THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 149, No. 1

Printed in U.S.A.

EFFECTS OF THIOPENTAL AND A TETRAHYDROCANNABINOL DERIVATIVE ON AROUSAL AND RECRUITING IN THE CAT[1]

E. S. BOYD AND D. A. MERITT

Department of Pharmacology, The University of Rochester, Rochester, New York

Accepted for publication February 11, 1965

Although barbiturates in moderate to large doses depress many parts of the central nervous system, they have a particularly powerful depressant action on the brain stem reticular formation. Two results of this action are: (a) inhibition of EEG and behavioral arousal because of a depression of the ascending reticular activating system (Moruzzi and Magoun, 1949; Arduini and Arduini, 1954) and (b) initiation of EEG arousal by selective bulbopontine circulation of barbiturate, because of a depression of a bulbar synchronizing system (Magni *et al.*, 1959). The former action is presumably related to the production of anesthesia by barbiturates (French *et al.*, 1953). It appears probable that small doses of barbiturates have a mild depressant action on the reticular activating system and that this action may be related to the production of sedation by barbiturates. An increased threshold for EEG arousal following small doses of barbiturates has been demonstrated (King, 1956) but an effect on behavioral arousal has not been shown. In addition, it has been reported that low doses of barbiturates enhance the recruiting response and that this action is probably secondary to a depression of the reticular formation (King, 1956).

The dimethylheptyl substituted tetrahydrocannabinol, DMHP, is a potent synthetic analogue of one of the active components of marihuana. In several ways its actions resemble those of small doses of barbiturates. It depresses motor systems in the cat from the level of the spinal reflex to that of the caudate nucleus and possibly higher (Dagirmanjian and Boyd, 1962; Boyd and Meritt, 1965). It depresses many measures of behavior in rats on various schedules of free operant behavior, as do both pentobarbital and chlorpromazine. It may, however, be distinguished from both pentobarbital and chlorpromazine in certain free operant schedules (Boyd *et al.*, 1963).

The present work was undertaken to determine: (a) whether small doses of thiopental would increase the threshold for behavioral, as well as EEG, arousal from stimulation of the reticular formation; (b) whether bulbopontine circulation of thiopental would cause behavioral, as well as EEG, arousal; (c) whether the sedative action of tetrahydrocannabinols could be related to a depression of the reticular formation; and (d) whether such a depression, if found, would result in an enhancement of the recruiting response, as reported for barbiturates.

METHODS. *General.* Adult cats of either sex were used. Thiopental and mephenesin were made up in 0.9% saline. DMHP was made up as a colloidal suspension in a solution of 0.9% saline and 1% Tween 80 as described by Dagirmanjian and Boyd (1962). All drugs were given intravenously and were controlled by a prior injection of an equal volume of the vehicle. DMHP was given only once in each acute experiment because of its long duration of action. In cases where an animal was given more than one drug, at least 30 minutes elapsed after thiopental or mephenesin and 2 hours after DMHP before the vehicle for the second drug was tested. In addition, drugs were given to different animals in different orders. In no instance did a drug effect, or lack of effect, appear to be influenced by preceding drug administration.

Bipolar, stainless steel electrodes were placed stereotaxically for stimulation of the thalamus or reticular formation and for recording from the thalamus. The electrodes were similar to those described by Stark *et al.* (1962), except that both wires projected 1.5 mm below the central strut. The atlases of Jasper and Ajmone-Marsan (1954) and of Snider and Niemer (1961) were used as guides. Cortical recording electrodes were stainless steel screws placed in various locations through the skull but not penetrating the dura. All electrode placements were confirmed histologically. Frozen sections of 40- to 80-micron thickness of

Received for publication December 15, 1964.
[1] This work was supported by U. S. Public Health Service Grant MH 04230-05.

formalin-fixed brain were examined by the method of Guzman *et al.* (1958).

A Grass S-4 stimulator and a Grass polygraph were used.

