of the blood vessels in the stimulated region after removal of the electrode. A white zone of constricted vessels was seen in the stimulated zone after a total of 25 hours (once per minute) of stimulation spread over 3 days. According to Florey (25), electrical stimuli (induction coil shocks applied through an entomological pin) near arteries, arterioles, and arteriolar capillaries (but not on the venous side) cause constriction. The latency was from 0.5 to 20 seconds; the duration of contraction was from 2 minutes to at least 2.5 hours; the amplitude of constriction could be carried to complete obliteration of the lumen. (No amplitude of current, distance of electrode from the reacting vessel, train durations, or waveform data are given.) His results may be due to the large changes in electrolytes around a metal (presumably steel) electrode arising from the very high current flux in the neighborhood of an electrode of small area. His observation (page 52) that bubbles were formed at the tip of his electrode at the "same strength" of current as to excite the motor cortex tends to support this explanation (40).

In general, these observations, and ours, suggest that vessel constriction may be one of the important causes of the loss of cortical excitability with increasing time of stimulation.

However, there are probably additional mechanisms of injury. By a study of histological sections of the brain on the 140949 monkey it can be seen that the cellular and fiber damage decreases in roughly hemispherical shells away from the location of the electrode's opening. This injury pattern would not be expected from blood vessel constriction alone; it indicates that the damage varies directly with the flux of ionic (positive and negative carriers) current flow from and to the electrode.

In order to evaluate more thoroughly the extent and the effects of injury by this type of current waveform, it would be desirable to implant many more than one electrode (over a fairly large region of cortex). In addition, it is obvious that a less injurious waveform (such as sine waves (35)) should be used for testing thresholds. Thus, by determining the current thresholds at each electrode with the relatively innocuous waveform intercurrently with this apparently noxious waveform at only one electrode, changes of threshold could readily be detected and followed, locally and in more distant regions. Such experiments are needed before this waveform (rectangular unidirectional pulse) is used extensively in mapping any cortex, especially that of the human patient at operation. It may well turn out that any unidirectional (or even unsymmetrical) waveform (condenser discharges or other) causes injury by some ionic transport mechanism. It is apparent that,

through the implanted electrode technique, such waveforms can be thoroughly evaluated, and hence should be thus tested over long periods of time in single animals before they are used in critical situations.

In stimulating an unanesthetized animal with only a single implanted electrode there is a danger of making a fundamental error in the interpretation of the results and in extrapolating to the mapping situation. If there is a hyperexcitable zone of cortex near (but not under) the electrode region, the observed threshold may be that of the nearby zone and not that under the electrode. Recently, in a series of experiments on unanesthetized animals to be reported elsewhere, we have found such a zone. By implanting 25 electrodes at once and deriving a map from stimulating through each one in turn, we found that a single responding part (thumb, for example) had the lowest threshold of all parts over a field 8 mm. by 8 mm. in a monkey. (Presumably such phenomena do not occur under anesthesia at the depths usually used for mapping motor responses, or the observation would have been reported earlier). By increasing the current, we found that new responding parts came into action for different electrodes at levels causing after-discharges in the thumb, and spread of response to fingers and arm. In the light of this finding it is obvious that the interpretation of the results on the unanesthetized monkey (140949) reported above must necessarily be tentative and cautious.

SUMMARY

1. The threshold currents for the production of first perceptible movements by excitation of some zones of the motor cortex of a series of cats and monkeys were measured.

2. The waveform used was a unidirectional rectangular pulse (with the anode on the pia).

3. Train repetition frequency was constant at one per minute.

4. Ranges of pulse duration, pulse repetition frequency, and train duration used were 0.1 to 500 ms., 1/60 to 7500 pps., 0.1 to 5 seconds, respectively.

5. The current of every stimulating train was observed and measured by means of a series resistor, a direct coupled amplifier, and a cathode ray oscilloscope.

6. The resulting data are presented in graphs relating the threshold current to the pulse repetition frequency at various pulse durations.

7. In some cases, the quantity of electricity (micro-coulombs) in the trains at threshold is shown graphically as related to the pulse repetition frequency and pulse duration.

8. The data from two unanesthetized monkeys (one with a reversible implanted electrode) are presented.

9. In general the thresholds for pulses longer than about 5 to 10 ms. (and for shorter pulses at frequencies giving a high duty cycle) are relatively insensitive to frequency changes. No pulses at frequencies less than about 5 pps. showed any frequency sensitivity. For short pulses (less than about 5 ms.) the frequency sensitive region is from about 10 to 200 pps.

10. In a parametric region showing a high frequency sensitivity (fast change of threshold current with change of frequency) one observes (with increasing current) summation of subthreshold stimuli and smooth threshold movements; easy spread to adjacent parts; after-discharges; traveling seizures; and generalized convulsions. This is best seen in the conscious animal. (With short pulses, single contractions with each pulse are seen at very low frequencies, without frequency sensitivity, without summation, and without spread.)

11. For the short (0.1 ms.) pulses the *coulomb* threshold is less than that for the longer (1 ms.) pulses, despite a higher *current* threshold for the shorter pulses.

12. At a single electrode position the difference between the currents producing threshold movement of a small peripheral region and that producing excitation of large peripheral regions is very much smaller in the conscious animal than in the anesthetized one.

13. Our results suggest that for 5-second trains, short pulses (0.1 to 1.0 ms.) at low repetition frequencies (less than 5 to 10 pps.) excite efferent fibers directly without exciting cortex; whereas at higher frequencies (greater than 5 to 20 pps.) such pulses excite mainly cortical strata.

14. Our results indicate that damage to cortex results from stimulation with this waveform (with something less than 800 trains at or near threshold at 1-minute intervals). It is suggested that the amount of damage may vary directly with the total micro-coulombs in a train and not with the peak current values. Thus, at threshold the 0.1 ms. pulses would be less damaging than any of the longer pulses.

Postscriptum. Since the time when we submitted this manuscript, the paper of Liddell and Phillips (J. Physiol., 1951, *112:* 392–399) has appeared and excited a very careful reconsideration of our protocols on macaca 140949. Except for their use of the cathode (anesthetized baboon) and our use of the anode (unanesthetized macaca) on the cortex, our data agree: in parametric region III (Table 1), we found elbow flexion most frequently (as in Ref. 48); in region II, thumb responded most frequently. This re-evaluation modifies our conclusions only to the following extent: two parts may be caused to move by stimuli in two parametric regions at the same electrode locus; however, the movement of the small part (stimulated by parametric region II) is due to stimulation of some structures not directly under the electrode, *i.e.*, not in the subjacent cortex; presumably, such movements are due to stimulation of white matter under cortex. In later experiments, to be reported elsewhere, we found that we could excite elbow (plus thumb) in parametric region II with very large currents; typical cortical summation was seen. In other words, at about 10 to 20 pulses per second, the curves of threshold current versus pulse repetition frequency (at constant pulse duration) for the cortical and the "non-cortical" systems cross one another. (We are indebted to C. N. Woolsey for stimulating our clarification; his gentle insistence and excellent maps caused us to re-evaluate our position.)

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