STUDIES ON THE ANALEPTIC ACTION OF ELECTRICAL STIMULATION IN BARBITURATE POISONING

by

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A THESIS

Presented to the Department of Physiology
and the Graduate Division of the University of Oregon Medical School
in partial fulfillment
of the requirements for the degree of
Master of Science

June 1955

APPROVED:

[redacted]

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ACKNOWLEDGEMENTS

The author is indebted to Dr. J. M. Brookhart for his ever-helpful advice and encouragement, to Dr. C. E. Hopkins for advice on statistical methods, to Dr. E. L. McCawley for suggesting a means of evaluating lethal dosage, to Dr. J. G. Shanklin for the use of his Reiter Electro-stimulator, and to Mrs. George Wolff for typing this manuscript.

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INTRODUCTION

Non-convulsive electrical stimulation applied to the head has been used in the treatment of barbiturate poisoning since 1949 by Robie (1-4), Pinch and Geoghegan (5) and Alexander (6). These psychitrists observed that the period of apnea following classical convulsive electro-shock therapy could be abolished by application of a short period of non-convulsive stimulation. This period of apnea could be prevented even when the patient had been heavily premedicated with pentothal sodium. From this observation Robie (1) concluded that non-convulsive stimulation applied to the head might be of value in the many cases of accidental barbiturate poisoning. After empirically treating many cases of barbiturate poisoning by electrical stimulation, Robie (1-4) and Pinch and Geoghegan (5) concluded that this form of stimulation was as effective as any of the commonly used chemical analeptics, and that it had the unusual advantage that the intensity (or dosage) could be regulated at will by the physician.

These authors attributed the mechanism by which electrical stimulation augmented respiration to stimulation of cortical (1,4, and 5) and diencephalic structures (2), probably on the basis that (a) there is known to be some cortical regulation of respiration and (b) since electrically induced convulsions are produced by direct passage of electrical current through the brain, the respiratory augmentation resulting from non-convulsive stimulation must likewise result from stimulation of the cortex and/or diencephalon directly. In addition Robie (2) and Pinch and Geoghegan (5) stated that electrical stimulation of the brain increased the rate of barbiturate excretion. They presented no

evidence which could support this statement, and suggested no mechanism by which it could be accomplished.

Their hypothesis as to the mechanism by which non-convulsive electrical stimulation augments respiration is at variance with previous neurophysiological experiments which have revealed that the predominant influence of cortical and diencephalic stimulation on respiration is inhibitory (7 and 8). One would expect that if this form of electrical stimulation acted upon a cortical area which controls respiration, the application of the therapeutic electrodes would have to be carefully localised to produce the desired results. This is not the case, for respiratory stimulation can be obtained from electrodes placed on most any part of the cranium (4, 5, and 6). One mechanism that the proponents of electrical stimulation failed to take into consideration was the well-known influence of nociceptive stimulation on respiration.

The evaluation of the therapeutic effect of any analeptic therapy is fraught with methodological and statistical difficulties. In order to have a statistically valid study one is limited to working with experimental animals where large numbers and complete control can be approached. But clinical application of this data is subject to prejudicial experience, and one is usually working on patients who have had an unknown amount of an unknown drug at an unknown time. Despite these factors and without any critical comparative studies, Robie (1-4) has recommended transcranial electrical stimulation as the treatment of choice in barbiturate poisoning.

Since so little factual knowledge is known about this form of therapy which is being used increasingly, the following study was undertaken in an attempt to analyze experimentally the mode of action and to determine

the effectiveness of electrical stimulation as a respiratory stimulant in barbiturate poisoning.

METHODS

General. The results are based upon a study of the reactions of 69 dogs. Pentobarbital sodium was chosen as the standard barbiturate because it is commonly used and short acting. A Reiter Electro-stimulator, Model CW 47 provided the stimulation. Kymographic recordings of respiration were made using an oxygen-filled spirometer equipped with a carbon dioxide absorber connected to a tracheal cannula. A few experiments were done with the dogs breathing air and records obtained with a Collins Respirometer. Blood pressure was recorded with a mercury manometer connected to the femoral artery. In those experiments where it was considered necessary to control the placement of cranial electrodes carefully, the head was fixed in a head-holder, the temporalis muscles reflected, and the stimulation carried out through the bone.

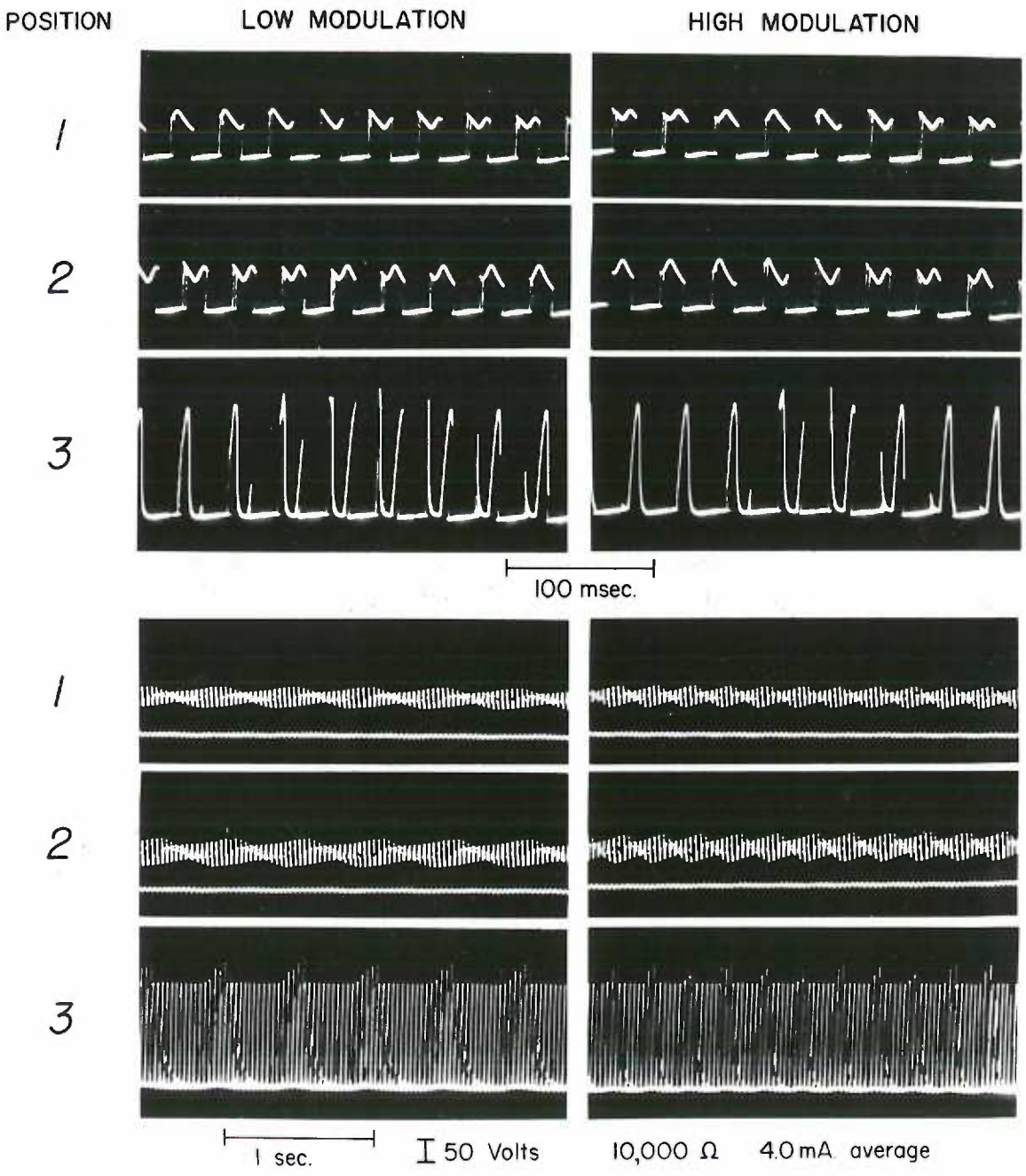
Some phases of the study required special methods adapted to each particular phase. These special methods will be described in conjunction with the results of each phase.

Output of Reiter Electro-stimulator, Model CW 47: It was found necessary to determine the output of our own Reiter Electro-stimulator since an adequate description of neither the instrument nor its output could be obtained from the manufacturer or any other source. The following description supplementing Figure 1 may be applicable only to the instrument which has been at our disposal.

The output of the instrument may be varied in three ways by controlling

FIGURE 1

Oscillograms of the output of a Reiter Electrostimulator, Model CW47. The upper set of recordings was made on a faster moving film than the lower set. For all records the average current through a 10 K load was 4.0 mA.


POSITION
LOW MODULATION
HIGH MODULATION
1
2
3
100 msec.
1
2
3
1 sec.
50 Volts
10,000 Ω
4.0 mA average

current intensity, pulse form, and modulation. The intensity control is continuous and permits adjustment of average current through the electrodes over the range from 0 to 20 milliamperes.

One of three pulse forms may be utilised by adjusting a three-position selector switch. In positions "1" and "2" the instrument generates a poorly filtered unidirectional current which is interrupted by a motor-driven switch forming pulses of roughly rectangular form at a frequency of 31-33 cps. The duty cycle can be varied by altering the duration of contact of the switch points. Our machine was set for a duty cycle of approximately 46-47 per cent. There is superimposed on the pulses a ripple whose frequency for our machine varies between 48 and 100 cps. The amplitude of the ripple varies between 22 per cent and 41 per cent of the maximum pulse amplitude in position "1" and between 27 per cent and 50 per cent of the maximum pulse amplitude in position "2". Position "3" provides an essentially unfiltered, fully-rectified, unidirectional current which likewise is interrupted by the mechanical switch so as to produce pulses at approximately thirty cycles per second with a duty cycle of roughly 50 per cent.

The function called modulation controls the rate at which the switch cam rotates. Since the cam rotates at a frequency which is slighly greater than 30 per second, a beat frequency phenomenon develops from the superimposition of the 60 cycle ripple from the power line. The output appears to consist of a rhythmic resetting of the time of occurrence of pulses, one group of pulses gradually undergoing foreshortening from their original point of onset at the same time that a new group of pulses grows during the off-periods of the initial group. Adjustment of the modulation

control varies the frequency of the modulation rhythm for all three pulse forms between the extreme of 2 cps. and 4 cps.

Two kinds of stimulating electrodes were used, the standard cloth-covered one-inch disc Reiter electrodes, and one-centimeter cloth-covered silver-silver chloride non-polarizable electrodes. These made contact with the animal through a saline bridge.