In acute experiments, operations were carried out under diethyl ether. Either the spinal cord was sectioned at C-1 or the animal was immobilized with gallamine as needed. All animals were artificially respired (150 ml, 16 times per min) and rectal temperature was maintained between 36 and 38°C by means of a heated table. Blood pressure in the carotid artery was recorded in all animals by means of a pressure transducer and the polygraph. At least 2.5 hours elapsed between the operative procedures and tests of drug effects to assure that all of the ether had been blown off. All wounds and pressure points from the stereotaxic instrument were infiltrated with lidocaine.

EEG arousal in acute preparations. EEG arousal was obtained by stimulation of the medullary, midbrain or hypothalamic reticular formation at times when the EEG showed predominantly the high voltage slow wave activity of sleep. Stimulus parameters were 300 cycles/second, 1 msec duration and 2 to 9 volts. Stimulus trains of 4 to 6 seconds were usually used. In some cats the spinal cord was sectioned at C-1 and both vagi were cut to decrease input to the central nervous system. In other cats the animal was immobilized with gallamine, rather than the C-1 section, and the vagi were left intact. Thresholds for EEG arousal were determined by stimulating at a voltage below threshold and then increasing the voltage in steps of either 0.5 or 1.0 volt.

EEG and behavioral arousal in chronic preparations. Cats were operated on under pentobarbital anesthesia. A bipolar stimulating electrode was placed in the midbrain reticular formation. An injection cannula was placed in the right external jugular vein. It ended externally in a metal cap with a rubber diaphragm. The stimulating electrode and monopolar cortical electrodes, as well as a monopolar electrode over the eye muscles and a bipolar electrode in the dorsal neck muscles in some cases, were connected to a miniature 7-contact Winchester socket. The socket and metal cap on the end of the injection cannula were sealed to the skull in a cap of dental acrylic. The animals were allowed to recover for at least 10 days before they were tested.

The animals were tested by placing them in a chamber in a sound-proofed room. A suspended cable connected them to the stimulator and polygraph. A long polyethylene tube connected to the injection cannula and running with the cable permitted injection of drugs and vehicles without disturbing the animal. The animals were observed through a "one-way" glass. They were allowed to go to sleep spontaneously and then tested as in the acute experiments. The criteria for sleep were a synchronized EEG and a normal sleeping position with the head resting on the floor or the forelimbs and the eyes closed. Both the threshold for EEG arousal and the threshold for behavioral arousal were determined. The criteria for behavioral arousal were the opening of both eyes and a rapid lifting of the head. The effects of both thiopental and DMHP were determined from 3 to 6 times in each animal. Both drugs were usually given once, in alternate sequences, on one day. The animal was then not tested again for at least 3 days. The stimuli consisted of 5-second trains of 300 cycles/second, 0.05 msec duration biphasic square waves. Thresholds were determined as in the acute experiments. Stimulus intensities varied from 0.05 to 7.5 volts.

Arousal by thiopental in chronic preparations. Cats were prepared with a chronic indwelling cannula in the left subclavian artery at the level of the vertebral artery as in the acute preparations of Magni *et al.* (1959). The external end of the cannula was brought to the top of the head under the skin and mounted together with connections to cortical recording electrodes as in the preceding section. The basilar artery was clipped at a midpontine level (Magni *et al.*, 1959). The animals were tested in the apparatus described in the preceding section 5 to 7 days postoperatively. Tests consisted of slow injections of 0.2 mg (total dose) of thiopental in saline at pH 9 or of injections of saline at pH 9, as a control, during periods when the animal was asleep. The criteria for sleep were the same as those used in the preceding section. In all animals the position of the cannula in the subclavian artery, in relation to the opening of the vertebral artery, was checked at autopsy. In addition, in two of the animals in which the drug had no effect, a small volume of india ink was injected immediately before sacrificing. Gross examination of the brains showed that the ink was distributed almost exclusively to the vessels of the brain stem, primarily at the bulbopontine level, but also, to a lesser extent, at pontine and mesencephalic levels above the clip, even though the clip was properly placed in both cases.

