Induction of Anesthesia, Seizures and Sleep by Steroid Hormones

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THIS DISCUSSION is limited to the acute effects of some naturally occurring steroid hormones on the central nervous system. The presentation reflects the chronological order in which these effects were discovered: First, some steroids were found to induce anesthesia. Later, other steroids were discovered to induce convulsive activity. Thereafter, the concept of slow wave hypersynchrony as a preconvulsive pattern was described. Finally, the induction of physiological sleep by systemically administered progesterone is a concept which we present here for the first time.

Anesthesia

In 1927, Cashin and Moravek [1] reported that high doses of cholesterol induce anesthesia. In 1941, Selye [2] found that pharmacological doses of progesterone, desoxycorticosterone and pregnanedione also induce anesthesia: rats lost their righting reflexes and abdominal operations could be performed without causing any motor activity.

Following these findings many steroids were tested for anesthetic activity in Dr. Selye's laboratory. Some were inactive, others caused excitation prior to sedation, still others induced fatal convulsions. None was found to a "better anesthetic" than progesterone, desoxycorticosterone, or pregnanedione. In 1955, hydroxydione, a pregnanedione derivative, was reported as an effective anesthetic agent in man. It was marketed as Viadril® for use in man and described as endocrinologically inactive.[3]

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When examining a number of steroid hormones for their possible anesthetic effects we found some which induced convulsions. The next chapter discusses these effects.

Seizures

In 1958, and again in 1961, we [4,5] described recurrent convulsions after single high doses of 11-desoxycortisol (Reichstein's compound S) and Dehydroepiandrosterone (DHEA). Depending on dose, rats and cats had one or more episodes of tonic-clonic grand mal seizures which were only fatal after particularly high doses. Both of these compounds are naturally occurring steroid hormones: 11-desoxycortisol is an immediate precursor of cortisol (hydrocortisone) and DHEA is a precursor of androgens and estrogens.

In cats, 11-desoxycortisol initially causes a marked change in the electrical activity of the hippocampus and amygdala (fig. 1). It is of interest to compare this pattern in the amygdala with that described by Dr. Wagman (this conference) after the administration of lidocaine. This local activity is then followed by recurrent tonic-clonic convulsions with generalized electrical seizures and postictal depression (fig. 1). With lower doses, spike discharges may remain localized within the hippocampus for hours and may never spread to other regions of the brain. Occasionally, abnormal electrical activity spreads to involve various subcortical structures, for instance after a sound stimulus.[6] As long as electrical seizure activity does not involve the cortex, no motor seizures are seen. Instead, the cat displays abnormal behavior (e.g., it is quiet and shows staring spells).
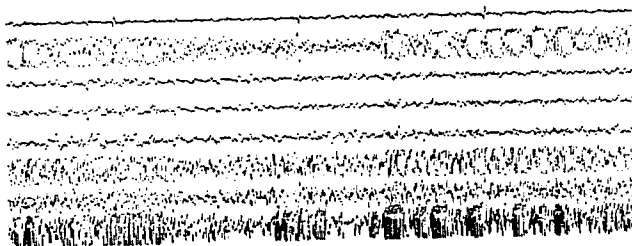
In monkeys, a spectrum of recurrent seizure activity can be elicited with both 11-desoxycortisol and DHEA: grand mal with postictal

CONVULSIONS AFTER Cpd. S SUCCINATE (400 mg/kg)