RESULTS

AN ANALYSIS OF THE MECHANISM OF THE RESPIRATORY RESPONSE

Respiratory Responses to Cranial Stimulation. The usual respiratory response to stimulation of the type used here was an immediate large increase in respiratory minute volume due to an increase in both the rate and depth of breathing. This lasted for 30 to 60 seconds and was followed by a gradual decrease in both rate and amplitude, especially the latter. After the initial increase, respiratory minute volume stabilized at a level which was well above the resting level. If the direction of the stimulating current was reversed during the period of relative stability, a second but shorter period of augmented respiratory minute volume occurred. A period of hyperventilation apnea occasionally followed the cessation of stimulation. More frequently, however, respiratory minute volume continued at a slightly increased value for a period of one to five minutes. The largest increases in respiratory minute volume were obtained from the anterior part of the skull. The stimulation became less effective as the stimulation site approached the lambdoidal crest. Part of the decreased response seemed to be due to interference with respiration produced by muscular activity in the shoulder girdle resulting from spread of current.

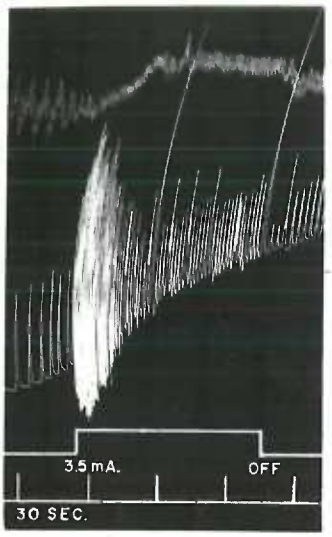
This description is illustrated by the records from a single dog presented in Figure 2. It is of particular interest to note that the response obtained in this dog was greatest from electrode placements over the frontal sinuses which were separated from the brain by a distance of about one centimeter of air.

Respiratory Responses to Peripheral Stimulation. Electrical stimulation of parts of the body other than the cranium was also found to produce an increased respiratory minute volume. Peripheral sites tested included the ear, the nose, the hind-legs and the sciatic nerve. For most dogs the greatest immediate response was obtained with stimulation through electrodes placed on each side of the nose. Binasal placement was always more effective than any of the cranial locations. Stimulation through the hindlegs produced the greatest sustained increase in respiratory minute volume, but developed much more slowly. Figure 3 illustrates the type of responses obtained from peripheral stimulation. From this figure one cannot compare the relative effectiveness of each electrode placement because the resting respiratory minute volume was different at the time of each recording and different current strengths were used as are indicated on each record.

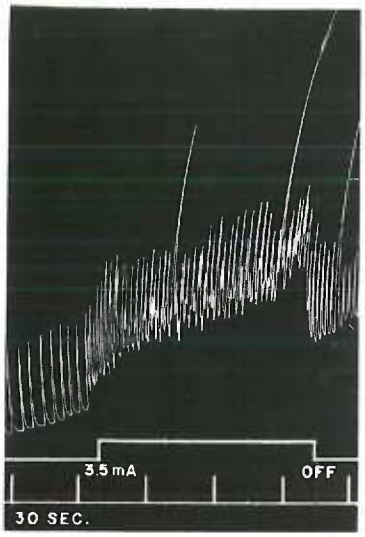
Influence of Current Intensity, Pulse Shape, and Depth of Anesthesia on Respiratory Response. For all sites of stimulation the respiratory response was proportional to the average electrode current except at high current values which at time inhibited respiration (See Fig. 4, bands B and E).

FIGURE 2

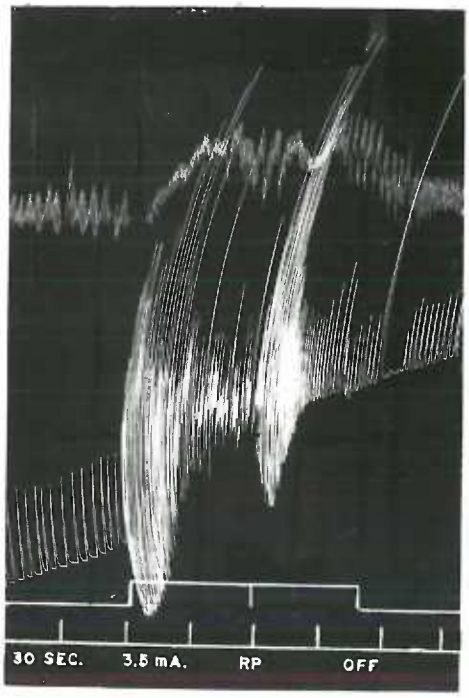
Respiratory and blood pressure changes produced by stimulation of various points on the skull of one dog. A. Electrodes placed bitemporally. B. Bi-occipital location. C. One electrode on the occipital region, the other over the right frontal sinus. D. One electrode over each frontal sinus. RP = reverse polarity of stimulating electrodes.


3.5 mA.
OFF
30 SEC.

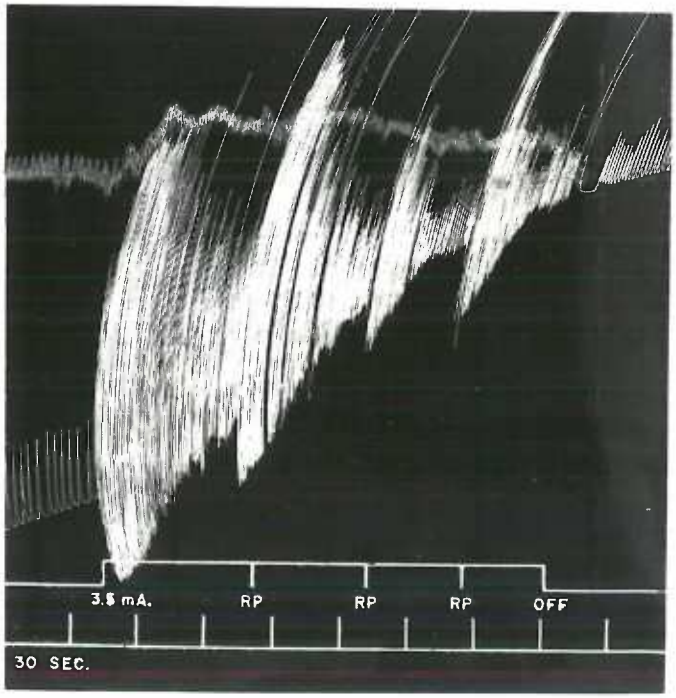
A


3.5 mA
OFF
30 SEC.

B


30 SEC.
3.5 mA.
RP
OFF

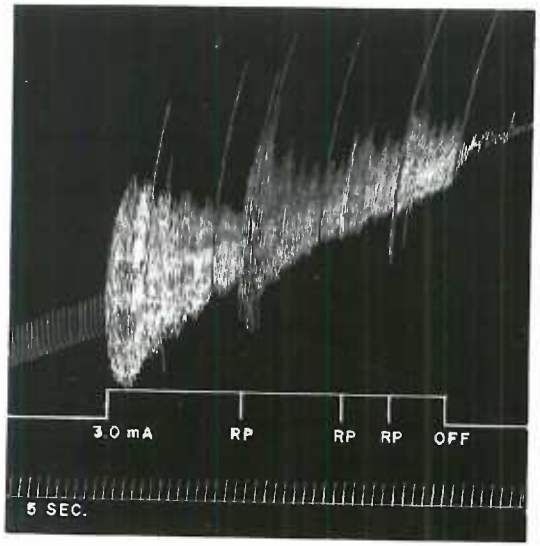
C


3.5 mA.
RP
RP
RP
OFF
30 SEC.

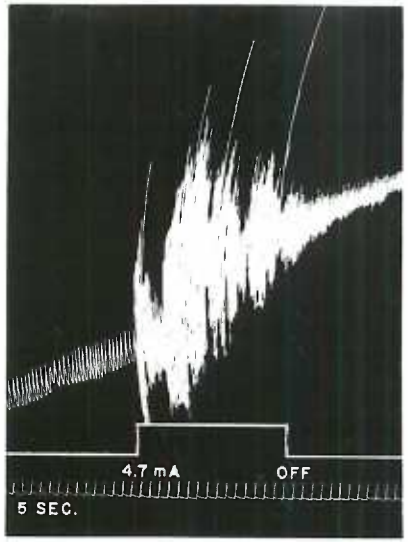
D

FIGURE 3

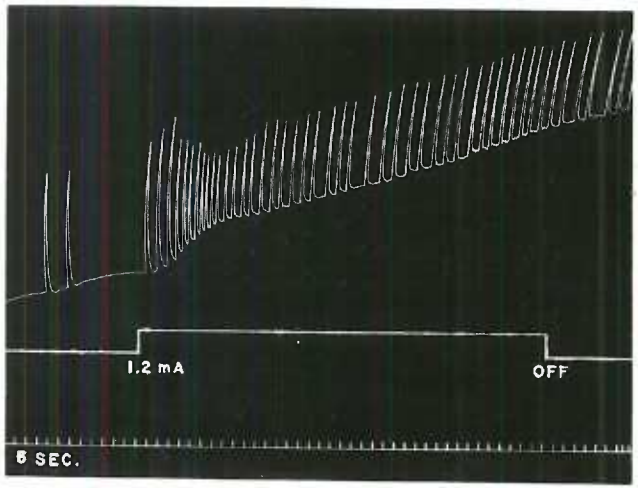
Respiratory responses from stimulation of various sites. A. One electrode on each side of the nose. B. One electrode on each side of one pinna. C. One electrode on each hind leg. D. Bipolar stimulation of the sciatic nerve. P - polarity of proximal electrode. RP - Reverse polarity of stimulating electrodes.


3.0 mA
RP
RP
RP
OFF
5 SEC.

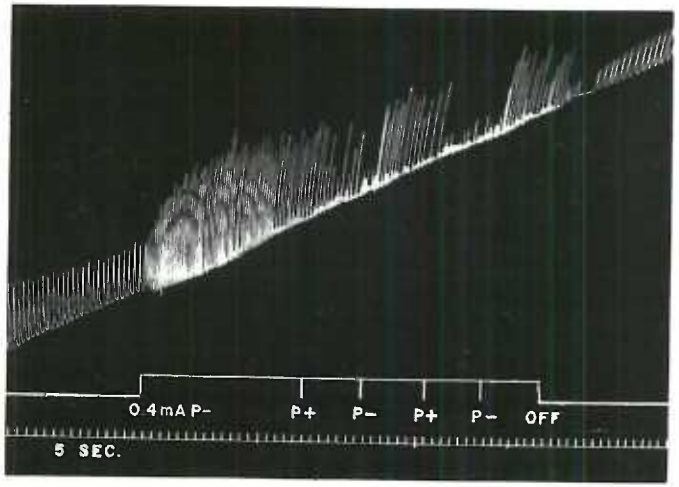
A


4.7 mA
OFF
5 SEC.

B


1.2 mA
OFF
5 SEC.