Recruiting response. The recruiting response was produced by stimulation of centralis lateralis or centrum medianum of the left thalamus. It was recorded from left ventralis lateralis or ventralis anterior, as well as from several sites in the cortex. It was identified by the phenomenon of recruitment in the response, as well as by its wide distribution over the cortex. The stimulus was a 5-second train of biphasic, 10 cycles/second, 0.2 msec duration square waves of 1.5 to 9.0 volts. Tests were made by starting below threshold and increas-

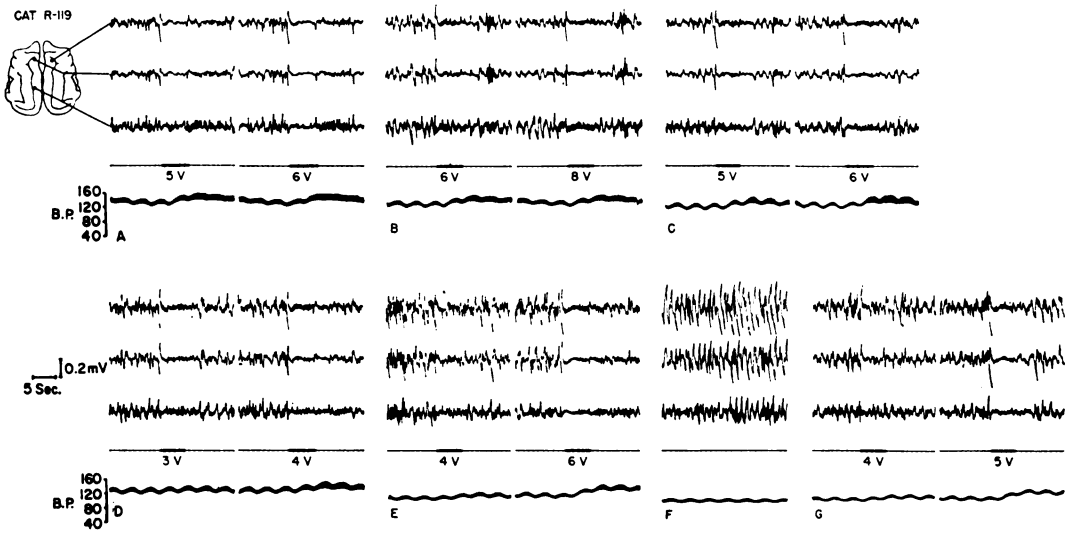

FIG. 1. Effects of thiopental and of DMHP on EEG arousal in an acute preparation.
The EEG arousal was produced by stimulation of the medullary reticular formation. The first 3 lines are cortical recordings. The 4th line shows the periods of stimulation (5 sec) at the voltages marked. The 5th line shows the arterial blood pressure. (A) Control. (B) Two minutes after thiopental, 2 mg/kg. (C) Eight minutes later, showing recovery. (D) Control 1 hour after the thiopental. (E) Twelve minutes after DMHP, 0.2 mg/kg. (F) Seventeen minutes after DMHP. (G) Twenty-eight minutes after DMHP, showing partial recovery.

ing the stimulus voltage in steps of 0.5 volt. Both the threshold voltage and the voltage necessary for a maximal response were determined in this way. All cats were paralyzed with gallamine.

RESULTS. *EEG arousal in acute preparations.* 1. *Depression of arousal by thiopental and DMHP.* The experiments summarized in this section were carried out both with animals with high spinal sections and with animals paralyzed with gallamine. In all cases the stimulating electrode was in the reticular formation. Control threshold values for EEG arousal varied from 2 to 7 volts. Thiopental, 2 mg/kg, was given to 8 animals. It increased the threshold in all cases. The average increase was 2.0 volts. Thiopental, 5 mg/kg, was given to 5 animals. It increased the threshold in all cases, and the average increase was 3.1 volts. DMHP, 0.2 mg/kg, was given to 10 animals. It increased the threshold in all cases. The average increase was 1.6 volts. In the experiment illustrated in figure 1, thiopental, 2 mg/kg, increased the threshold by 2 volts with complete recovery within 10 minutes and DMHP, 0.2 mg/kg, increased the threshold by 3 volts with partial recovery in 28 minutes. It should be noted that the increases in threshold caused by DMHP were not related to the decrease in blood pressure seen in animals paralyzed with gallamine (as in fig. 1) since they also occurred in animals with C-1 sections in which DMHP did not decrease the blood pressure.

