

ALTERATIONS IN THE NOCTURNAL SLEEP CYCLE RESULTING FROM LSD¹

JOSEPH N. MUZIO, M. A., HOWARD P. ROFFWARG, M. D. AND EDWARD KAUFMAN, M. D.

*Department of Psychiatry, College of Physicians and Surgeons, Columbia University; Sleep Physiology Laboratory,
New York State Psychiatric Institute, New York, N.Y. (U.S.A.)*

(Accepted for publication: April 21, 1966)

D-Lysergic acid diethylamide (LSD-25) is a potent pharmacological agent that causes psychological and autonomic alterations in awake humans when administered in conventional doses of 1-2 $\mu\text{g}/\text{kg}$ of body weight (Bercel *et al.* 1956; Klee 1963; Kuramochi and Takahashi 1964). LSD's effects on the human EEG have been studied primarily in the waking state. These would seem to be minimal (Forrer and Goldner 1951; Schwarz *et al.* 1955) or to consist of slight increases or decreases in the frequency of the alpha rhythm (Rinkel *et al.* 1952; Anderson and Rawsley 1954; Bercel *et al.* 1956).

During a typical night's sleep there are predictable shifts in the EEG pattern (Dement and Kleitman 1957). The intervals characterized by a relatively low voltage, fast, non-spindling EEG, accompanied by rapid eye movements (REMs), and loss of tonus of the head and neck musculature — designated as REM Sleep (REMS) — alternate with spindle and high voltage slow waves, without REMs, and associated with measurable resting muscle potentials — designated as Slow Wave Sleep (SWS). REMS is associated with complex and intense hallucinatory sequences or "dreams" in humans (Dement 1964.)

Because of LSD's imagery evoking properties, it was felt that investigation of the drug's effect during sleep might be fruitful. The mechanisms which underly most hallucinatory phenomena are not well understood, but a body of neuro-

anatomical and neurophysiological data pertaining to brain-stem triggering zones of REMS is available (Jouvet 1965). Attention has just begun to focus on the ascending pathways which might be responsible for the hallucinations of dreaming (Roffwarg *et al.* 1966). Inasmuch as dreaming and other types of hallucinations may be related, we hypothesized that an enhancement of REMS by LSD might indirectly support a commonality of hallucinatory mechanisms.

SUBJECT MATERIAL AND METHOD

Twelve selected, psychiatrically sound individuals were requested to maintain their sleep at the amount they reported as typical for themselves for 3 nights prior to every series of experimental nights and to abstain from alcohol, other stimulant beverages and food. Subjects were told that each night, either just before going to bed or about 1 h after falling asleep, they would be awakened and given an ounce of fluid to drink. They were informed that the fluid would contain either a "stimulant", "sedative", LSD, or plain water. Expected sensations, if any, resulting from each agent were explained to the subjects. The descriptions emphasized that drug doses as well as possible effects would be minimal. This reduced expectations and attendant apprehensions about "an LSD experiment".

In actuality, the experimental design provided that each subject would receive only a distilled water placebo on all nights except for the night (in each series) when LSD was added as a colorless, tasteless and odorless liquid.

Subjects were divided into two groups. One group received the placebo and LSD just prior

¹ This study was supported in part by grant MH-18, 739, MH-06383 and MH-06858 from the National Institute of Mental Health. The paper was presented to the meeting of the Association for the Psychophysiological Study of Sleep, Palo Alto, Calif., March, 1964.

to sleep, whereas the other group was briefly awakened for that purpose after approximately 1 h of SWS (just prior to the expected appearance of the first REMS period). A series of consecutive night recordings consisted of 2 or 3 control nights on distilled water placebo whereupon the LSD was added on the subsequent night. In many cases a recording was obtained on the following night as well, at which time the subject again received the placebo. A single control night, if typical for the subject, was considered sufficient after the second experimental series. Every morning, whether the subject received the placebo or the active substance, the same questions were asked concerning his experiences and physical state during the night.

Using the standard technique for sleep EEGs, referential tracings were obtained between frontal, posterior frontal, and parieto-occipital electrodes and ear electrodes. Electro-oculo-

grams (EOGs) were recorded by means of electrodes placed over the lateral canthi. Submental EMGs were monitored on four subjects. An 8-channel Grass Model III electroencephalograph or a Grass Model 7 polygraph were used for continuous monitoring of the overnight patterns. The EEG patterns were divided into sleep stages which were plotted against time (Dement and Kleitman 1957). Because physiological tolerance develops under circumstances of short interval administration in normal humans (Abramson *et al.* 1956), a minimal period of at least 1 week was observed between administrations.