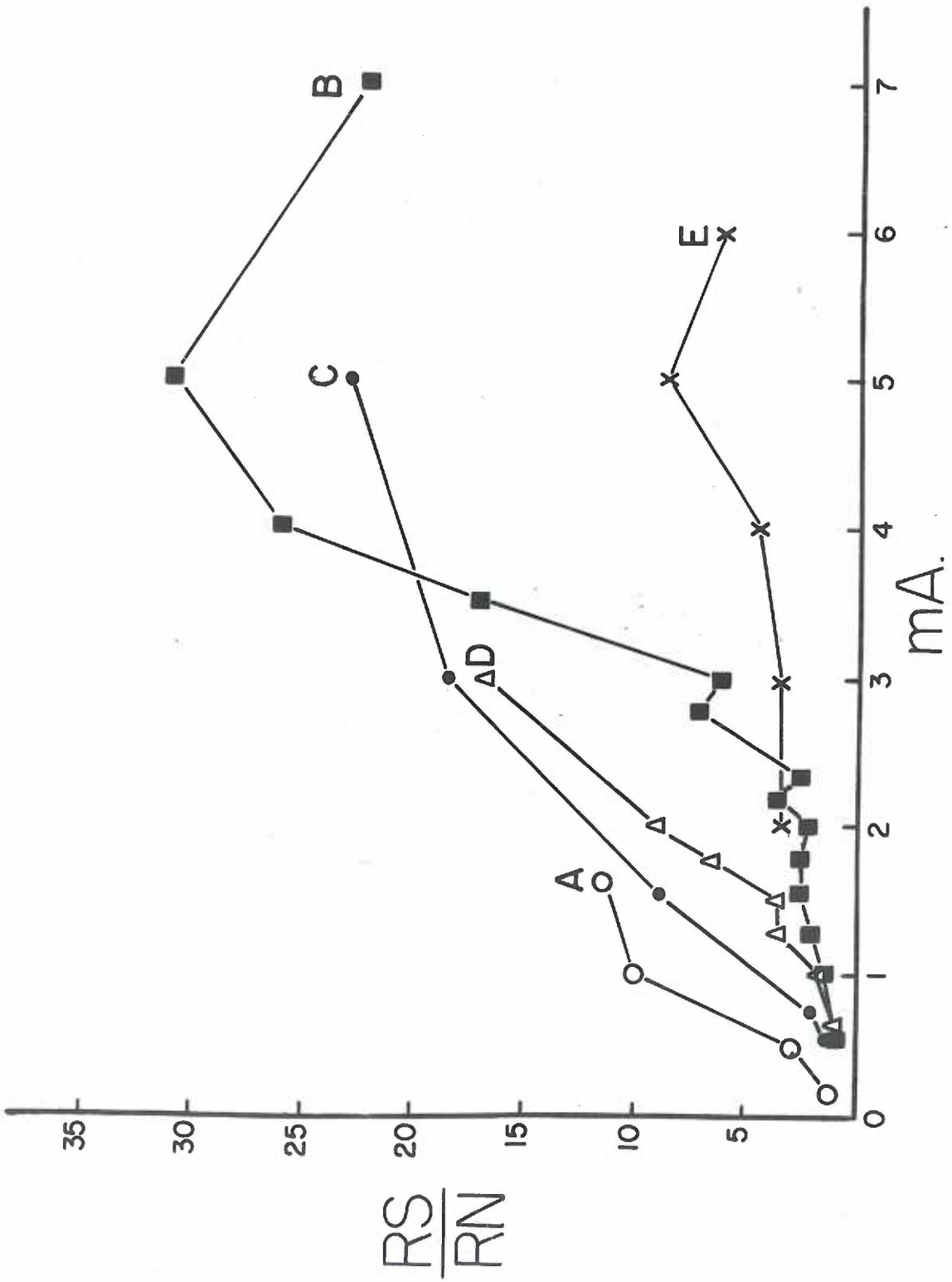
C


0.4mA P-
P+
P-
P+
P-
OFF
5 SEC.

D

FIGURE 4

Influence of intensity of stimulation on the respiratory response to stimulation in various locations in five animals. RS/RW is the ratio of respiratory minute volume during stimulation to respiratory minute volume during the normal period and expresses the intensity of the respiratory response. A. Nose - vertex. B. Pia in bi-temporal location. C. Binasal. D. Nose - vertex. E. Bitemporal on cranium.


RS/RN
35
30
25
20
15
10
5
0
1
2
3
4
5
6
7
mA.
A
B
C
D
E

The shape of the pulse form also influenced the response. The number "3" current was a much more effective stimulant than the number "1" current, as illustrated in the graphs of Figure 5.

The effectiveness of electrical stimulation on respiratory minute volume diminished as the depth of anesthesia was increased. When the animal was lightly anesthetized a very large increase in respiratory minute volume was obtained (to 62 times the resting rate in one experiment) whereas when the animal was very deeply anesthetized there was often no respiratory or blood pressure response. This effect is graphically shown in Figure 6.

The form of "modulation" did not influence the response.

The Mechanism of the Respiratory Response. It has been suggested that the respiratory responses to cranial stimulation in man are due to the direct transcranial activation of cortical or diencephalic structures (1, 2, 4, and 5). The results just described raise the possibility that such responses may be due solely to the activation of general somatic afferent fibers. These possibilities have been tested by determining the effects of decerebration at the level of the superior colliculus.

Effects of Decerebration. In 10 dogs under pentobarbital anesthesia, the respiratory response to bitemporal, bifrontal, and binasal electrical stimulation was recorded following craniotomy. The brain stem was then sectioned at the level of the superior colliculus, and the brain anterior to this level was scooped out. Hemostasis was provided by Gelfoam and cotton packing. After allowing five minutes for recovery, the animals were re-stimulated in the previous locations. In no case did the decerebration

FIGURE 5

Comparison of respiratory response to stimulation with two different pulse forms.

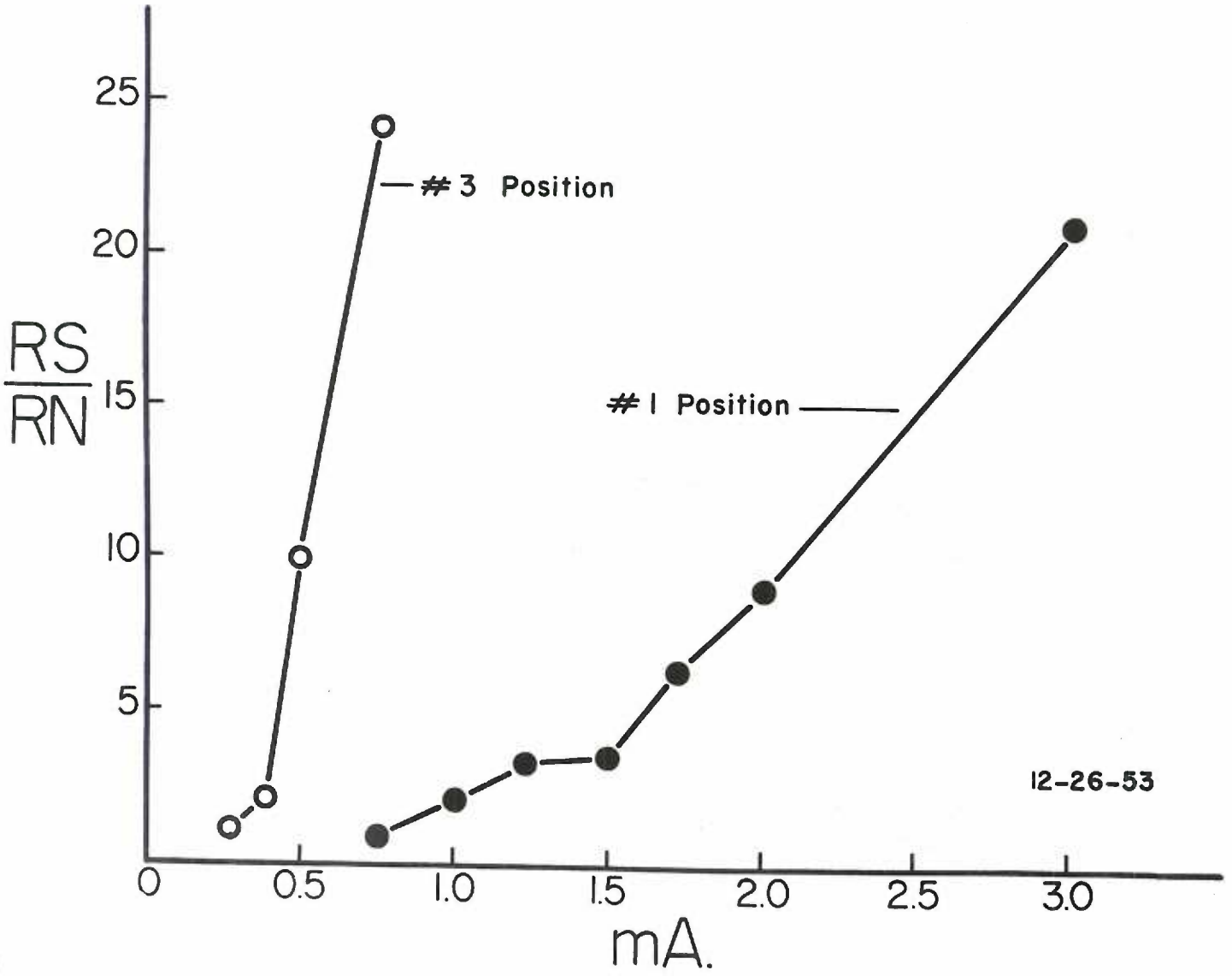
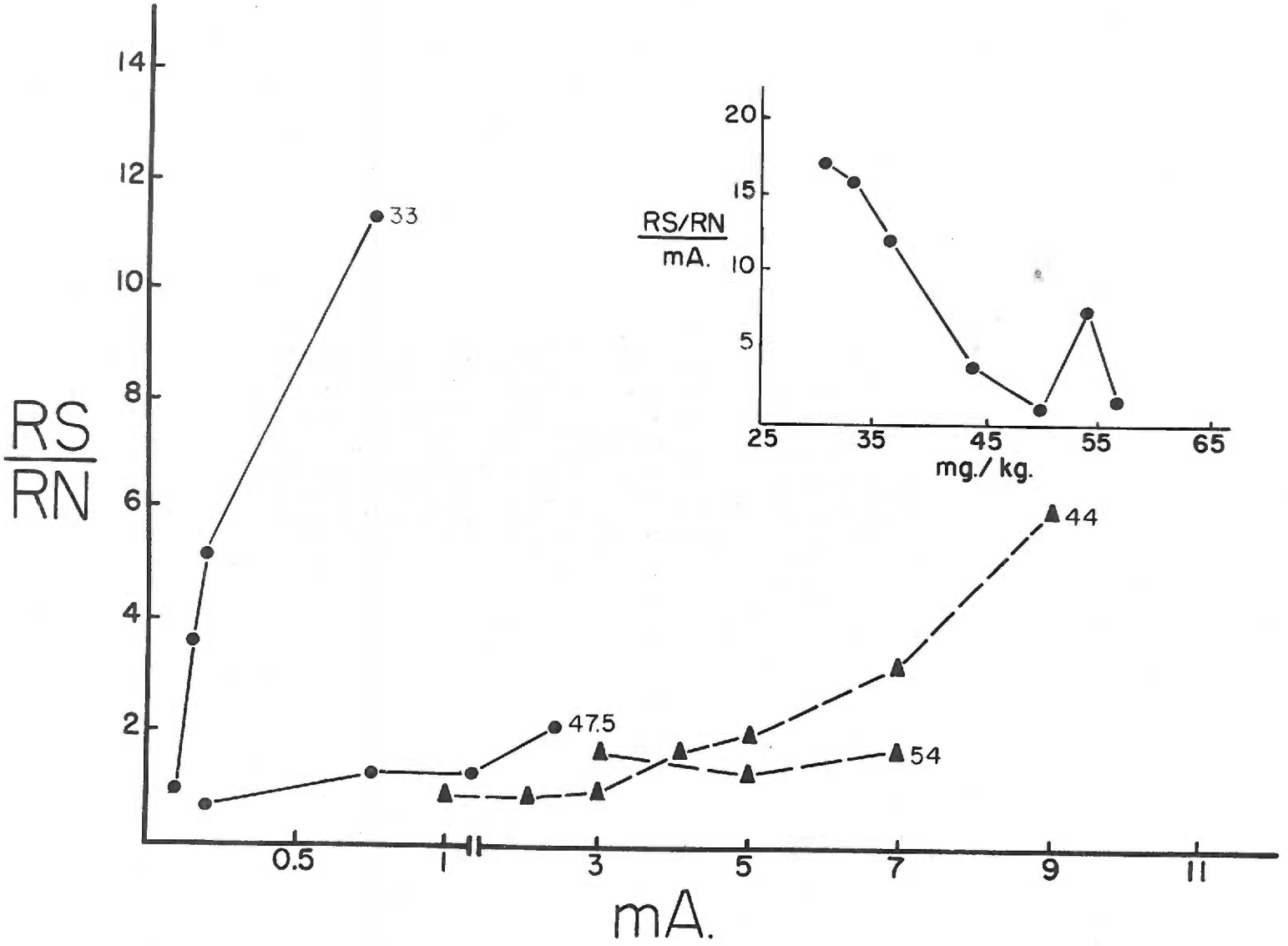