In 4 of the 13 cats given thiopental an initial decrease in threshold for arousal was observed in the first few seconds after administration. This was then followed by an increase above the control level. In 3 of the 10 cats given DMHP, the same phenomenon was observed with the decreased threshold occurring in the 7- to 8-minute "latent" period of the drug. This was always followed by an increase in threshold above the control value.

2. *Other responses to thiopental.* In 3 cats with high spinal sections, the administration of 5 mg/kg of thiopental was followed by mixed periods of high voltage synchronous activity and of extreme asynchrony. These are illustrated in figure 2. In these animals stimuli given during a period of synchronous activity tended to cause asynchrony, as in part B and the third record of part C of the figure. In 1 animal, shown in part B, this EEG "arousal" could be produced by intensities which were too low to affect the animal except under the

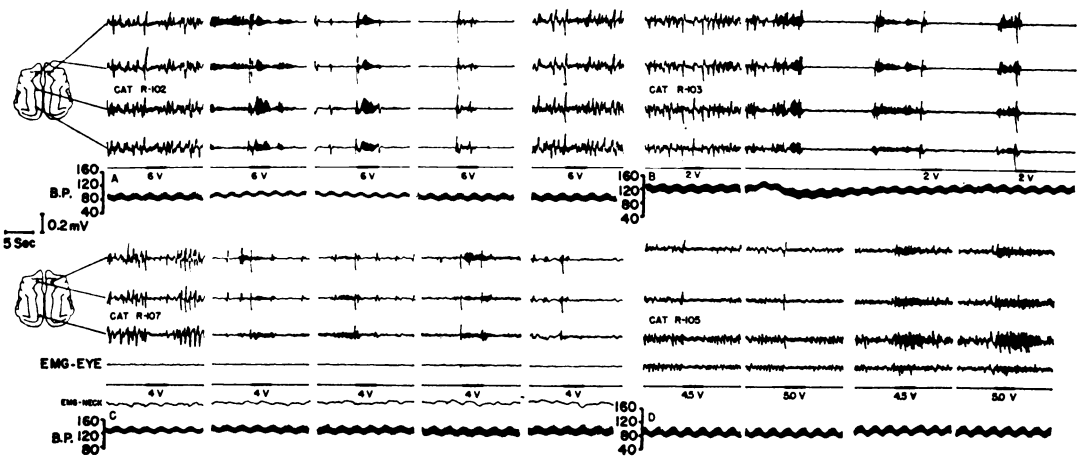

FIG. 2. Records from four cats with C-1 section showing (a) periods of background asynchrony or (b) hypersynchrony in response to stimulation, after thiopental, 5 mg/kg.

(A) Control response to stimulation followed by responses 2, 3, 7 and 11 minutes after thiopental. At 2 and 3 minutes, the stimulus resulted in hypersynchrony. (B) Control record and alternating periods of hypersynchrony and asynchrony starting 10 seconds after the drug. During this period the previously ineffective stimulus caused the hypersynchrony to change to asynchrony. (C) Control record followed by three records taken about 3 minutes after thiopental. The stimulus tended to produce hypersynchrony during periods of asynchrony, but to suppress hypersynchrony if it was present. The final record was taken 6 minutes after drug. (D) Two arousal responses before drug followed by hypersynchrony to the same intensities of stimulation 4 minutes after thiopental.

influence of the drug. On the other hand, stimuli given during a period of asynchrony in the early part of the response to thiopental tended to produce marked synchrony, with regular waves of 8 to 10 per second. This can be seen in part A and the second and fourth records of part C of the figure. At times the duration of the synchronous activity produced by the stimulus outlasted the stimulus, as seen in the fourth record of part C and in part D. In a fourth animal, also with a C-1 section, illustrated in part D, the drug itself had no effect on the EEG but, after the drug, stimuli which had previously caused a desynchronized EEG or "arousal" now caused a marked increase in synchrony that outlasted the duration of the stimulus.