A. Control

L. Sig. Cx.

L. Amygd.

L. SS Cx.

L. V. PL.

L. Ret. F.

L. Hipp.

R. Hipp.
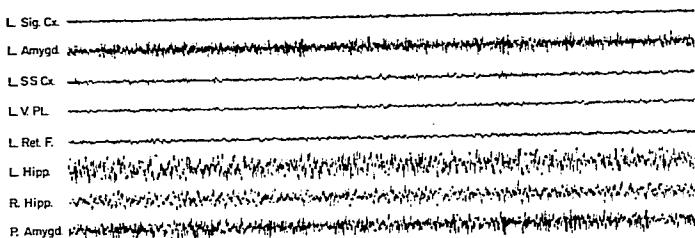
R. Amygd.

B. 10 min. after injection
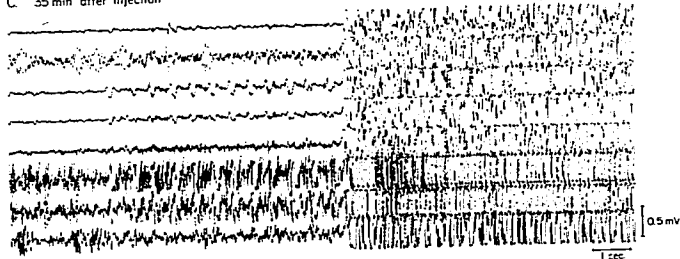
C. 35 min after injection

0.5 mV

1 sec

FIG. 1. Records from chronically implanted electrodes in a freely moving cat. A. Control.
B. Rhythmic, high frequency amygdaloid activity. The cat shows all preconvulsive changes
described in the text, but no overt seizures. C. Seizure activity begins in the dorsal hippo-
campal leads and becomes generalized. Abbr.: Sig. CX. = Sigmoid (sensori-motor) cortex;
SS CX. = Suprasylvian cortex; V.PL. = Thalamic n. ventralis posterolateralis; Ret. F. = Reticu-
lar formation of the brain stem. From Heuser and Eidelberg.[5]

depression; tonic seizures or falling spells without any postictal depression. These various types of convulsive activity have been described in detail elsewhere.[7]

When examining the effects of subconvulsive doses of these steroids we saw interesting patterns of electrical slow-wave hypersynchrony which are discussed in the following chapter.

Slow Wave Hypersynchrony

When convulsive steroids (11-desoxycortisol, DHEA) are given to monkeys in low subconvulsive doses, intermittent behavioral sedation and concurrent electrical slow wave hypersynchrony can be observed (figs. 2, 3, 4). When we first saw this pattern we considered it unique since convulsant agents were not generally known at that time to induce slow wave hypersynchrony prior to the occurrence of generalized electrical seizure activity. In looking through the literature, however, we learned that some antihistamines, tranquillizers and other compounds display patterns similar "bimodal" actions.[7] In the meantime, Winters[8] has independently demonstrated that many convulsant compounds, when carefully tested, induce slow wave hypersynchrony prior to generalized seizure activity.

Winters[8] speculated that abnormal behavior, including hallucinations and aura, probably are associated with this hypersynchronous activity. Our data seem to substantiate this interesting interpretation. The following observations illustrate this point: mice show "retropulsion" (i.e. they walk backward) when given hallucinogenic drugs such as phencyclidine (Sernyl). This drug causes retropulsion in rats, too, and Winters found that it induces slow wave hypersynchrony in cats prior to the appearance of generalized seizures.

It is interesting that after the administration of convulsant steroids, rats become quiet, place their hind paws far apart and often walk a few steps backward (retropulsion), prior to developing a full blown seizure. This can be interpreted as further evidence that preconvulsive slow wave hypersynchrony may be related to abnormal behavior including hallucinations.
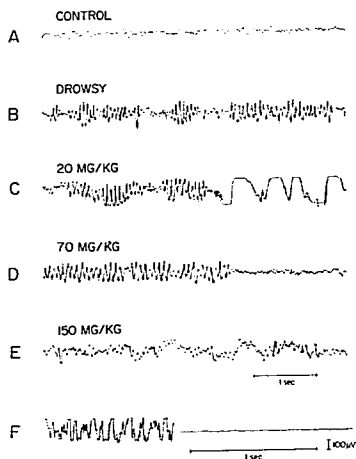
While investigating behavior of animals

FIG. 2. Tracing obtained from motor cortex of Cebus monkey. A. Control preceding intraperitoneal instillation of 11-desoxycortisol. After increasing doses of 11-desoxycortisol (C to F) slow wave activity alternates with movement artefact in C. Slow waves have disappeared in E which shows tracing about one minute prior to the development of tonic-clonic seizures and postictal depression (F). B. Tracing on another day when monkey became spontaneously drowsy after having spent about one hour in the chair. From Heuser et al.[7]

which showed slow wave hypersynchrony we turned our attention to sleep and possible sleep induction by steroids. The following chapter summarizes our most recent findings.

Sleep

Terminology. In recent years, the physiology of sleep has been intensively investigated and diagnostic criteria for the different stages of sleep are now well defined.[9, 10]

One stage of normal sleep is characterized by an electrocorticogram which cannot be distinguished from that seen during wakefulness. This stage was therefore named paradoxical. Other features of paradoxical sleep in cats include: intermittent twitching of whiskers, ears, paws and tail; irregular, sometimes labored, respiration; irregular heart rate; rapid eye movement (REM); a flattening of the activity

L-R MOT. CX.

