STUDIES ON THE ANALEPTIC ACTION OF ELECTRICAL STIMULATION IN BARBITURATE POISONING * † ‡

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Nonconvulsive electrical stimulation to the head has been recommended for the treatment of barbiturate poisoning (1-5). To date this therapy has been entirely empirical and little is known concerning the indications and contraindications for its use, its mode of action, or its effect on the duration of barbiturate action. This study was made 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 65 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 in which it was considered necessary to control the placement of cranial electrodes carefully, the head was fixed in a head-holder, the temporalis muscles were reflected, and the stimulation was carried out through the bone.

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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 Electrostimulator, Model CW 47. It was found necessary to determine the output of our own Reiter electrostimulator since an adequate description of either the instrument or its output could not be obtained from the manufacturer or any other source. The following description, which has been derived from a study of single frame and moving film cathode ray oscillograms 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 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 utilized 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 to 33 cycles per second. 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 to 47 per cent. There is superimposed on the pulses a ripple whose frequency for our machine varies between 48 and 100 cycles per second. The amplitude of the ripple varies between 22 per cent and 41 per cent of the maximal pulse amplitude in position "1" and between 27 per cent and 50 per cent of the maximal 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 30 cycles per second with a duty cycle of roughly 50 per cent.

The function called modulation controls the rate at which a rhythmic alteration in pulse amplitude and contour occurs. 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 and 4 cycles per second.

Two kinds of electrodes were used, the standard cloth-covered, 1 inch disk Reiter electrodes, and 1 cm., cloth-covered silver-silver chloride nonpolarizable electrodes. These made contact with the animal through a saline bridge.

Results

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 as a result of an increase in both the rate and depth of breathing. This lasted for thirty to sixty 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 hyper-ventilation apnea occasionally followed the cessation of stimulation.

Fig. 1. 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.
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 1. 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 1 cm. 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 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. Figure 2 illustrates the type of responses obtained from peripheral stimulation. From this figure the relative effectiveness of each electrode placement cannot be compared 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 times inhibited respiration (fig. 3, B and 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.

The effectiveness of electrical stimulation on respiratory minute volume decreased 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 deeply anesthetized there was often no respiratory or blood pressure response. This effect is graphically shown in figure 4.

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**Fig. 3.** Influence of intensity of stimulation on the respiratory response to stimulation in various locations in five animals. RS/RN 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. Pin in bitemporal location. C. Binasal. D. Nose—vertex. E. Bitemporal on cranium.
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 the result of the activation of cortical or diencephalic structures (6). 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 in 10 dogs. In no case did this traumatic procedure diminish the respiratory response, even from bitemporal electrode placements. However, bilateral trigeminal

![Graph showing intensity response curves at different levels of anesthetic dosage.](image)

**Fig. 4.** 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 averages of results obtained from ten animals and expresses the slope of the dose-response curves for each of the indicated dose levels.

neurotomy following the decerebration abolished all respiratory responses previously obtainable from stimulation of the head. Trigeminal neurotomy was performed without decerebration in 6 dogs. 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 5.

The Effect of Electrical Stimulation on Waking Times of Animals Anesthetized 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 on 13 groups of 2 dogs was carried out. In a single experiment each of the 2 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 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 series was done with an anesthetizing dose of 33 mg. per kilogram and continuous bitemporal stimulation through the skin with standard Reiter electrodes. A second series was done with an anesthetizing dose of 26 mg. per kilogram. In the second series bitemporal stimulation, hind leg

![Fig. 5. The mechanism of the respiratory response to electrical stimulation applied bitemporally. Note that the response was not significantly altered by decerebration but was completely abolished by bilateral trigeminal neurotomy.](image)

stimulation, continuous stimulation, and intermittent stimulation were used in various combinations. Intermittent stimulation consisted of stimulation for five minutes interrupted by no stimulation for five minutes.

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 26 observations on 7 dogs fail to indicate that stimulated dogs awakened earlier or later than control animals. Tables 1
and 2 show the data, which suggest that if there was any consistent difference, it was the stimulated dogs which showed the later waking times. Analysis of the data indicated, however, that the variability between dogs is so great as to conceal even considerable differences between treatments. The means for treatments and between treatment differences are accompanied 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 the differences between the means for all six experiments are considered, or between —378 and +462 minutes if