In these 4 cats the stimulating electrodes turned out to be in the cerebellum in those illustrated in parts A and B (in the region of the fastigial nucleus and nucleus interpositus, respectively) and in the mesencephalic reticular formation in those illustrated in parts C and D. It should be noted that in the 1 of these 4 animals in which neck and eye muscle activity was monitored, there was no increase in either during the periods of desynchronization following thiopental.

TABLE 1

Effects of thiopental and of DMHP on thresholds for arousal in cats with chronically implanted electrodes in the reticular formation

Drug	Criterion for Arousal	Total Trials	Trials in Which Drug Increased Threshold	Change in Threshold Mean and Standard Error
				volts
Thiopental 2 mg/kg	EEG	21	20	+0.7 (±0.1)
Thiopental 2 mg/kg	Behavioral	21	20	+0.8 (±0.1)
DMHP 0.2 mg/kg	EEG	22	16	+0.7 (±0.2)
DMHP 0.2 mg/kg	Behavioral	22	19	+0.8 (±0.1)

This desynchronization and reversal of effects of stimulation was not seen with DMHP.

Behavioral and EEG arousal in chronic preparations. Thiopental, 2 mg/kg, and DMHP, 0.2 mg/kg, were tested in 5 cats. Each animal was tested on from 3 to 6 different days for a total of 21 trials with thiopental and 22 trials with DMHP. The results are summarized in table 1. Thiopental caused an increase in

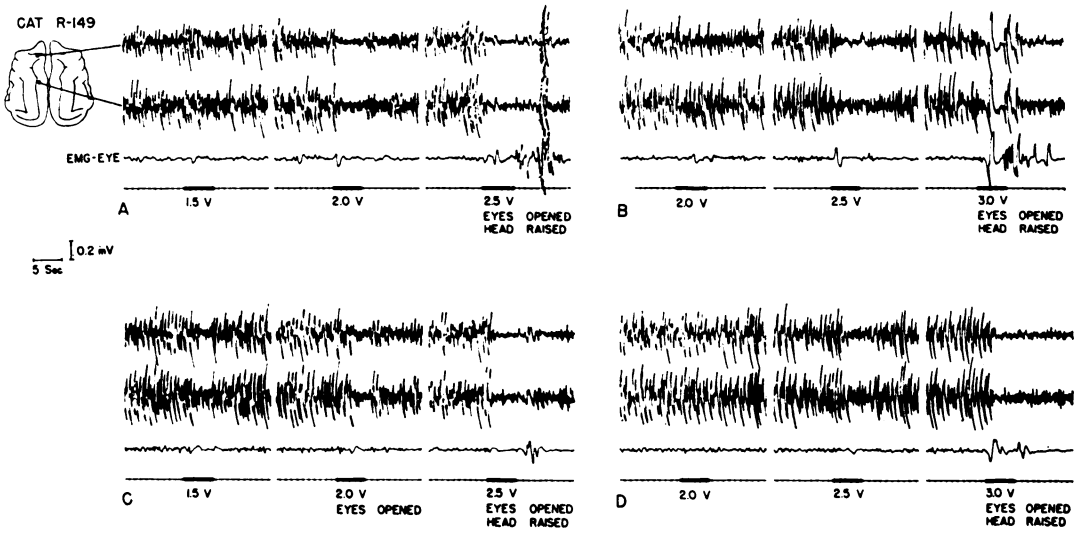

FIG. 3. Effect of thiopental and DMHP on EEG and behavioral arousal due to midbrain stimulation in a cat with a chronically implanted electrode.