25
20
15
10
5
RS/RN
3 Position
1 Position
12-26-53
0
0.5
1.0
1.5
2.0
2.5
3.0
mA.

FIGURE 6

Intensity response curves at different levels of anesthetic dosage. Curves from two dogs are indicated by similar symbols. The figures at the ends of the curves indicate dosage of pentobarbital sodium in mg./kg. The insert graph represents the average of results obtained from ten animals and expresses the slope of the dose-response curves for each of the indicated dose levels.


RS/RN
14
12
10
8
6
4
2
33
47.5
44
54
0.5
1
3
5
7
9
11
mA.
RS/RN
mA.
20
15
10
5
25
35
45
55
65
mg./ kg.

diminish the respiratory response to stimulation. However, bilateral trigeminal neurotomy following the decerebration abolished all respiratory responses previously obtainable from stimulation of the head.

Effects of Trigeminal Neurotomy. Under pentobarbital anesthesia the respiratory response to bitemporal, bifrontal, and binasal electrical stimulation was recorded following craniotomy and resection of the occipital regions of the cerebrum. Trigeminal neurotomy was then performed bilaterally using a fine scalpel after removal of sufficient tentorium to permit adequate visualization of the trigeminal nerve at its exit from the pons. Care was taken not to disturb the brain stem or impair cerebral venous drainage. Section of each trigeminal nerve provoked an immediate large increase in respiratory minute volume similar to that seen in Figure 2D. Following this procedure, no response could be obtained from cranial or nasal stimulation.

High spinal cord transection abolished the respiratory response previously elicited by stimulation of the hind legs.

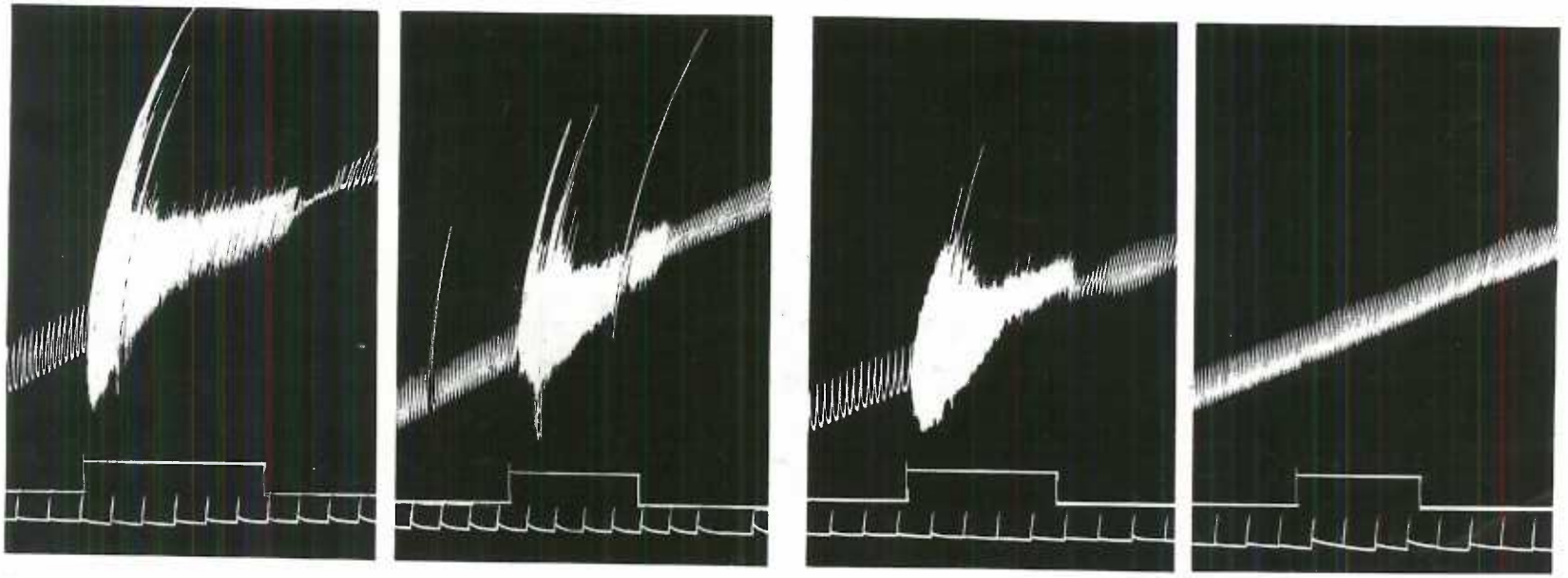
These results are illustrated in Figure 7.

THE EFFECTIVENESS OF ELECTRICAL STIMULATION AS AN ANALEPTIC AGENT

The Effect of Electrical Stimulation on Waking Times of Animals Anesthetised with Pentobarbital Sodium. It has been stated that this form of stimulation actually shortens the period of depression induced by the administration of barbiturates (1). To test the validity of this statement a series of observations of 25 groups of two dogs was carried out. In a single experiment each of the two dogs was given equal amounts of pentobarbital sodium per unit weight intravenously. Fifteen minutes later stimulation of one dog was started and adjusted to produce an

FIGURE 7

The mechanism of the respiratory response to electrical stimulation applied bi-temporally. Note that the response was not significantly altered by decerebration but was completely abolished by bilateral trigeminal neurotomy.



Dog S
BEFORE DECEREBRATION
2.0 mA bitemporal
Time 20 sec.

Dog S
AFTER DECEREBRATION
2.0 mA bitemporal

Dog T
BEFORE V CUT BILAT.
(not decerebrated)
1.8 mA bitemporal

Dog T
AFTER V CUT BILAT.
(not decerebrated)
1.8 mA bitemporal

obvious increase in respiratory rate. Stimulation was continued until either of the dogs awakened. A few days later using the same pair of dogs the procedure was reversed so that the previously unstimulated animal was stimulated and vice versa. One small series was done with an anesthetizing dose of 33 mg./kg. and continuous bitemporal stimulation through the skin with standard Reiter electrodes. A second larger series was done with an anesthetizing dose of 26 mg./kg. In the second series bitemporal stimulation, hindleg stimulation, continuous stimulation, and intermittent stimulation were used in various combinations. Intermittent stimulation consisted of five minutes of stimulation interrupted by five minutes of no stimulation.

It was soon found that waking time must be distinguished from arousal time. Fairly soon after stimulation was started the animal would react to high current intensities by whining, making running movements, or even turning to paw at the electrodes. But as soon as the current was decreased the dog would fall back to sleep. For this reason, waking time was arbitrarily defined as that period required from the administration of the anesthetic to the time that the animal made a coordinated effort to get on its feet.

The results of 51 observations on 11 dogs fail to indicate that stimulated dogs awakened earlier or later than control animals. Tables 1, 2, and 3 show the data, which suggest that if there was any consistent difference it was the stimulated dogs which showed the longer waking times. Analysis of the data indicated, however, that the variability between dogs is so large as to conceal even considerable differences between treatments. The mean for treatments and between-treatment differences are accompanied

TABLE 1

WAKING TIME IN ANIMALS ANESTHETIZED WITH 33.0 mg./kg. PENTOBARBITAL SODIUM. CONTINUOUS BITEMPORAL STIMULATION VS. NO STIMULATION

Dog	Waking time (Min.) Unstimulated	Stimulated	Difference
A	185	—	—
B	—	480	—
C	180	280	
	180	298	
Mean C	180	289	+109
D	257	270	
	420	360	
Mean D	339	315	- 24
Mean of Dogs ± 90% limits on estimate(1)	235 ± 152 (3 dogs)	361 ± 175 (3 dogs)	
Difference ± 90% limits on estimate(1)	+126 ± 169 (Difference - means, 6 expts.)		+42 ± 420 (mean difference, 2 dogs

(1) Student's t method

TABLE 2

WAKING TIME IN DOGS ANESTHETIZED WITH 26 mg./kg. PENTOBARBITAL SODIUM

Dog	Waking Time (Min.) Unstimulated	Stimulated	Stim. more than unstim.	Diff.	Stim. Site	Stim. Type
E	125	141	+		bitemp.	cont.
	152	145	-		bitemp.	intermit.
	162	173	+		hindlg.	cont.
	174	169	-		hindlg.	intermit.
Mean E	153	157		+3.7		
F	169	163	-		bitemp.	cont.
	158	179	+		hindlg.	cont.
Mean F	163.5	171		+7.5		
G	170	284	+		bitemp.	intermit.
	180	280	+		hindlg.	intermit.
Mean G	175	282		+107.0		
H	420	383	-		hindlg.	cont.
	272	342	+		binasl.	cont.
	323	382	+		bitemp.	cont.
Mean H	338.3	369.0		+30.7		
J	375	420	+		hindlg.	cont.
	340	506	+		binasl.	cont.
	304	385	+		bitemp.	cont.
Mean J	339.6	437.0		+97.4		
K	190	167	-		hindlg.	cont.
	154	144	-		binasl.	cont.
	130	116	-		bitemp.	cont.
	127					
Mean K	150.3	142.3		-8.0		
L	250	214	-		hindlg.	cont.
	186	143	-		binasl	cont.
	163	125	-		bitemp.	cont.
Mean L	199.7	160.7		-39.0		