L-R SEN. CX.

L-R C.M.

L-R OCC. CX.

CONTROL   eyes closed   open   closed   open

+II min

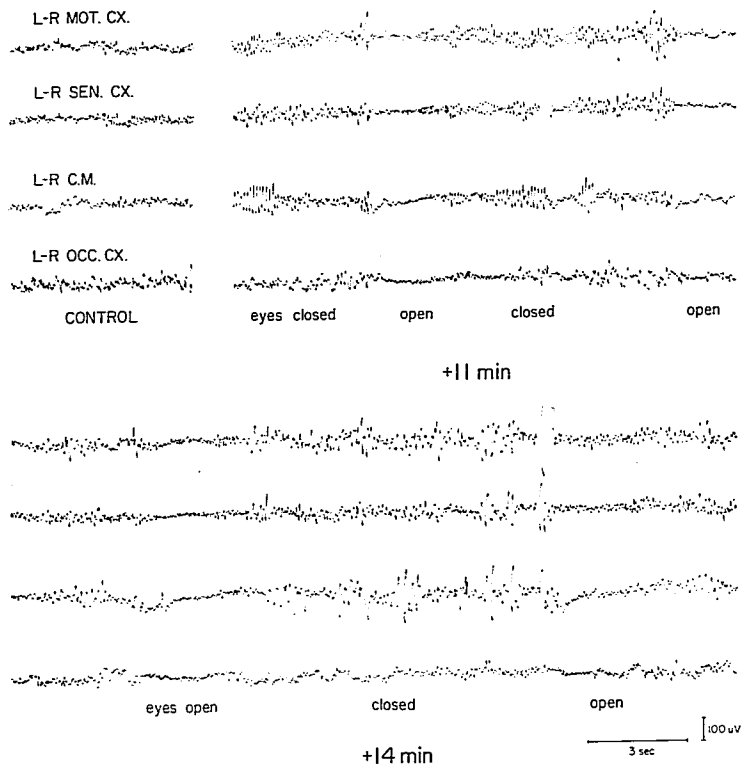eyes open   closed   open

+14 min

100 uV
3 sec

Fig. 3. Eleven minutes after 40 mg./kg. of 11-desoxycortisol administered intravenously this Rhesus monkey showed his first episode of intermittent slow wave activity with eye closure. Fourteen minutes after injection the amplitude of the record was further increased and the frequency decreased. Abbreviations: MOT. CX. = Motor cortex; Sen. CX. = Sensory cortex; C.M. = Central median thalamic nucleus; OCC. CX. = Occipital cortex. From Heuser *et al.*[?]

(EMG) of the dorsal neck muscles; an increase in brain temperature [11, 12, 13] (figs. 5, 6, 7); and hippocampal theta activity. This paradoxical phase of sleep has also been named: (1) *Activated*, referring to an alert type of EEG. Yet, after small doses of atropine most features of paradoxical sleep remain although the electrocorticogram shows slow wave activity.[14] (2) *Rhombencephalic*, thus implying that it always originates in the rhombencephalon, since the rhombencephalon continues to initiate characteristic features of paradoxical sleep in animals after removal of other parts of the brain. However, stimulation of the forebrain (with cholinergic drugs or, in our investigations, with progesterone) in intact animals appears to initiate alternating slow wave and paradoxical sleep. (3) *Rapid eye movement*
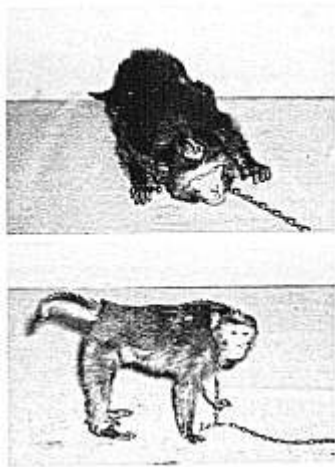
Fig. 4. After 70 mg./kg. of 11-desoxycortisol administered intravenously this monkey's behavior alternated between crouching and standing. From Heuser *et al.*[5]

(REM), thus implying that rapid eye movements are always present during paradoxical sleep. However, we will present data which indicate that many features of paradoxical sleep may remain under certain conditions, even though rapid eye movements do not occur. (4) *D-state,* since on awakening from the REM stage a human subject most often recalls a dream. This implies that dreaming only occurs during REM sleep. However, dream-like activity can be present during phases other than REM sleep. For example, sleepwalking occurs during slow wave sleep.[15] All that we can really test by awakening an individual is his ability to recall a dream but not the presence or absence of dreaming.