All night EEG and EOG measurements were recorded on six female (ages 19–25) and six male (ages 21–30) paid volunteers during 118 subject nights. There were 69 control nights preceding the administration of LSD, 36 nights when the effects of LSD were studied and 13 nights

TABLE I
Comparison of LSD-prolonged REMS period and single, longest same REMS period control

Subject	REMS period prolonged	Duration on control nights (min)	Duration on nights LSD administered (min)	% increase
A	2nd	23	47.5	106.5
			29.5	28.3
			64.5	180.4
B	2nd	41	67.5	64.6
			71	73.2
			141	243.9
C	1st	12.5	24	92.0
C ^a	2nd	30	103.5	245.0
D	1st	17.5	31.5	80.0
			29.5	68.6
F	2nd	32.5	39	20.0
G	1st	20	27	35.0
			32.5	62.5
			43.5	117.5
			52	160.0
			43	115.0
H	2nd	36.5	54.5	49.3
I	2nd	21	28.5	35.7
J	2nd	17	29	70.6
K	2nd	18	24	33.3
L	2nd	19	25	31.6

^a Same subject as C (see Tables II and III).

following the night when LSD was administered. In order to avoid excessive arousals, very small LSD doses were used. In the first few subjects, the starting dose was between 0.41 and 0.57 $\mu\text{g}/\text{kg}$ (25–30 μg total dose). Because of awakenings from REMS, the starting dose for remaining subjects was lowered to between 0.13 and 0.31 $\mu\text{g}/\text{kg}$ (7–22 μg total dose). Depending on a subject's response to this initial concentration, his dose in ensuing trials was modified.

RESULTS

The most striking finding in this study was an appreciable prolongation of either the first or second REMS period in 21 of 36 instances of LSD administration. Eleven of the twelve subjects eventually exhibited this response on some dose of LSD. The REMS periods following LSD administration lasted 20–245% longer than the same REMS periods on any control night. Their duration was of 24 to 141 min (Table I). These effects occurred with doses between 0.13 and 0.73 $\mu\text{g}/\text{kg}$. In nine cases in which the drug concentrations were of 0.08 to 0.55 $\mu\text{g}/\text{kg}$, LSD did not alter the sleep EEG cycle but caused moderate increases of body motility. In the remaining

six cases, on LSD in concentrations of 0.11–0.41 $\mu\text{g}/\text{kg}$, arousals continually interrupted sleep.

Table II summarizes the data obtained from the group of subjects who received LSD after 1 h of sleep. When the drug was given at this time; *i.e.*, only minutes in advance of the time of onset of the first REMS period, this REMS period remained unmodified. When a prolonged REMS period was observed in the subjects referred to in Table II, the REMS period affected was invariably the second. Table III describes the results in the group that received the drug prior to sleep. The time from the onset of sleep to the beginning of the first REMS period was not affected for this group. An increase in duration of REMS in the subjects referred to in Table III occurred either in the first or second REMS period, but never in both. Furthermore, each subject was individually consistent in terms of which REMS period was affected; for example, if a subject reacted in the first REMS period, he always reacted in this same period.

A. Sleep stage characteristics

No qualitative changes of the waking and sleep EEG patterns followed the administration

TABLE II
Comparison of the 2nd REMS periods on LSD-25 and placebo nights for each subject.
LSD-25 and placebo administered 1 h after sleep onset

Subject	Sex	Total number of baseline placebo nights	Duration on LSD nights (min) ^a		Duration on placebo nights (min)	
			1st series	2nd series	Maximum	Mean
C ₁	f	3	103.5 (0.48)		30	22.5
H	m	2	54.5...awake ^b (0.20)		36.5	26.5
I	f	2	28.5...awake ^b (0.57)		21	10
J	m	4	10...awake ^b (0.41)	29...awake ^b (0.31)	17	13.8
K	f	2	24 (0.20)		18	13.5
L	m	2	25 (0.31)		19	16.5

^a Drug dosage ($\mu\text{g}/\text{kg}$) is given between brackets.

^b REMS terminated in arousal.