Mean of dogs ± 90% limits on estimate	217 ± 51 (7 dogs)	246 ± 87 (7 dogs)

Difference ± 90% limits on estimate	34.5 ± 41 (mean difference, 7 dogs)

TABLE 3

EFFECT OF DIFFERENT ELECTRODE SITES ON WAKING TIME IN DOGS ANESTHETIZED WITH 26 mg./kg. PENTOBARBITAL SODIUM

Dog	Waking Time (Min.) Unstimulated	Stimulated	Stim more than unstim.	Diff.
HINDLEG ELECTRODE PLACEMENTS				
E	162	173	+	
F	158	179	+	
G	180	280	+	
H	420	383	-	
J	375	420	+	
K	190	167	-	
L	250	214	-	
Means	247.9	259.4		11.6
S.D.	107	116		
BITEMPORAL ELECTRODE PLACEMENTS				
E	125	141	+	
F	169	163	-	
G	170	284	+	
H	323	382	+	
J	304	385	+	
K	130	116	-	
L	163	125	-	
Means	197.7	228.0		30.3
S.D.	78	120		
BINASAL ELECTRODE PLACEMENTS				
H	272	342	+	
J	340	506	+	
K	154	144	-	
L	186	143	-	
Means	238.0	283.7		45.7
S.D.	84	175		

by an interval within which the probability is 0.90 that the true mean lies. Thus, from Table 1, the mean difference between stimulated and unstimulated dogs is between -43 and +295 minutes if we consider the differences between the means for all six experiments, or between -378 and +462 minutes if we consider only the two dogs on which we have paired contrasts. We have purposely used 90 per cent limits, thus incurring a 10 per cent risk of mistakenly concluding there is a difference when none exists, in order to hold reasonably low the other risk of failing to detect a difference if one does exist.

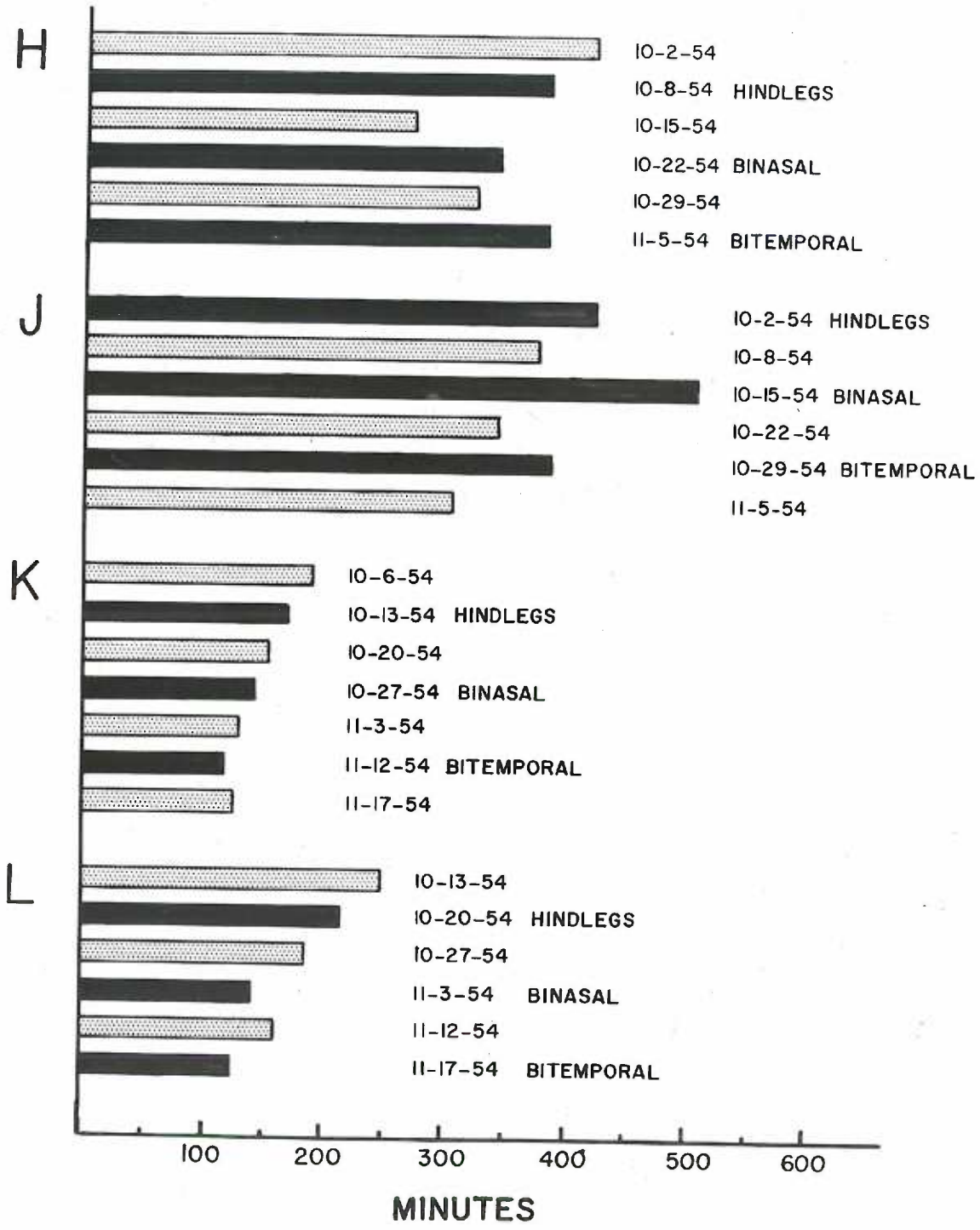
All of the indicated differences in the tables have very wide intervals of uncertainty, all of which include zero. Thus, it can be said that this experiment failed to detect any significant differences between treatments, either positive or negative. If such a difference exists it would require a much more sensitive experiment to detect it. The sensitivity of the experiment could be increased by reducing the variation or by greatly increasing the number of dogs.

The calculation of waking time in dogs used more than once, is complicated by a temporal or habituation factor, for even when an interval of seven days elapses between pentobarbital administrations, the animals develop a definite tolerance to the drug, and waking time is gradually shortened. This is illustrated by Figure 8 for dogs N, J, K, and L. However, this temporal factor is largely compensated by pairing the observations, that is, two dogs started the series with stimulation, and two were started with no stimulation.

Additional observations were made on such variables as electrode placement and continuity of stimulation. Data from Table 2 has been

FIGURE 8

The development of tolerance to pentobarbital sodium. Note that the waking times gradually decrease from week to week. Stippled columns indicate no stimulation. Solid black columns indicate the animal was stimulated at the sites indicated.


H
10-2-54
10-8-54 HINDLEGS
10-15-54
10-22-54 BINASAL
10-29-54
11-5-54 BITEMPORAL
J
10-2-54 HINDLEGS
10-8-54
10-15-54 BINASAL
10-22-54
10-29-54 BITEMPORAL
11-5-54
K
10-6-54
10-13-54 HINDLEGS
10-20-54
10-27-54 BINASAL
11-3-54
11-12-54 BITEMPORAL
11-17-54
L
10-13-54
10-20-54 HINDLEGS
10-27-54
11-3-54 BINASAL
11-12-54
11-17-54 BITEMPORAL
100
200
300
400
500
600
MINUTES

rearranged in Table 3 so as to enable easy comparison between the effects obtained from different stimulation sites. The variability of the data is such that no significant difference appeared between the effectiveness of different sites of stimulation. There was, however, a qualitative difference in the respiratory responses of the unstimulated as compared to the stimulated animals. In the unstimulated animals the respiratory rate remained constant or gradually increased until awakening. The respiratory rate of the stimulated animals gradually increased to a value above that of the resting unanesthetized state and remained elevated until, and often for some time after, awakening.

The Effect of Electrical Stimulation in Barbiturate Induced Apnea. Since electrical stimulation becomes a less effective respiratory stimulant with increasing depth of barbital depression, it was considered desirable to determine whether the electrical stimulation would be effective in an animal that is depressed to the point of apnea. Dogs were anesthetized with 33 mg./kg. of pentobarbital sodium intravenously and connected to the oxygen-filled spirometer and mercury manometer as before. Pentobarbital sodium was added intravenously from a burette at the rate of about 20 mg. per minute until the animal had been apneic for a period of at least one minute. The pentobarbital was stopped, and electrical stimulation started in the bitemporal location.

In a series of six unstimulated animals it was found that dogs could remain apneic for a remarkably long time, ten minutes in one case, and then resume respiration and recover completely. During the apneic periods the oxygen consumption remained quite constant, and it was assumed that gaseous exchange was maintained by diffusion respiration. In all six of