**TABLE 1**

**Waking Time in Animals Anesthetized with 33.0 mgm./kgm. Pentobarbital Sodium. Continuous Bitemporal Stimulation vs. No Stimulation**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Waking Time (Min.)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstimulated</td>
<td>Stimulated</td>
</tr>
<tr>
<td>A</td>
<td>185</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>—</td>
<td>480</td>
</tr>
<tr>
<td>C</td>
<td>180</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>298</td>
</tr>
<tr>
<td>Mean C</td>
<td>180</td>
<td>289</td>
</tr>
<tr>
<td>D</td>
<td>257</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>420</td>
<td>360</td>
</tr>
<tr>
<td>Mean D</td>
<td>339</td>
<td>315</td>
</tr>
</tbody>
</table>

| Mean of dogs ± 90% limits on estimate* | 235 ± 152 | 361 ± 175 |
| (3 dogs)                               |           |           |

| Difference ± 90% limits on estimate* | +126 ± 169 | +42 ± 420 |
| (Difference — means, 6 expts.)        |           | (mean difference, 2 dogs) |

* Student’s t method.

only the 2 dogs are considered on which paired contrasts were obtained. 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.

The differences estimated in tables 1 and 2 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.

Additional observations were made on such variables as electrode
placement and continuity of stimulation. Electrode placements on the hind legs were as effective in arousing the animal as were bitemporal placements, and intermittent stimulation was as effective as continuous. There was a qualitative difference, however, in the respiratory responses of the unstimulated as compared with 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

**TABLE 2**

**Waking Time in Animals Anesthetized with 26 mgm./kgm. Pentobarbital Sodium. Stimulation Vs. No Stimulation. Two Sites of Stimulation and Continuous Versus Intermittent Stimulation**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Waking Time (Min.)</th>
<th>Difference</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstimulated</td>
<td>Stimulated</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>125</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td></td>
<td>152</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td></td>
<td>162</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td></td>
<td>174</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>Mean E</td>
<td>153</td>
<td>157</td>
<td>+3.7</td>
</tr>
<tr>
<td>F</td>
<td>169</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td></td>
<td>158</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>Mean F</td>
<td>163.5</td>
<td>171</td>
<td>+7.5</td>
</tr>
<tr>
<td>G</td>
<td>170</td>
<td>284</td>
<td></td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>Mean G</td>
<td>175</td>
<td>282</td>
<td>+107.9</td>
</tr>
</tbody>
</table>

Mean of dogs ± 90% limits on estimate:

|               | 104 ± 19 (3 dogs) | 203 ± 116 (3 dogs) |

Difference ± 90% limits on estimate:

|               | +39 ± 86 (difference – means, 6 exps.) | +39 ± 99 (mean difference, 3 dogs) |

* Student's t method.

unanesthetized state of rest 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. per kilogram of pentobarbital sodium intravenously and connected to the oxygen-filled spirometer and mer-
cury manometer as before. Pentobarbital sodium was added intravenously from a buret at the rate of about 20 mg. per minute until the animal had been apneic for at least one minute. Administration of pentobarbital was stopped, and electrical stimulation started in the bitemporal location.

In a series of 6 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 6 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 again to induce apnea and restart respiration by electrical stimulation several times, until the lethal dose had been given.

*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 whether such a protective effect exists, the minimal lethal dose of pentobarbital sodium administered by slow intravenous infusion was determined for a group of 6 unstimulated and a group of 6 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. of 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. per kilogram, with standard deviation ± 3.6 mg. per kilogram, and for the stimulated dogs was 58.3 mg. per kilogram. The difference is estimated (90 per cent limits) at 0.8 ± 4.5 and hence is considered not significantly different from zero. There was, however, a qualitative difference in the course of the tracings of the blood pressure and respiratory minute volume between the two groups, as shown in figure 6. In the stimulated animals the respiratory minute volume and blood pressure were maintained 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 decrease in blood pressure until the time of death.
By means of 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 observa-

![Graphs showing blood pressure changes](image)

**Fig. 6.** 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 high dose levels in the stimulated animals than in the unstimulated animals. Within each group, data from a single animal are plotted with similar symbols.

...tions were made on 7 animals breathing air. The lethal dose for four unstimulated air-breathing animals was 59.1 mg. per kilogram, with standard deviation ± 6.5 mg. per kilogram, and for 3 stimulated animals breathing air it was 53.3 mg. per kilogram, with standard devia-
tion $\pm 1.52$ mg. per kilogram, giving a nonsignificant difference of $6.8 \pm 6.4$ (90 per cent limits). Both controls and stimulated animals, however, while breathing air, were better able 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.

**Description of a Case of Phenobarbital Poisoning Treated with Electrical Stimulation Through Leg Electrode Placements.** This 30 year old epileptic white woman entered the Kaiser Permanente Hospital, Vancouver, Washington, May 7, 1954, in deep coma. It was later found that she had ingested 5.0 Gm. 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. She had attempted suicide on one previous occasion.