For these reasons, and particularly in view of the fact that some features of paradoxical sleep may be suppressed by drugs while other features remain, we prefer the term *paradoxical* since it does not limit us in our thinking about this fascinating phase of sleep.

Drug-Induced Sleep. If natural sleep is behaviorally and neurophysiologically defined as a type of reduced motor activity which, a) is

reversible with the return of coordinated motor activity on presentation of an alerting stimulus, and b) shows recurrent phases of paradoxical sleep totaling a constant percentage of the sleep time, then no drug presently available has so far qualified as capable of inducing natural sleep. Barbiturates for instance significantly reduce the percentage of time spent in the paradoxical phase of sleep. During barbiturate anesthesia all the usual manifestations of paradoxical sleep are lost with the exception of intermittent discharges in the lateral geniculate bodies.[16]

In our laboratory, we used pentobarbital intraperitoneally and intravenously and studied its effect on sleep patterns in 8 cats by means of chronically implanted electrodes (table 1). We found pentobarbital significantly reduced, if not eliminated paradoxical sleep. After small doses, paradoxical sleep was still seen but its manifestations were incomplete: rapid eye movement and twitching were absent (fig. 6). Figure 7 shows the cortical temperature curve of a cat during a 3 hour period of undisturbed rest (with sleep) as compared with the curve seen after a small dose of pentobarbital given to the same cat on another day. It can be seen that the normal range of temperature was not maintained after administration of this barbiturate. Paradoxical sleep in this case only occurred late when
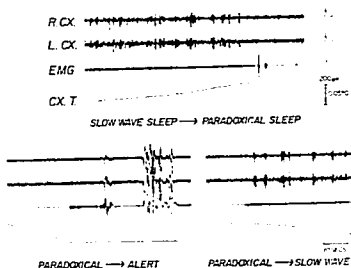

Fig. 5. Typical features of paradoxical sleep in the cat with an "activated" EEG, flattening of EMG (at times initiated with a twitch) and rise in cortical temperature (CX. T.). When slow wave sleep starts the temperature usually falls. Note that a temperature change may precede (in some cases for several minutes) a change in stage of sleep but does not necessarily do so.

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TABLE 1. Suppression of Paradoxical Sleep by Pentobarbital

Treatment	Paradoxical Sleep			
	Onset*	1 Hour†	2 Hours†	3 Hours†
Pentobarbital (20 mg./kg., i.p.)	—	0	0	0
Saline i.p.	36	5	23	42
None	32	13	23	48
Pentobarbital (5 mg./kg., i.p.)	43‡	2	17	31
None	66	0	16	43
Pentobarbital (5 mg./kg., i.v.)	77‡	0	4	12
None	33	6	14	20
Pentobarbital (10 mg./kg., i.v.)	154‡	0	0	2

Double horizontal lines separate individual cats.
* First time, in minutes, of appearance of paradoxical sleep after beginning of experiment.
† Sum total of time, in minutes, spent in paradoxical sleep during first hour, first 2 hours and first 3 hours after beginning of experiment.
‡ Incomplete (see text) manifestations of paradoxical sleep.

the normal temperature range was finally approached.

Oswald[17] discovered, in man, that upon withdrawal of barbiturate a rebound occurs during which the subjects spend an excessive percentage of sleep in the paradoxical stage and then often experience nightmares (fig. 8).

Oswald believes that this may be one explanation for the fact that patients resist withdrawal and prefer to continue on barbiturates once they have started on them.

In view of these data, the question arises whether there are compounds which ·induce natural sleep with no reduction in the paradoxical phases, and with no rebound after withdrawal.

The following data, in part preliminary, show that progesterone is perhaps such a compound.

Progesterone-Induced Sleep. Some time ago we became interested in the acute effects of steroids when locally applied to a number of distinct subcortical areas in the chronically implanted freely moving cat. All experimental animals in this part of the program were observed during the morning hours when the cats were quite alert, and had last eaten the day before.