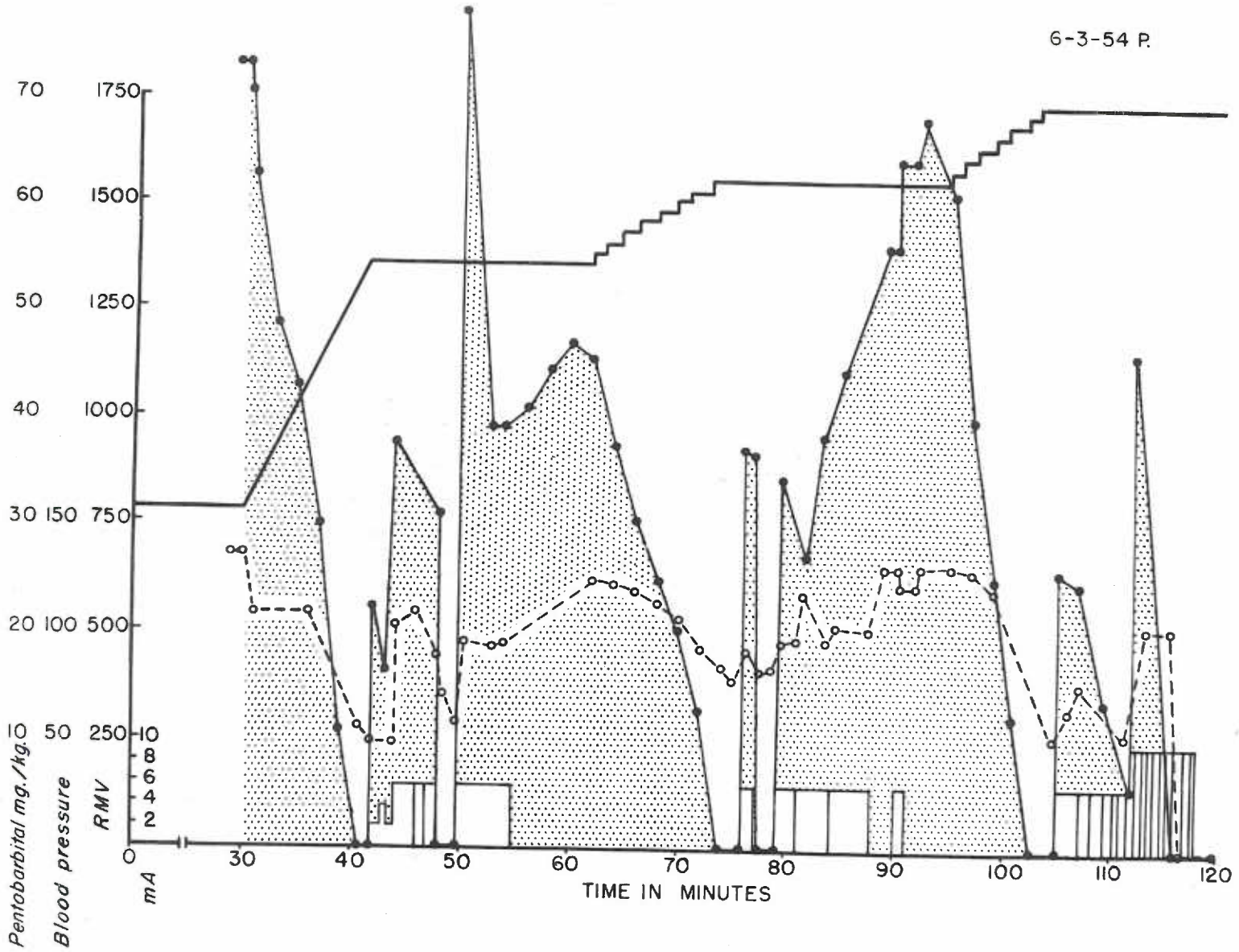
a series of stimulated animals it was found that respiration could be started, and blood pressure increased by applying the stimulation during this apneic period. In several animals it was possible by giving more pentobarbital to re-induce apnea and re-start respiration by electrical stimulation several times, until the lethal dose had been given. Figure 9 illustrates this response pattern.

Lethal Dosage of Barbiturate Required for Unstimulated Versus Stimulated Dogs. One of the unanswered questions concerns the ability of electrical stimulation to provide protection against the otherwise lethal effects of a large dose of barbiturate. In order to determine if such a protective effect exists, the minimum lethal dose of pentobarbital sodium administered by slow intravenous infusion was determined for a group of six unstimulated and a group of six stimulated dogs. This procedure was similar to the preceding one, but more rigorously controlled. Exactly thirty minutes elapsed from the time the animal was given the initial anesthetizing dose to the time the continuous infusion was started. The infusion was administered by a constant rate injector calibrated to deliver 10 mg. pentobarbital sodium per minute. Electrical stimulation from bitemporal electrode placements was begun forty seconds after the start of the infusion and was adjusted to produce a definite increase in respiratory minute volume. Stimulation and infusion were continued until the time of death as indicated by cardiac arrest.

The mean lethal dose for the unstimulated dogs was 59.1 mg./kg. with standard deviation 3.6 mg./kg. and for the stimulated dogs was 58.3 mg./kg. with standard deviation 4.9 mg./kg. The difference is estimated (90% limits) at 0.8 ± 4.5 and hence is considered not significantly different from zero.

FIGURE 9

Respiratory and blood pressure changes induced by bitemporal electrical stimulation during the administration of progressively larger doses of pentobarbital sodium o —— o. Arterial pressure in mm. Hg. • —— •. Respiratory minute volume in ml./min. _____. Total pentobarbital dose in mg./kg. The white blocks along the base of the figure indicate the time and intensity of electrical stimulation. Vertical lines within these blocks indicate reversal of polarity of stimulating electrodes.


6-3-54 P.
70
60
50
40
30
20
10
1750
1500
1250
1000
150
100
50
750
500
250
10
8
6
4
2
0
Pentobarbital mg./kg.
Blood pressure
RMV
mA
30
40
50
60
70
80
90
100
110
120
TIME IN MINUTES

There was, however, a qualitative difference in the course of the blood pressure and respiratory minute volume tracings between the two groups as shown in Figure 10. The stimulated animals maintained their respiratory minute volume and blood pressure fairly well until they received the critical dose, after which there was a comparatively abrupt drop to zero. On the other hand, the respiratory minute volume in the unstimulated dogs very soon dropped to zero and remained there during a gradual drop in blood pressure until the time of death.

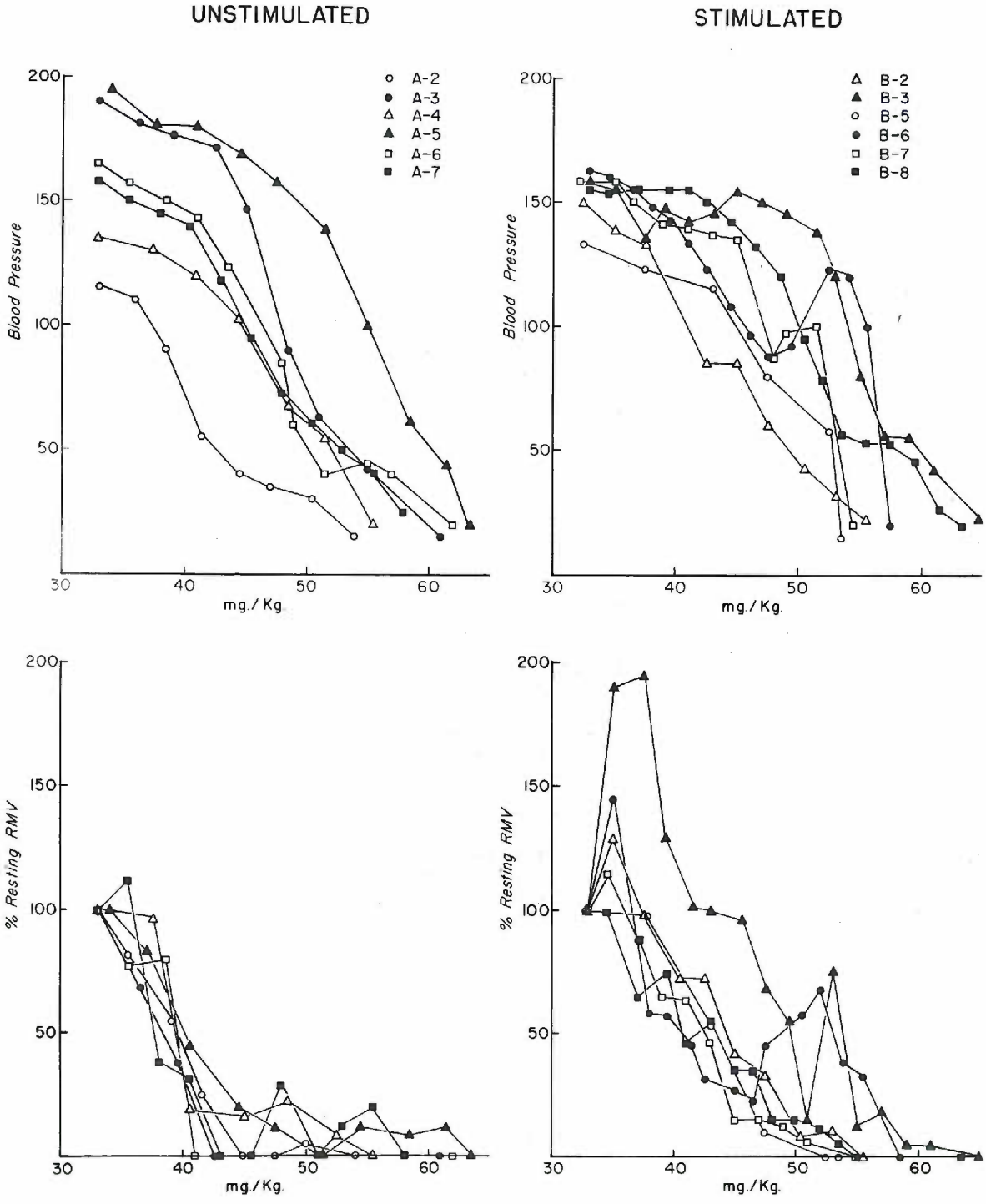
Through the inhalation of pure oxygen in the foregoing experiments the animals were deprived of the usual anoxic chemoreflex drive to respiration. In consideration of the possibility that this may have altered the response to barbiturate and stimulation, additional observations were made on seven animals breathing air. The lethal dose for four unstimulated air-breathing animals was 59.1 mg./kg. with standard deviation 6.5 mg./kg. and for three stimulated animals breathing air was 53.3 mg./kg. with standard deviation 1.5 mg./kg. giving a non-significant difference of 6.8 ± 6.4 (90% limits). Both controls and stimulated animals were, however, better able while breathing air to maintain blood pressure and respiratory minute volume until the critical dose was reached. The response of the air-breathing unstimulated dogs very closely resembled that of the oxygen-breathing stimulated dogs.

ELECTROENCEPHALOGRAPHIC CHANGES OCCURRING DURING PERIPHERAL ELECTRICAL STIMULATION

A series of experiments were undertaken to determine if prolonged electrical stimulation produced any gross changes of the electroencephalographic pattern in dogs anesthetized with pentobarbital sodium.

FIGURE 10

The course of blood pressure and respiratory changes in stimulated and unstimulated dogs receiving 10 mg./min. of pentobarbital sodium intravenously. Note that respiration and blood pressure were sustained at higher dose levels in the stimulated animals than in the unstimulated animals. Within each group, data from a single animal are plotted with similar symbols.


UNSTIMULATED
STIMULATED
Blood Pressure
% Resting RMV
mg./Kg.
A-2
A-3
A-4
A-5
A-6
A-7
B-2
B-3
B-5
B-6
B-7
B-8
200
150
100
50
30
40
50
60

In a preliminary operation, six stainless steel screws, insulated with polyethylene tubing except at the tips, were screwed into the calvarium of each of four dogs in the frontal, parietal, and occipital areas bilaterally. The screw tips extended to, but not through, the dura. The screw heads protruded through the skin so that recording electrodes could be easily clipped to them. Electroencephalograms were recorded with a Grass III-D electroencephalograph.