The animal was behaviorally asleep (lying down, head down, eyes closed) unless otherwise indicated. The bottom line in each record shows a time base (1 sec) and the duration of the stimulus to the midbrain reticular formation at the voltages indicated. The behavioral responses indicated occurred at the beginning or during the period of stimulation. (A) Control. (B) Two minutes after thiopental (2 mg/kg). (C) Control 80 minutes later. (D) Eleven minutes after DMHP (0.2 mg/kg).

the threshold for both behavioral and EEG arousal in 20 of 21 trials. Although the effect of DMHP was not as consistent as that of thiopental, DMHP did cause increases in thresholds in all 5 animals and in at least three quarters of all trials. The average increases in thresholds for both EEG and behavioral arousal were practically the same with both drugs; the 2 drugs were approximately equipotent in the doses used. The results of a typical experiment are shown in figure 3.

Arousal by thiopental in chronic preparations. Eight animals were prepared successfully and tested. Of these, only 2 showed arousal. In 1, injections of saline were without effect, but injections of 0.2 mg (total dose) of thiopental resulted in immediate EEG arousal accompanied by sudden behavioral awakening. This was immediately followed by shifting of body position and looking around. The general picture presented was that of an animal startled awake. A second animal showed EEG and behavioral arousal to injections of the drug but they were not as dramatic as in the other animal. In the remaining 6 cats the injection of the thiopental was without effect.

Recruiting response. Thiopental was tested in 5 animals at 5 mg/kg and in 1 at 10 mg/kg. In spite of the fact that increases in high voltage activity produced by thiopental made observation of the recruiting response more difficult, it was quite clear that the drug did not affect the threshold or the size of the response to submaximal stimuli. DMHP, 0.2 mg/kg, was tested in 8 animals. It had no significant effect in any of the animals, either on the threshold for the response or on the size of the response to submaximal stimuli.

Since the lack of effect of thiopental was contrary to reports of others, the effect of mephenesin, which has been reported to depress the recruiting response, was determined in 6 of the same animals. At 30 to 50 mg/kg it raised the threshold for the recruiting response by 0.5 to 2.5 volts in 5 of the 6 animals.

The results of one of the experiments are shown in figure 4. Thiopental, 10 mg/kg, and DMHP, 0.2 mg/kg, had no significant effect. Mephenesin, 50 mg/kg, increased the threshold from 4.0 to 5.5 volts.

Effect of drugs on EEG. If the control level of synchronization of the EEG was not too great, thiopental, 2 to 5 mg/kg, caused an increase in synchronization, except in the 4 animals illustrated in figure 2. In a similar manner, in 10 of 15 cats which showed only