TABLE III
Comparison of individual REMS periods on LSD-25 and placebo nights for each subject.
LSD-25 and placebo administered prior to sleep onset

Subject	Sex	Total number of baseline placebo nights	REMS period affected	Duration on LSD nights (min); drug dosage ($\mu\text{g/kg}$) is given between brackets				Duration on placebo nights (min)	
								Maximum	Mean
A	f	5	2nd	<i>1st series</i> 47.5 (0.27)	<i>2nd series</i> 29.5 (0.32)	<i>3rd series</i> 64.5 (0.38)	<i>4th series</i>	23	14.5
B	m	6	2nd	67.5..awake ^a (0.21)	71 ^b (0.27)	awake..141 ^c (0.16)		41	32
C	f	5	1st	24..awake ^a (0.48)				12.5	8.5
D	f	9	1st	31.5 (0.22)	12.5..awake ^a (0.26)	3..awake..26.5 ^d (0.24)		17.5	7.5 ^e
E	m	7	2nd	awake (0.21)	awake (0.14)	9..awake ^a (0.11)	12.5 (0.08)	33	16.5
F	f	5	2nd	39.5 (0.13)	10.5 (0.18)	awake (0.29)		32.5	22.5 ^f
G	f	17	1st	skipped ^g (0.22)	2.5 (0.22)	skipped (0.28)	skipped (0.33)	20	6.8 ^h
				<i>5th series</i> 6.5 (0.33)	<i>6th series</i> 27 (0.39)	<i>7th series</i> 2.5 (0.44)	<i>8th series</i> 32.5 (0.50)		
				<i>9th series</i> 2 (0.55)	<i>10th series</i> 43.5 (0.61)	<i>11th series</i> 52 (0.66)	<i>12th series</i> 43..awake ^a (0.73)		

^a REMS terminated in arousal.

^b Subject may have been partially tolerant to drug.

^c 141 min REMS period was preceded by an arousal.

^d REMS interrupted by transient arousal.

^e 5 of 9 baseline nights, D did not have a 1st REMS period. "Skipped" periods not averaged.

^f 1 of 5 baseline nights, F did not have a 2nd REMS period. "Skipped" periods not averaged.

^g REMS period considered "skipped" if there was no REMS in 1st 120 min of sleep.

^h 10 of 17 baseline nights, G did not have a 1st REMS period. "Skipped" periods not averaged.

of LSD. The eye movements in REMS, however, were less numerous and slightly less rapid on drug nights (Fig. 1 and 2). The EMG was consistent with EEG criteria in that it was isoelectric during REMS, low during SWS, and maximal during waking (Fig. 2).

B. Tendency to arousal

Six of the 21 LSD-induced REMS prolongations terminated in awakenings; on six other occasions (0.11–0.41 $\mu\text{g/kg}$) arousal occurred at the commencement of a REMS period. No such

episodes of arousal and periods of sustained wakefulness occurred in control nights. When extended arousals followed administration of LSD, periodicity, or the usual alternation of the REMS and SWS patterns was disrupted.

C. Reactions to increase and decrease in dose

Unless arousals occurred, increases in the dose of LSD in successive experimental series were usually correlated with greater prolongations of REMS periods. The relationship was not uniform (subjects A and G) or seen in all sub-