After applying progesterone ° (approximately 30–100 mcg. as crystals or suspension) to the preoptic area of the forebrain, we observed sleep within a few minutes. The animals could be awakened from this sleep which otherwise lasted several hours, and showed recurrent episodes of paradoxical sleep. These studies were reported in detail elsewhere.[18] They raised two interesting points: (1) Natu-

° Obtained as Grade A from Calbiochem, Los Angeles, California.
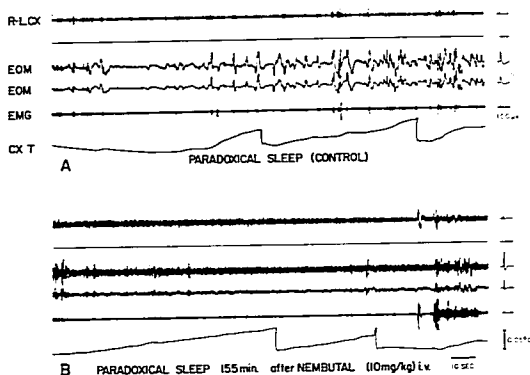

FIG. 6. A. During a control period this cat showed typical paradoxical sleep with rise in cortical temperature (for which we had to correct twice since upper limit of pen excursion was reached), recurrent twitching (see EMG discharges) and rapid eye movement (EOM channels). B. During the first episode of paradoxical sleep after Nembutal, all manifestations of this phase of sleep (including irregular respiration) were present except for rapid eye movement and twitching. Temperature rise again exceeded maximal pen excursion which had to be corrected for twice.
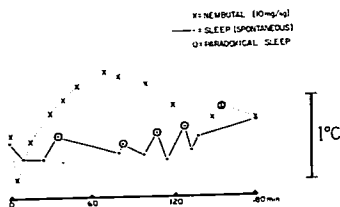
FIG. 7. Illustrates cortical temperature variations with peaks (during paradoxical sleep in the control = ⊙ and in the Nembutal experiment = ⊗) and low values (during slow wave sleep) during 3 hours of control observations as compared with the temperature changes after Nembutal. Note that the first episode of paradoxical sleep only occurred when the temperature had reached the "normal" range for this cat. Higher doses of Nembutal lead to a more pronounced and longer lasting drop in temperature and eliminate paradoxical sleep altogether (at least for the 3 hour period of observation).

ral sleep rather than anesthesia was apparently induced by progesterone which until then had been classified as an anesthetic. (2) Paradoxical sleep, within the framework of natural sleep, was induced by stimulating the forebrain. This is rather distant from the rhombencephalon which is generally postulated as the triggering center for paradoxical sleep.

The next step was to investigate the effect of the systemic administration of progester-

one.† Progesterone is not water soluble and was therefore given in warm sesame oil intraperitoneally. Eight chronically implanted cats were used and observed for three hours in the afternoon when cats are normally sleepy.

At all dose levels short of induction of anesthesia (under our conditions the righting reflex was lost and responses to alerting and painful stimuli were markedly reduced or absent after intraperitoneal administration of 150 mg./kg. or more in oil), progesterone appeared to induce the early appearance of slow wave and paradoxical sleep. The percentage of time spent in paradoxical sleep was normal or slightly above normal but definitely not reduced (table 2). We concluded that subanesthetic doses of progesterone had induced natural sleep in our cats.

When an anesthetic dose of progesterone was administered, the manifestations of paradoxical sleep became incomplete: rapid eye movement and twitching disappeared while thermia occurred even after high doses of progesterone. This is in contrast to the effect of pentobarbital.

In view of the fact that both hypnotic and other criteria remained (fig. 9). It is our preliminary impression that no significant hypo-

† Obtained as Grade A from Calbiochem, Los Angeles, California.
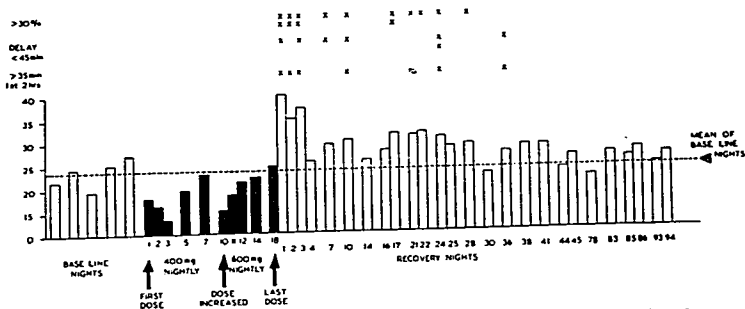

FIG. 8. Effect of sodium amylobarbitone on the sleep of two volunteers who served as their own controls. The drug at first causes suppression of paradoxical sleep and withdrawal a rebound. The crosses indicate where either or both volunteers on the night concerned gave values beyond the arbitrary limits indicated. The crosses are seen only after drug withdrawal and peter out in the sixth recovery week. The time scale is not linear. The ordinate shows percentage of paradoxical sleep. From Oswald.