At least a week after implantation of the screw electrodes, two animals were anesthetized with 26 mg./kg. of pentobarbital sodium intravenously, and shortly thereafter control EEGs were recorded. One of the animals was then subjected to continuous electrical stimulation until it became aroused to the point where it could no longer be left on the table. It was then placed on the floor and observed until it awakened. Because of sixty cycle electrical interference it was impossible to record the EEG during stimulation. For this reason the stimulation was interrupted every 15 minutes for an EEG on each animal. As before, the waking time was defined as that period of time from the administration of the anesthetic until the animal first made a coordinated effort to get to its feet. The following week the previously unstimulated animal received stimulation, while the other did not. Only sufficient stimulation was administered to produce a definite increase in the respiratory minute volume to gross inspection. This generally required from 2.0-5.0 mA at the number "3" position.

The EEG pattern from dogs receiving prolonged stimulation through the binasal or bitemporal electrode positions was not significantly different from the control patterns. However, prolonged stimulation through the

hindlegs always resulted in a low voltage fast pattern, most marked from the frontal electrodes, which gradually developed after an hour or more of stimulation at the mild stimulus intensities. During a period of no stimulation, the pattern would revert to the usual anesthetized type over a period varying from three seconds to several minutes, depending on the depth of anesthesia and the intensity of the preceding stimulation. Then, often a very short period of stimulation, as little as 15 seconds, would be sufficient to reproduce the low voltage fast activity. This low voltage fast activity was of about the same rate as the normal waking activity, but of somewhat higher amplitude. Generally more spontaneous motor activity occurred during the periods of low voltage fast activity, but often the fast activity would occur in the absence of any overt movements. Very rapid panting was usually, but not always seen during the low-voltage fast activity. If instead of using mild stimulation, the current intensity was adjusted to produce severe tonic contractions (8-12 mA at number "3" position), the duration of stimulation required to first produce the low voltage activity was shortened in each animal. There was considerable difference in the EEG of each dog, but each one maintained its own characteristic pattern from week to week.

The usual physical pattern of awakening from pentobarbital anesthesia was one of progressively increasing activity until the dog was walking around and apparently normal. However, the two dogs (H and J) with long waking times slept for a long period of time following a brief period of awakening. During this period of sleep they gave the clinical appearance of being extremely fatigued, but EEG records taken at this time gave no evidence of true depression, but only of light sleep. They could be

aroused from this sleep fairly easily by shaking, but upon cessation of this stimulation, would soon return to sleep.

Representative EEG tracings are given in Figure 11.

DESCRIPTION OF A CASE OF PHENOBARBITAL POISONING TREATED WITH ELECTRICAL STIMULATION VIA LEG ELECTRODE PLACEMENTS

This 30 year old white female entered the Kaiser Permanente Hospital, Vancouver, Washington, May 7, 1954 in deep coma. It was later found that she had ingested 5.0 grams of phenobarbital about six hours before admission. It was known that she was an epileptic whose seizures had been controlled over the past four years with dilantin and phenobarbital and who had attempted suicide on one previous occasion.

Physical examination at admission: Pulse 110, respiration 16, blood pressure 50 systolic, 30 diastolic, and temperature 96.0°. All reflexes were absent with the possible exception of the light reflex.

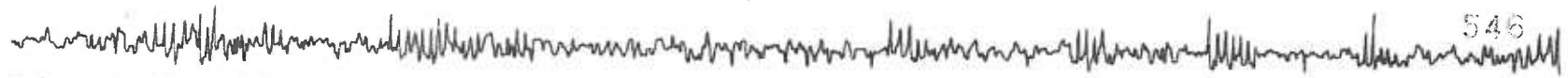
Course: She was treated with Metrazol (R), Coramine (R), caffeine and sodium benzoate, and Benzedrine (R). Blood pressure was maintained with shock blocks and continuous intravenous drip of Levophed (R). She received adequate amounts of penicillin and chloromycetin. Despite these measures the patient did not rouse, her temperature began to rise, and she was placed in an oxygen tent on the fourth day as her condition continued to deteriorate.

The author saw her at 7:30 p.m. on the fourth day. Except for a sluggish corneal reflex she was areflexic, would not respond to noxious stimuli, and moist rales were audible over both lung fields. Her temperature was 102.4°, respiratory rate 30, respiratory amplitude very shallow, skin cold and pale, and blood pressure 100 systolic, 60 diastolic.

FIGURE 11

Electroencephalographic exerpts from anesthetized dog receiving prolonged electrical stimulation through the hindlegs.

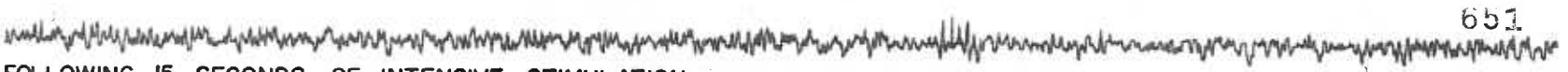
EEG FROM LEFT FRONTAL REGION



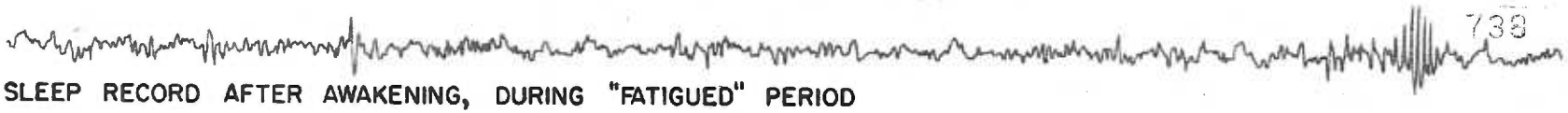
EARLY BARBITURATE COMA

AFTER PROLONGED STIMULATION OF HINDLEGS

FOLLOWING SIX MINUTES WITHOUT STIMULATION



FOLLOWING 15 SECONDS OF INTENSIVE STIMULATION



SLEEP RECORD AFTER AWAKENING, DURING "FATIGUED" PERIOD

ANIMAL AWAKE, NO PREVIOUS ANESTHESIA

TWO SECONDS

200 μV.

One standard Reiter electrode was applied to the medial aspect of the middle part of each lower leg and the instrument set to deliver the number "3" current. The current was gradually increased until a definite respiratory response was obtained at about 5.0 mA. This response consisted of a slight increase in respiratory rate to 36 per minute and estimated fourfold increase in amplitude. There was a concomitant rise in blood pressure of 20 mm. of mercury, and there was considerable muscular activity in the region between the two electrodes. The intravenous drip of Levophed was discontinued after this blood pressure rise was obtained. One half hour after stimulation was started one of the attending physicians thought he could elicit a knee jerk, thought that the corneal reflex had improved, and found that a gag reflex had appeared. The increase in respiratory minute volume was so pronounced that it was feared she might develop a respiratory alkalosis. About 45 minutes after the start of stimulation her skin was warm and moist. At the end of an hour of continuous stimulation when no further improvement seemed forthcoming, it was decided to try the bitemporal stimulation to see if it would produce a different response. From this location no improvement of response was obtained, but it was found very easy to inhibit respiration if the current was greater than 3.0 mA at the number "1" position. At the end of two and one-half hours of continuous stimulation her temperature had dropped from 102.4° to 98.8°, she was breathing easily and deeply, her blood pressure was 110 systolic, 60 diastolic, and her lungs were completely free of rales. Stimulation was discontinued at 11:00 p.m. after three and one-half hours total stimulation. One-half hour following discontinuation of electrical stimulation her blood pressure had fallen to

80 systolic, 50 diastolic and the continuous drip of Levophed was re-started and maintained twelve hours longer. Otherwise, from the time of the institution of electrical stimulation her recovery was progressive, and three days later she was able to sit up in bed and take water by mouth.

Comment: This case is of interest as the first in which electrical stimulation was found to be effective as a respiratory stimulant in man when the electrodes were elsewhere than on the head. The chief benefit of electrical stimulation in this case was probably through its supportive action on respiratory exchange. The improvement in the respiratory and circulatory status was probably the cause of the disappearance of the pulmonary edema. Positive pressure breathing might have done as well. The increase in blood pressure may have been due to the noxious stimulation, to better oxygenation, or both. Her fall in temperature of 3.6° was probably due to the sweating that was seen after 45 minutes of stimulation. It was felt that the peripheral stimulation on the legs was more effective than cranial stimulation since it is less likely to produce respiratory inhibition. Stimulation of this patient was not maintained longer than it was because of our findings on dogs that if the respiration and blood pressure are adequate, stimulation does not actually shorten the waking time.

DISCUSSION

In view of the evidence that decerebration does not alter the respiratory response obtained from transcranial electrical stimulation, but section of sensory nerves to the stimulated area abolishes the response,

there remains no doubt that respiratory augmentation resulting from electrical stimulation in barbitalized dogs is a reflex mechanism dependent on the excitation of general somatic afferent fibers. Previous suggestions (1, 2, 4, and 5) that central nervous system structures were directly involved in this respiratory response were probably based on the fact that alterations of respiration may be produced by electrical excitation of selected portions of the cerebral cortex (7), diencephalon and mesencephalon (8). It is possible that failure to consider other mechanisms has been conditioned by the fact that this form of therapy was first introduced, and has since been largely used, by psychiatrists who are accustomed to apply electro-shock therapy to regions about the head (1-6, 10 & 11). The present study offers no clue as to the relative importance of the various modalities of sensory stimulation in the production of this reflex respiratory response. It might be argued that the relatively high potency of stimulation in the trigeminal area is evidence of the importance of nociceptive or pain-initiating stimuli, because of the ease with which pain may be initiated from various face structures. However, other modalities of sensation are also transmitted over trigeminal fibers. Thus, the role played by proprioceptive, tactile, and other afferents cannot at present be evaluated. Since many of the effective procedures utilized in barbiturate poisoning (continuous forced ambulation, tactile, thermal, and auditory stimulation, etc.) also involve vigorous afferent excitation it might have been predicted that electrical stimulation would operate through similar mechanisms.

Because of the reflex nature of the respiratory response elicited by this form of electrical stimulation, it seems highly probable that the peculiarities of the current generated by the Reiter instrument are not

an essential feature in the production of the response. This conclusion is supported by the observation that the responses obtained using the different pulse forms generated by the instrument vary only in a quantitative way. No differences whatsoever were detectable when the selector was switched from position "1" to position "2". The difference noted between position "1" and "3" consisted of an exaggeration of the response with position "3". By proper adjustment of intensity, results obtained by using either position could be duplicated with the selector in the alternate position. Furthermore, variations in the function called "modulation" did not affect respiration but produced only alterations in the frequency of muscular activity in the electrode regions. We conclude, therefore, that any form of electrical stimulation capable of initiating a massive barrage of impulses in sensory nerve fibers would serve as well as the instrument used in this study for the stimulation of respiration.