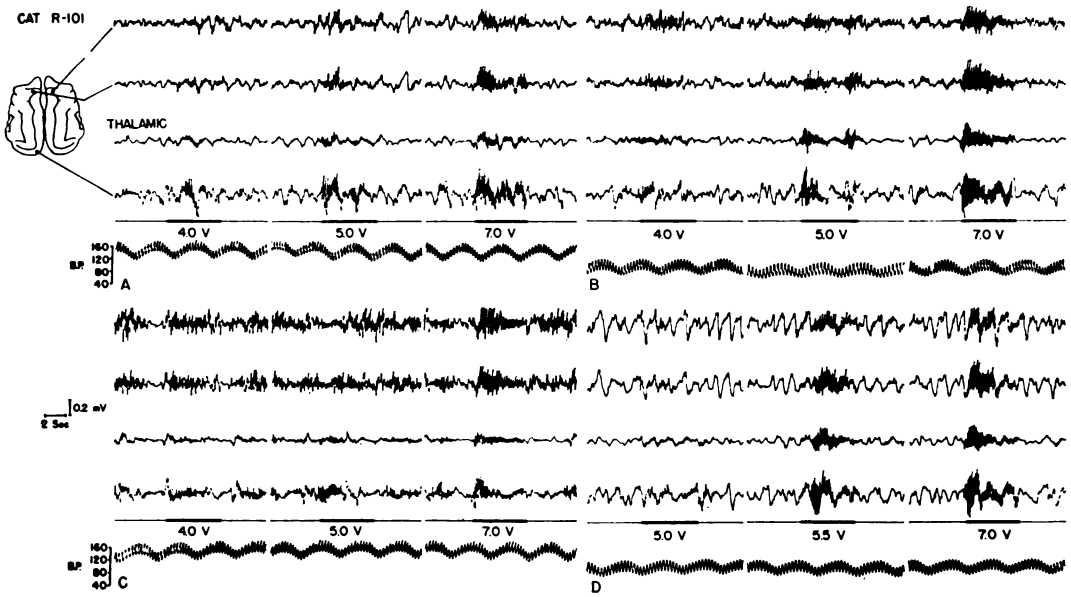

FIG. 4. Effects of DMHP, thiopental and mephenesin on the recruiting response.
The recruiting response was produced by stimulation of the left nucleus centralis lateralis. The 1st, 2nd and 4th lines are cortical recordings. The 3rd line is a recording from the left nucleus centralis anterior. The 5th line shows the periods of stimulation (5 sec) at the voltages marked. The 6th line is arterial blood pressure. (A) Control. (B) Nineteen minutes after 0.2 mg/kg of DMHP. (C) Thirty minutes later, 2 minutes after 10 mg/kg of thiopental. (D) Thirty minutes later, 8 minutes after 50 mg/kg of mephenesin.

moderate synchronization at the time of administration of DMHP, 0.2 mg/kg, this drug caused a marked increase in synchronization. The increase started 7 to 8 minutes after administration and reached a peak 8 to 13 minutes later. An example of this is shown in part F of figure 1.

DISCUSSION. High frequency electrical stimulation of the reticular formation has been shown to cause both EEG and behavioral arousal (Moruzzi and Magoun, 1949; Killam *et al.*, 1957). The thresholds for both are increased by barbiturates (Arduini and Arduini, 1954; Domino, 1955; King, 1956; Killam *et al.*, 1957). However, previous reports have dealt with the results of rather large doses of barbiturates (5 to 20 mg/kg), except that Arduini and Arduini (1954) showed an increase in threshold for EEG arousal with 2 mg/kg of pentobarbital. The previous work with behavioral arousal in chronic preparations, that of Killam *et al.* (1957), used a minimum dose of 10 mg/kg of pentobarbital. In the present work 2 mg/kg of thiopental caused an increase in threshold for behavioral arousal in 20 out of 21 trials. This dose of a barbiturate comes within the range of therapeutic hypnotic doses and thus makes possible the hypothesis that sedation and hypnosis, as well as anesthesia, with barbiturates is due to a depression of the ascending reticular activating system.

The present observation that 0.2 mg/kg of DMHP is approximately as effective as 2 mg/kg of thiopental in raising the thresholds for both EEG and behavioral arousal furnishes a possible explanation of the sedative effects of tetrahydrocannabinol derivatives (Williams *et al.*, 1946). The induction of high voltage slow wave activity in the EEG by DMHP in 10 of 15 animals is also indicative of a depressant action on the reticular activating system.

There is at present a large amount of evidence for the existence of a system or systems in the brain, the activity of which causes both EEG and behavioral deactivation or sleep. The first such evidence was provided by Hess (1944) who showed that stimulation of some regions of the thalamus in the cat caused behavioral sleep. Since then it has been shown that electrical stimulation of many regions of the brain such as the preoptic area (Sterman and Clemente, 1962) and the bulbar reticular

formation (Moruzzi, 1960) can produce EEG deactivation and behavioral sleep. This field is reviewed by Magoun (1963) who feels that the common pathway is a thalamocortical system. However, the work of Schlag and Chaillet (1963) showing that EEG arousal from thalamic stimulation is blocked by mesencephalic transections indicates that the common pathway may be the mesencephalic reticular formation.