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anesthetic effects can be seen after the administration of progesterone, we propose to describe these acute effects of progesterone on the central nervous system as *hypnesthetic.*

Since hydroxydione is a known steroid anesthetic without endocrine effects we wondered whether it might have sleep–inducing effects. The next paragraph discusses the negative findings with this compound.

TABLE 2. Effects of Progesterone
on Paradoxical sleep

Treatment	Paradoxical Sleep			
	Onset*	1 Hour†	2 Hours†	3 Hours†
None	56	4	36	51
Progesterone‡ (8 mg./kg.)	18	12	36	52
Saline	32	22	38	59
Progesterone‡ (30 mg./kg.)	85	0	21	49
None	66	0	30	51
Progesterone (30 mg./kg.)	12	23	58	66
Oil	35	8	22	37
None	90	0	2	17
None	41	6	13	19
Progesterone (20 mg./kg.)	32	6	16	27
Oil	60	0	6	8
None	148	0	0	0
None	168	0	0	3
Progesterone (50 mg./kg.)	51	2	13	28
None	34	15	35	45
Oil	36	8	36	52
Oil	68	0	15	25
Saline	36	5	23	42
Progesterone (100 mg./kg.)	28	20	37	47

When progesterone was administered in suspension (‡) it induced a short period of retching (peritoneal irritation) which was not seen when this hormone was thereafter administered in sesame oil. Note that in four separate cats progesterone at various dose levels facilitated the occurrence of paradoxical sleep. The second and third cats were males whereas the first and fourth were females. Double horizontal lines separate individual cats.
 * First time in minutes of appearance of paradoxical sleep after beginning of experiment.
 † Sum total of time in minutes, spent in paradoxical sleep during first hour, first 2 hours and first 3 hours after beginning of experiment.

TABLE 3. Effects of Hydroxydione on Paradoxical Sleep during a Three-Hour Observation Period in Two Separate Cats

Treatment	Paradoxical Sleep			
	Onset*	1 Hour†	2 Hours†	3 Hours†
None	25	10	20	42
Hydroxydione (20 mg./kg., i.p.)	93	0	4	16
None	65	0	19	33
Hydroxydione (70 mg./kg., i.p.)	—	0	0	0
None	25	0	15	46
Hydroxydione (50 mg./kg., i.v.)	124	0	0	16
None	53	2	10	29
Hydroxydione (20 mg./kg., i.v.)	64	0	11	28

In both animals hydroxydione (Viadril) delayed the first appearance of, and reduced the number of minutes spent in paradoxical sleep. Double horizontal lines separate the individual cats.
 * First time in minutes of appearance of paradoxical sleep after beginning of experiment.
 † Sum total of time in minutes, spent in paradoxical sleep during first hour, first 2 hours and first 3 hours after beginning of experiment.

Hydroxydione-Induced Sedation. Hydroxydione (Viadril) was administered in water intraperitoneally and intravenously. This synthetic steroid was found to reduce the occurrence of paradoxical sleep (table 3) which, however, was complete in all its manifestations. This reduction was less striking than that seen after pentobarbital. When anesthetic doses (70 mg./kg. intraperitoneally or more) were given, paradoxical sleep was eliminated altogether.

Summary and Conclusions

(1) Some steroids, in high doses, cause a spectrum of recurrent convulsive activity in animals.

(2) Convulsive steroids may cause behavioral abnormalities (sedation, and hallucination? aura? tranquillization?) with concomitant localized subcortical seizure activity or generalized slow wave hypersynchrony.