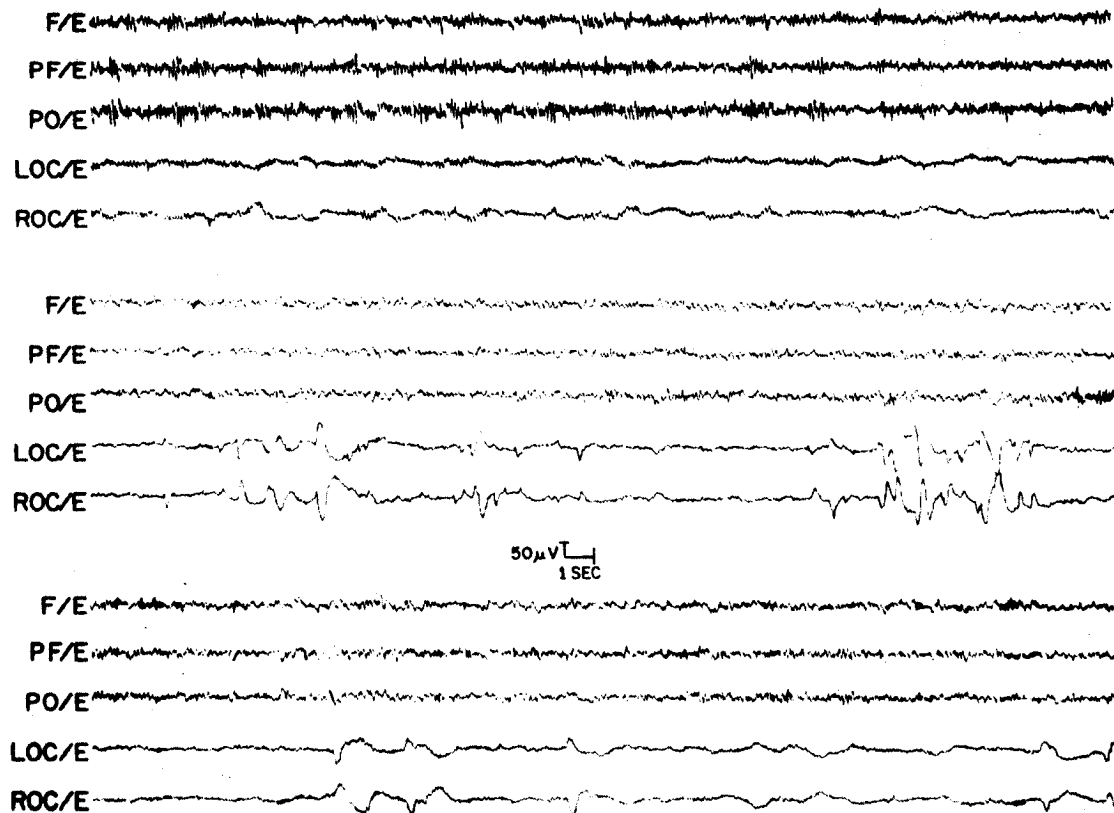


Fig. 1

EEG (channels 1-3) and EOG (channels 4-5) in subject during wakefulness (top section) and REMS during control night (middle section), and REMS on LSD night (bottom section). F/E: frontal to ear; PF/E: posterior frontal to ear; PO/E: parieto-occipital to ear; LOC/E: left outer canthus to ear; ROC/E: right outer canthus to ear.

jects (subject F). Fig. 3 is an example of this dose-response relationship. Although there were inconsistent responses to the midrange of LSD doses (0.33–0.55 μ g/kg) there was a trend towards longer first REMS periods on higher doses. This subject's longest first REMS periods (43.5, 52 and 43 min) were recorded in conjunction with the 3 highest LSD doses (0.61, 0.66, and 0.73 μ g/kg). Elevating dose to increase the length of REMS periods was limited because of arousals (subject D).

Decreases in the dose of LSD were also carried out where the initial dose had caused an arousal. In one case (subject J) a reduced dose resulted in a prolongation, whereas in another (subject E) a prolongation was not observed.

D. Alterations following LSD-induced REMS prolongations

1. *Later REMS periods.* When an *LSD Sleep Response* occurred there was a disruption of the pattern typically observed in the young adult of brief early REMS periods and longer subsequent ones (Dement and Kleitman 1957). REMS periods following drug-induced REMS prolongations did not show the typical increases in duration. In fact after the long early REMS periods, subsequent periods for the most part were abbreviated (Fig. 4 and 5). REMS continued to recur more or less at 70–90 min intervals (Fig. 5).

2. *Brief REMS sequences.* After termination of a prolonged REMS period, the ensuing SWS