A postulate of inhibitory components, as well as activating components, in the ascending reticular system was made by Jasper (1954). Pharmacological indications were provided by Domino (1955), who postulated the existence of an inhibitory system on the basis of experiments in which stimulation of the reticular formation (a) after pentobarbital caused decreased spindling frequency and (b) after mephenesin caused flattening of the EEG record. Later Magni *et al.* (1959) showed that selective circulation of thiopental to the bulbopontine region resulted in EEG arousal in animals showing a synchronized EEG.

Some of the results with thiopental reported here may be explained by, and furnish indications for, the existence in the brain stem of an inhibitory system closely associated with the ascending reticular activating system. The two systems would presumably be in some state of balance at all times. It should be noted that the experiments of Domino (1955) and of Magni *et al.* (1959), as well as those illustrated in figure 2, all were carried out in *encéphale isolé* preparations. The effects do not appear to be related to a low blood pressure which is often seen after high spinal section since 3 of the 4 cats reported on here had blood pressures of well over 100 mm Hg. However, in such preparations it would be expected that the decreased afferent input would decrease the level of activity in the reticular activating system and thus shift the balance more in favor of an inhibitory system than normally occurs. If barbiturates are capable of depressing both systems, as the work of Magni *et al.* (1959) indicates, the administration of a barbiturate in some of our experiments could have resulted in depression primarily of an inhibitory system, producing the activated EEG responses in figure 2 (A) and (C). The response in figure 2 (B) could have been due to an alternating change in dominance of an activating system and an inhibitory system. If the two systems were close anatomically a stimulating electrode would be capable of stimulating both systems. If the combination of the barbiturate and decreased afferent input produced a state where either system could easily exert dominance, electrical stimulation could change activation to deactivation and *vice versa*, as seen in the experiments reported here. This is particularly well illustrated in figure 2 (D), where the stimuli caused activation before thiopental but deactivation after thiopental.

The initial decrease in the threshold for arousal from stimulation of the reticular formation seen with thiopental in 4 of 13 cats and with DMHP in 3 of 10 cats could be explained by an initially greater depression of the inhibitory system than of the activating system.

The hypothesis that decreased afferent input, as in the *encéphale isolé*, is necessary to decrease the level of activity in the activating system in order to show easily effects on the inhibitory system could explain the difficulty we had in demonstrating, in intact cats, the ability of thiopental to cause arousal as demonstrated by Magni *et al.* (1959) in *encéphale isolé* preparations. On the other hand the difficulty may have been due to other causes, such as a development of collateral circulation in the pontobulbar region during the period of recovery from the operation.

The recruiting response from stimulation of "nonspecific" thalamic nuclei was first demonstrated by Morison and Dempsey (1942). It is generally considered to be carried from thalamus to cortex by way of a diffuse thalamic projection system. Depression of the recruiting response by mephenesin has been demonstrated by Domino (1955) and King (1956). These results have been confirmed in the present work. King reported a facilitation of the recruiting response by low doses (3–5 mg/kg) of thiopental and pentobarbital. This consisted of a slight lowering of threshold and an increased response to submaximal stimuli. Domino reported a "frequent" lowering of threshold with 10 mg/kg of pentobarbital, although the response was depressed by larger doses. In the experiments reported here, a significant de-

crease in threshold or increase in response to submaximal stimuli was not seen with thiopental, 5 to 10 mg/kg, or with DMHP, 0.2 mg/kg.

SUMMARY

Thiopental, 2 mg/kg, and DMHP, 0.2 mg/kg, increased the threshold for EEG arousal in acute preparations, and for behavioral, as well as EEG, arousal in chronic preparations. Arousal was induced in all preparations by electrical stimulation of the reticular formation.

It is suggested that some responses following thiopental, such as cortical desynchronization from the drug and synchrony instead of asynchrony during stimulation, as well as occasional initial lowering of threshold for arousal by both thiopental and DMHP, may be explained on the basis of an ascending inhibitory reticular system.

An attempt to produce EEG and behavioral arousal by the selective circulation of thiopental to the pontomedullary region in chronically prepared animals was successful in only 2 of 8 preparations.

Thiopental, 5 to 10 mg/kg, and DMHP, 0.2 mg/kg, had no effect on the recruiting response.

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