(3) Pentobarbital does not induce natural sleep. After a small dose the first episode of paradoxical sleep occurs comparatively late

Fig. 9. A. Control. B. After 100 mg./kg. of progesterone in oil intraperitoneally this cat showed recurrent paradoxical sleep with activation of the electrocorticogram, rapid eye movements (EOM), flattening of the EMG, a rise in cortical temperature, irregular respiration, and twitching. C. After a total of 250 mg./kg. of progesterone in oil this cat appeared anesthetized and showed marked electrical slow wave activity. Intermittently however, there was "activation" of the electrocorticogram, a rise in cortical temperature (again the pen excursion had to be corrected for), and irregular respiration. However, during these episodes of what appeared to be paradoxical sleep, no rapid eye movements and no twitching were seen (D).
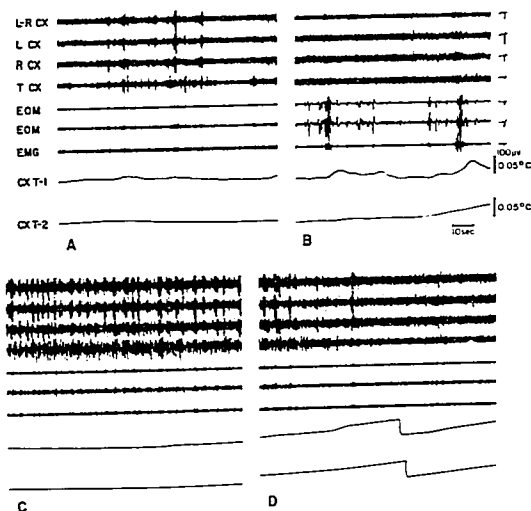
and its manifestations are incomplete (rapid eye movements and twitching appear to be most easily affected by this drug). Higher, subanesthetic and anesthetic doses eliminate all the usual criteria for paradoxical sleep.

In the light of these findings, Pentobarbital would not appear to be the "hypnotic" of choice. However, it may well have a place in the therapeutic approach to the acute phase of illnesses which are aggravated in one way or another during paradoxical sleep, e.g., peptic ulcer,[19] coronary insufficiency,[20] and nocturnal asthma.[21] Further investigations are necessary to elucidate this possibility.

(4) Some steroids, in high doses, induce anesthesia (e.g., progesterone).

(5) Progesterone, in subanesthetic doses, facilitates the occurrence of natural sleep. The term "hypnesthetic" is suggested, as it refers to both the hypnotic and anesthetic activities of this hormone.

A drug which induces natural sleep (without reduction of paradoxical sleep during and without rebound after treatment) is indicated as a therapeutic agent in all situations of uncomplicated sleeplessness. A search for a hormonally inactive sleep inducing steroid or any other truly sleep-inducing drug is clearly indicated and, in view of our data, holds great promise.

(6) Finally, we should like to quote M. Kawakami et al. who concluded in their paper[22]: "The present results point to sex steroids as one of the crucial elements of the internal environment responsible for sleep."

References

1. Cashin, M. F., and Moravek, V.: Physiological action of cholesterol, Amer. J. Physiol. 82: 294, 1927.

2. Selye, H.: Anesthetic effect of steroid hormones, Proc. Soc. Exp. Biol. Med. 46: 116, 1941.

3. Gardocki, J. F., P'An, S. Y., and Brown, J.: Lack of biological activities of 21-hydroxy-pregnane-3-20-dione sodium succinate, Endocrinology 59: 129, 1956.

4. Heuser, G.: Experimental anesthesia and convulsions with steroids, Rev. Canad. Biol. 17: 229, 1958.

5. Heuser, G., and Eidelberg, E.: Steroid-induced convulsions in experimental animals, Endocrinology 69: 915, 1961.

6. Heuser, G., and Eidelberg, E.: Convulsions induced by a steroid hormone in cats, West. Pharm. Soc. Proc. 4: 67, 1961.

7. Heuser, G., Ling, G. M., and Buchwald, N. A.: Sedation or seizures as dose-dependent effects of steroids, Arch. Neurol. 13: 195, 1965.

8. Winters, W. D.: Neurophysiology of anesthesia, This meeting.

9. Hartman, E. L.: The D-state, New Eng. J. Med. 273: 30 and 87, 1965.

10. Roffwarg, H. P., Muzio, J. N., and Dement, W. C.: Ontogenetic development of the human sleep-dream cycle, Science 152: 604, 1966.

11. Kawamura, H., and Sawyer, C. H.: Elevation in brain temperature during paradoxical sleep, Science 150: 912, 1965.

12. Rechtschaffen, A., Cornwall, P., and Zimmerman, W.: Brain temperature variations with paradoxical sleep in the cat. Presented to Assoc. for Psychophysiol. Study of Sleep, Washington, D. C., 1965.

13. Hull, C. D., Buchwald, N. A., Dubrovsky, B., and Garcia, J.: Brain temperature and arousal, Exper. Neurol. 12: 238, 1965.