On physical examination, the pulse was 110, respiration 16, blood pressure 50 mm. systolic and 30 mm. diastolic, and temperature 96 F. All reflexes were absent with the possible exception of the light reflex. She was treated with pentylemetrazol (metrazol\(^{\circledR}\)), nikethamide (coramine\(^{\circledR}\)), caffeine and sodium benzoate, and amphetamine sulfate (benzedrine\(^{\circledR}\)). Blood pressure was maintained with shock blocks and continuous intravenous drip of levophed\(^{\circledR}\). 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.

One of the authors (P. H. B.) saw her at 7:30 p.m. on the fourth day. Except for a sluggish corneal reflex she was areflexic, did not respond to noxious stimuli, and moist rales were audible over both lung fields. Her temperature was 102.4 F., respiratory rate 30, respiratory amplitude very shallow, skin cold and pale, and blood pressure 100 mm. systolic, 60 mm. diastolic.

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 milliamperes. This response consisted of a slight increase in respiratory rate to 36 per minute and an 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 was present. The increase in respiratory minute volume was so pronounced that it was feared a respiratory alkalois might develop. About forty-five minutes after the start of stimula-
tion 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 whether 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 F. to 98.8 F., she was breathing easily and deeply, her blood pressure was 110 mm. systolic and 60 mm. diastolic, and her lungs were completely free of rales. Stimulation was discontinued at 11:00 p.m. after a total of three and one half hours of stimulation. One half hour following discontinuation of electrical stimulation her blood pressure had fallen to 80 mm. systolic and 50 mm. diastolic, and the continuous drip of levophed was again started and maintained twelve hours longer. 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 placed 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. The fall in temperature of 3.6 F. was probably the result of the sweating that was seen after forty-five minutes of stimulation. It was thought that the peripheral stimulation on the legs was more effective than cranial stimulation since it is less likely to produce respiratory inhibition. The response in this patient was similar in all respects to that seen in dogs under deep barbital anesthesia.

Discussion

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 nerve fibers. Previous suggestions (6) 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 electroshock therapy to regions about the head (6, 10). The present study offers no clue as to the relative im-
portance 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 region is evidence of the importance of nociceptive or pain-initiating stimuli, because of ease with which pain may be initiated from various structures of the face. Other modalities of sensation, however, 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, and so forth) 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. In our hands, 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 data presented here do not support the hypothesis that electrical stimulation will shorten the period of depression of the central nervous system resulting from barbiturate administration to dogs and thus lead to a more rapid awakening. It is true that the massive afferent barrage does bring about behavioral changes which are best interpreted as arousal or return toward consciousness. While effective concentrations of the barbiturate persist in tissue fluids, however, 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 one or more ways. Many of the human cases studied have been individuals subjected to administration of pentothal\textsuperscript{b} in the course of nonconvulsive electroshock therapy. It is well-known that pentothal is very rapidly destroyed. Perhaps afferent stimulation arouses the patient for a period of time sufficient to permit reduction of thiobarbiturate concentrations to an ineffective level, or to prevent these individuals from making the usual transition from heavy sedation to natural sleep, or both. 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 individuals 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 depressant properties of the drug on the central nervous system. In addition, the improvement in function of the circulatory system might result in 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 drug 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 our knowledge, this is the first time this technique has been used for the study of depressants of the central nervous system.

**CLINICAL IMPLICATIONS**

We believe that the results of this study shed considerable light upon the utilization of electrical stimulation in the therapy of acute
barbiturate poisoning. We are strongly inclined to the belief 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 shorten the period of barbiturate depression, its failure to combat the lethal effects of barbiturate, and the results of the utilization of peripheral stimulation in the one 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).

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 is not, as far as we can determine, accompanied by any deleterious side-effects such as characterize the actions of some of the chemical analeptics. We have not attempted to compare this therapy with other commonly used forms of treatment, and do not think that it should be used to the exclusion of them. It remains to be seen whether electrical stimulation will be as effective in the treatment of depression induced by other drugs as it is in barbiturate poisoning.

We are of the opinion that electrical stimulation in barbiturate poisoning should be applied peripherally rather than transcranially. 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 that excessive nonconvulsive electroshock 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 the development of 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, therefore, should be given to improving the general status of the patient with rational measures used in conjunction with peripheral electrical stimulation.

It cannot be emphasized too strongly that our 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 bar-
biturate 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**

A study has been made of analeptic action of electrical stimulation in 65 dogs anesthetized with pentobarbital sodium.

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.

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 administration of barbiturates.

A case of phenobarbital poisoning treated with peripheral electrical stimulation is reported.

The clinical implications of these findings are discussed.

**REFERENCES**