The hypothesis that electrical stimulation will abbreviate the period of central nervous system depression resulting from barbiturate administration to dogs and thus lead to a more rapid awakening could not be ~~continued~~ confirmed. The studies on waking times in dogs anesthetized with pentobarbital sodium failed to indicate that electrical stimulation shortened the waking time. Electrical stimulation failed to give any protection after an otherwise lethal dose of barbiturate. It is true that the massive afferent barrage does bring about behavioral changes which are best interpreted as arousal or return toward consciousness. However, while effective concentrations of the barbiturate persist in tissue fluids, the cessation of the afferent stimulation

results in a return to the depressed condition. Failure to find a significant difference between waking times for stimulated and unstimulated dogs further argues against the possibility that the electrical stimulation influences the rate of excretion or metabolic destruction of the barbiturate.

These conclusions are in contradiction to those derived from the study of human responses to electrical stimulation during barbiturate-induced depression (1-5, 11). This apparent discrepancy may be explained in several ways. The most obvious explanation is that in these experiments a very rigorous standard for the time of awakening was chosen; the dog had to be sufficiently coordinated to get to its feet. Physicians resuscitating patients usually consider the patient awake when he first opens his eyes or can say a few words. This is not a good criterion of awakening because quite a time elapses between the period when the patient can talk and when he can stand unassisted. Furthermore, many patients have relapsed into coma and died after brief periods of arousal. Another explanation is that many of the human cases studied have been individuals subjected to administration of Pentothal (R) in the course of non-convulsive electro-shock therapy. It is well-known that Pentothal (R) is very short acting. Perhaps afferent stimulation arouses the patient for a period of time sufficient to permit reduction of thiobarbiturate concentrations to an ineffective level and/or to prevent these individuals from making the usual transition from heavy sedation to natural sleep. In the experiments reported here the longer lasting effect of pentobarbital sodium may have been responsible for our ability to arouse the animals incompletely with a subsequent return to a depressed state. Another group of human cases

consists of individuals who have been subjected to excessive amounts of barbiturates and receive electrical stimulation after a prolonged period of coma. Such cases may very well derive their benefit from the effects of the stimulation on the respiratory and circulatory systems rather than from any influence on their susceptibility to the CNS depressant properties of the drug. In addition the improvement in function of the circulatory system might result in a more rapid elimination of those barbiturates excreted through the kidney. The animals used in this study, on the other hand, were anesthetized for relatively short periods, with quantities of drugs which were not severely depressing to respiration or circulation and therefore would not show the beneficial effects of improvement in their circulatory and respiratory status.

The data concerning the inability of electrical stimulation to protect against lethal effects of large doses of barbiturates must also be viewed in the light of the short time-span of these experiments. In the acute situation dealt with here, secondary depressing influences resulting from stagnant or anoxic anoxia did not enter into the picture in a significant way. These animals may be regarded as having died specifically from the effects of the pentobarbital sodium alone. Indeed, the uniformity of the lethal dose under all conditions of the experiments raises the possibility that the lethal effect was exerted through interference with the action of a critical enzyme system, perhaps in cardiac muscle. If such were the case, electrical stimulation could not be expected to exert any protective action against the lethal effect of the drug.

Attention should be called to the method utilized in the measurement of lethal dose. This method is similar to that utilized by Bliss and

Allmark (9) in the bio-assay of digitalis. To the author's knowledge, this is the first time this technique has been used for the study of central nervous system depressants.

Although many workers have described the electroencephalographic changes induced by barbiturates (14-20), and others have demonstrated the influence of short duration afferent stimuli thereon (21-40), the electroencephalographic studies reported in this paper are of value because they deal with the effects of prolonged intensive afferent stimulation during barbiturate depression.

It was found that prolonged stimulation through the hindlegs resulted in a pattern of low voltage fast activity which persisted for a few seconds to several minutes after cessation of stimulation, depending on the depth of anesthesia and the duration and intensity of the preceding stimulus. However, prolonged transcranial or binasal stimulation did not produce this low voltage fast activity. It is difficult to explain this discrepancy, for Gellhorn (31) has shown that for short periods of stimulation, nociceptive stimuli are slightly more effective in producing arousal than are proprioceptive stimuli. Little in the way of an explanation for the different effects of varying the stimulation sites can be obtained from anatomical studies of the distribution of trigeminal and ascending spinal tracts (41, 42). Reflection upon the type of respiratory responses elicited from the different stimulation sites may give a hint as to the explanation of this discrepancy. It will be recalled that the respiratory response to binasal or bitemporal stimulation, although immediately very large, quickly declined to a level only slightly greater than the resting respiratory minute volume, whereas hindleg stimulation

resulted in a progressively increasing respiratory minute volume. If it is assumed that the binasal and bitemporal stimulation is predominantly nociceptive, whereas the hindleg stimulation is primarily proprioceptive, the discrepancy can be resolved by assuming that adaptation occurs more readily to nociceptive than to proprioceptive stimulation. Unfortunately there is little evidence to support this concept of differential adaptation. A second explanation is that both types of respiratory response result from nociceptive stimulation, but the binasal and bitemporal stimulation produces primarily superficial pain, whereas the hindleg stimulation causes deep pain from tendon and muscle receptors, the latter undergoing less adaptation and accommodation. A third explanation, almost as tenuous as the others, is that the hindleg stimulation may affect a much larger area of the brain stem than trigeminal stimulation. This is partly supported by Berry et al (34) who found that sciatic stimulation produced very widespread excitation of the medulla.

By what mechanism does this afferent stimulation alter the EEG pattern? Magoun and others (43-55) have investigated an extralemniscal sensory system in the anterior brain stem which is essential for the production and maintenance of behavioral arousal and consciousness. This system, usually referred to as the reticular activating system, appears to be dependent upon afferent sensory input, for the maintenance of its activity (43-46, 52) and is highly susceptible to a variety of depressant influences such as anesthesia, anoxia, etc., at levels which have no apparent influence on activity conducted over the classical lemniscal systems of the brain. It is entirely possible that repetitive intensive stimuli such as those used in these experiments, may activate this reticular system sufficiently to

overcome the barbiturate induced depression and produce an EEG arousal pattern.

Additional evidence supporting this concept results from Kabat's (8) stimulation studies of the anterior brain stem which revealed respiratory responses somewhat similar to those from hindleg stimulation, elicited from structures now commonly included in the title "reticular activating system".

It is true that an EEG arousal pattern can be produced by afferent stimulation in animals with lesions of the reticular activating system, but as Lindsley et al (44) pointed out, this pattern is usually abolished immediately on cessation of stimulation. They emphasized that although this stimulation did produce an EEG arousal pattern, it did not result in behavioral arousal.

Since in our experiments the arousal pattern was not always accompanied by behavioral arousal of the dogs, we may have to conclude that sometimes the arousal pattern after prolonged stimulation is not dependent upon reticular formation activity. It might be argued that when the arousal pattern lasted for only a few seconds after the end of stimulation it was being mediated primarily via the lemniscal system, whereas in those cases where the pattern persisted for several minutes, the reticular activating system was exerting its influence as well. This may explain the observation that very early in each experiment, a few seconds of activation pattern would be present following stimulation, whereas later when the barbiturate effects were wearing off with presumably less depression of the reticular activating system, the activation would persist much longer.

CLINICAL IMPLICATIONS

It is felt that the results of this study shed considerable light upon the utilisation of electrical stimulation in the therapy of acute barbiturate poisoning. It seems most probable that the beneficial effects of this therapy are attributable to the reflex effects on cardiovascular and respiratory functions induced by the excitation of afferent nerve fibers. The failure of electrical stimulation to abbreviate the period of barbiturate depression, its failure to combat the lethal effects of barbiturate, and the results of the utilisation of peripheral stimulation in the one human case reported all point in this direction. The opinion has been expressed that other forms of analeptic therapy exert their beneficial action in large part indirectly through cardiovascular and respiratory stimulation (12, 13). Undoubtedly the increased respiratory movements produced by electrical stimulation will counteract the tendency to pulmonary atelectasis so often seen with barbiturate depression as shown by Swank and Smedal (56). The pulmonary atelectasis alone will apparently give rise to hyperthermia without a pneumonitis being necessarily present, although it is a frequent complicating and terminal event.

The use of electrical stimulation offers certain advantages not shared by other forms of analeptic therapy. The principal advantage lies in the ease and precision of control which is afforded the physician by virtue of his ability to grade dosage accurately and rapidly. Furthermore, peripheral electrical stimulation takes advantage of normal physiological mechanisms, and no dangerous side-effects have yet been seen such as characterise the actions of some of the chemical analeptics. This therapy has not been critically compared with other commonly used forms of treatment, and there is no evidence to indicate that it should be used to the

exclusion of them. However, as seen in the case described herein, it proved to be quire effective when the intensive use of other analeptics had failed. That this form of stimulation is useful in the treatment of other forms of drug induced depression is shown by its effectiveness in arousing patients from deep hypoglycemic coma (57).

From the results of this study it would seem preferable to apply electrical stimulation in barbiturate poisoning peripherally rather than trans-cranially. The possibility of producing respiratory irregularities, respiratory inhibition and generalized convulsions is reduced by using peripheral stimulation. Furthermore, prolonged electrical stimulation applied cranially may actually be detrimental to the psychiatric status of the individual, since it is commonly held (6) that excessive non-convulsive electro-shock therapy may precipitate states of mental depression.

It should be obvious that there are certain conditions and situations which must be guarded against in the utilization of this form of therapy. Care should be taken to prevent occlusion of the airway or aspiration of buccal contents as a result of the augmented ventilation. Consideration should be given to the possibility of developing respiratory alkalosis through the maintenance of pulmonary ventilation far in excess of the metabolic requirements. As was pointed out above, there is no reason for believing that one can dispense completely with other forms of supportive therapy. Attention should therefore be given to improving the general status of the patient with rational measures used in conjunction with peripheral electrical stimulation.

It cannot be too strongly emphasized that the evidence offers no support for the idea that electrical stimulation will shorten the duration

of action of the barbiturates. The fundamental reason for the disappearance of barbiturate depression is the reduction of the barbiturate concentration by metabolic detoxication or renal excretion. Electrical stimulation cannot directly influence the rate at which these processes occur. It will, however, help the organism to maintain the proper cardiovascular and respiratory conditions which form the necessary foundation for these processes.

SUMMARY

1. The analeptic action of electrical stimulation has been studied in 69 dogs anesthetized with pentobarbital sodium.

2. Augmentation of respiratory minute volume was found to be dependent upon the activation of sensory nerves. It was found that direct electrical stimulation of the cortex or diencephalon was not a factor in this respiratory augmentation. Peripheral stimulation was found to be as effective as cranial stimulation.

3. A distinction was made between behavioral arousal and awakening. Waking time was not shortened by any form of electrical stimulation although temporary arousal could be produced. Electrical stimulation did not protect against the lethal effects of barbiturate administration.

4. The EEG changes resulting from prolonged hindleg stimulation consisted of the appearance of low voltage fast activity which persisted a variable time after stopping stimulation. The low voltage fast activity was not always accompanied by behavioral arousal. Prolonged bitemporal and binasal stimulation did not produce this pattern. These findings are discussed in regard to the reticular activating system of Magoun.

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