14. Zanchetti, A.: Personal communication.

15. Jacobson, A., Kales, A., Lehmann, D., and Zweizig, J. R.: Somnambulism: all night electroencephalographic studies, Science 148: 975, 1965.

16. Jouvet, D., and Delorme, F.: Evolution des signes electriques du sommeil paradoxal au cours de la narcose au pentobarbital, C. R. Soc. Biol. 159: 387, 1965.

17. Oswald, I., and Priest, R. G.: Five weeks to escape the sleeping-pill habit, Brit. Med. J. 2: 1093, 1965.

18. Heuser, G., Ling, G. M., and Kluver, M.: Sleep induction by progesterone in the preoptic area in cats, Electroenceph. Clin. Neurophysiol. 22: 122, 1967.

19. Armstrong, R. H., Burnap, D., Jacobson, A., Kales, A., Ward, S., and Golden, J.: Dreams and gastric secretions in duodenal ulcer patients, New Physician 14: 241, 1965.

20. Nowlin, J. B., Troyer, W. G., Collins, W. S., Silverman, G., Nichols, C. R., McIntosh, H. D., Estes, E. H., and Bogdonoff, M. D.: The association of nocturnal angina pectoris with dreaming, Ann. Intern. Med. 63: 1040, 1965.

21. Ervin, F.: Personal communication.

22. Kawakami, M., Ishida, S., Yoshida, K., Ibuka, K., Terasawa, E., and Negoro, H.: The effect of brain lesions upon the spontaneous EEG-afterreaction in rabbits treated with sex hormones, Gunma Symposia on Endocrinology 1: 221, 1964.

Discussion

Dr. Zanchetti: I should like to ask two questions of Dr. Heuser. The first concerns the effect of implantation of progesterone into the preoptic area. How specific is this effect with respect to the substance implanted? For example, if you implanted testosterone or progesterone, would you get the same effect? Also, is this specific with regard to location? The second point concerns the effect of barbiturate on so-called paradoxical or desynchronized sleep. Are you aware of a recent paper by Jouvet's group (Jouvet, D. and Delorme, F.: Evolution des signes électriques du sommeil paradoxal au cours de la narcose au pentobarbital, C. R. Soc. Biol. 159: 387, 1965) in which they observed that so-called ponto-geniculate-occipital waves are rather well preserved under pentobarbital. This

suggests that pentobarbital does not act on the pacemaker mechanisms of paradoxical sleep.

As a comment, I should like to offer a word of caution on quantitative studies concerning the effects of drugs on paradoxical or synchronized sleep. Everybody who works on the sleep mechanism of cats knows how finicky cat's sleep is: quantity of sleep varies not only from cat to cat, but also in the same cat, from session to session. Sometimes the same cat will be excited during the first hours of a session, then quiet, or the reverse. As a safeguard, this sort of study can best be done in prolonged sessions, with randomized experimental design for administering drugs.

Dr. Heuser: I fully agree with Dr. Zanchetti. It is difficult to be sure that you have induced sleep. However, we have used a randomized experimental design with many control periods of

observation. Our cats, when studied hungry and in the morning hours almost never went into slow wave sleep within 5 minutes, or into paradoxical sleep within 15 minutes, after being handled and given a sham-injection (or an injection of a control substance like cholesterol, saline, glucose). In contrast, progesterone, when applied to the pre-optic area, induced sleep within a few minutes in these cats. We have not used other steroids for comparison, nor used cholinergic agents which, according to Hernandez-Peon, also induce sleep when applied to the pre-optic area. Since we have not screened the brain systematically, we cannot make a definite statement as to the specificity of the area of the progesterone effect.

I am aware of Jouvet's findings that even under pentobarbital anesthesia, some subcortical electrical activity characteristic of paradoxical sleep persists. Our data add to his findings, by showing that depending on dose, more or less of the "classic" manifestations of paradoxical sleep may be effected.

Dr. Fink: Do you think that there is any suggestion of relation between the dialyzable sleep-inducing factor of Monet and the substances you are using?

Dr. Heuser: I do not know.

Dr. Butler: I would like to make a point about the cortical temperature. This is probably related to blood flow, hence to P_{CO_2}, and a time of changing P_{CO_2} may very well be associated with the burst of activity. Will you comment on this? Your data showing depression with barbiturate are similar to those of the CO_2 response curve in man.

Dr. Heuser: I can only assume that the temperature change reflects blood flow and, therefore, also changes in P_{CO_2}; but we have not measured either.