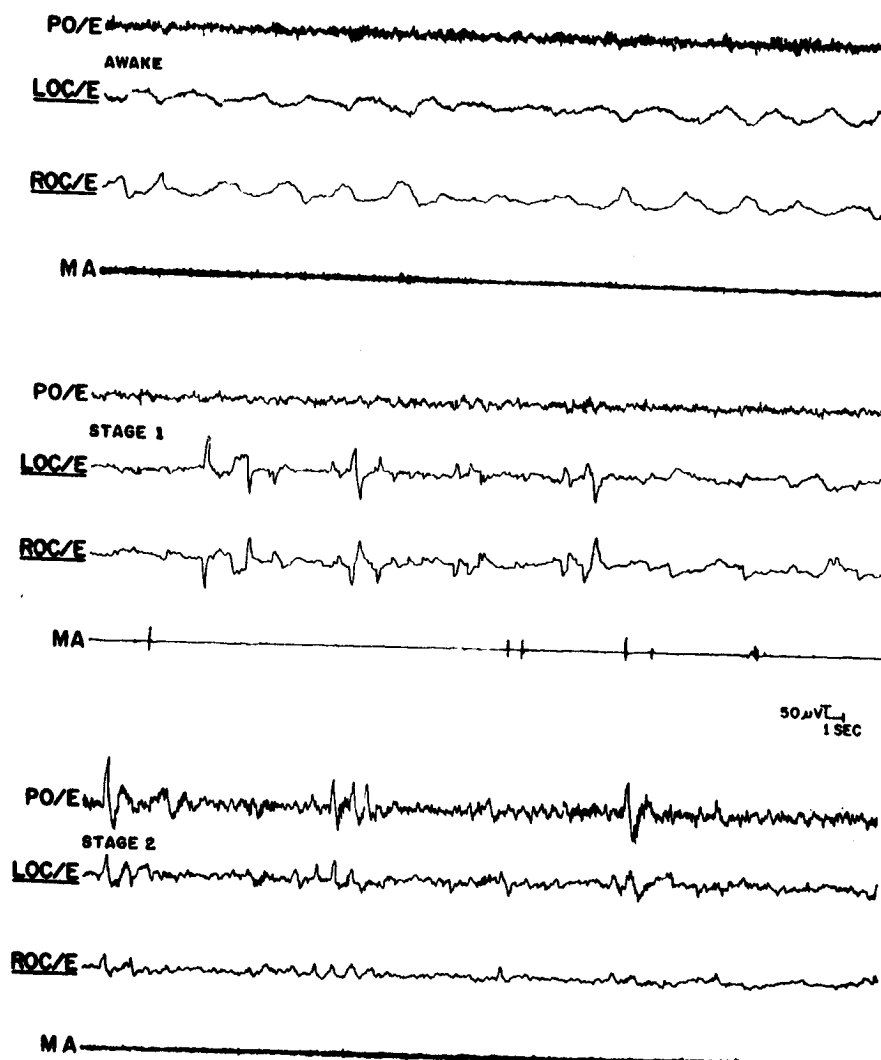


Fig. 2
EEG (channel 1), EOG (channels 2-3) and EMG (channel 4) recordings during wakefulness (top section), REMS (middle section) and SWS (stage 2) (bottom section) in a subject on 0.27 μ g/kg of LSD.

was at times punctuated by brief recurrent bursts of REMs accompanied by reappearances of a low voltage fast EEG and of sawtooth waves. These periods each lasted 2-12 sec, then gave way again to the SWS pattern. In rare instances, a REM burst and a spindle were virtually simultaneous, at which time immediate disruption or attenuation of the spindle occurred (Fig. 6). These short sequences of REMS appeared up to 3.5 h after the end of a prolonged REMS period. Fig. 5 shows the characteristic position of the REMS bursts in an all-night sleep graph. Sometimes

such bursts were also observed following LSD-induced periods of wakefulness.

E. Total REMS

In spite of the prolonged first or second REMS periods and the additional bursts of REMS seen on nights LSD was administered, there was no consistent increase in total REMS. The extent that later REMS periods were abbreviated, and the length of arousals, if any, following an LSD-induced prolongation of an early REMS period, were factors as to whether or not there

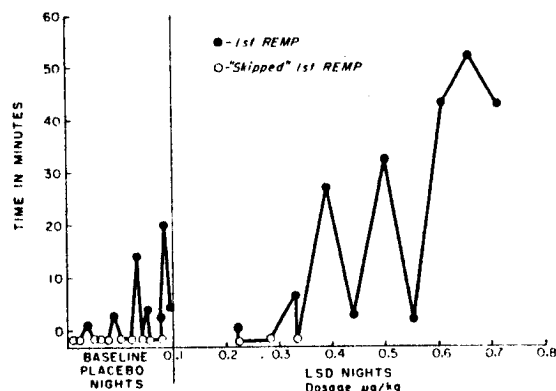
COMPARISON OF 1ST REM ON BASELINE (Placebo) NIGHTS
TO 1ST REM ON LSD-25 NIGHTS
subject G

Fig. 3

Response to increasing dose of LSD. Subject frequently "skipped" first REM period on control nights, and on 3 of 12 nights on LSD at lower doses.

was an increase in total REMS. In all thirteen cases when the night immediately following the *LSD Sleep Response* was recorded, the recordings were comparable to the typical patterns in control nights, and total REMS was at control levels.

F. Subjective experiences

While lying awake, the subjects given LSD reported, either spontaneously or after questioning, experiences including: (a) restlessness; (b) physical sensations of increased warmth, dizziness, nausea, dryness of mouth; and (c) irregular heart beat. A few reported visual hallucinations, colored flashes, geometric patterns, and vivid images of human forms. Such reports were never given in control nights. During one such period of wakefulness, a subject described seeing two people talking, but instead of hearing their conversation, she saw hieroglyphic symbols tumbling out of their mouths. These hallucinations occurred when the subjects' eyelids were closed.

DISCUSSION

This study demonstrates that LSD may promote alterations in the nocturnal sleep EEG cycle, specifically prolongations of early REMS periods, and the occurrence of brief REMS bursts interrupting SWS. On the basis of our data, it is uncertain whether the prolonged REMS

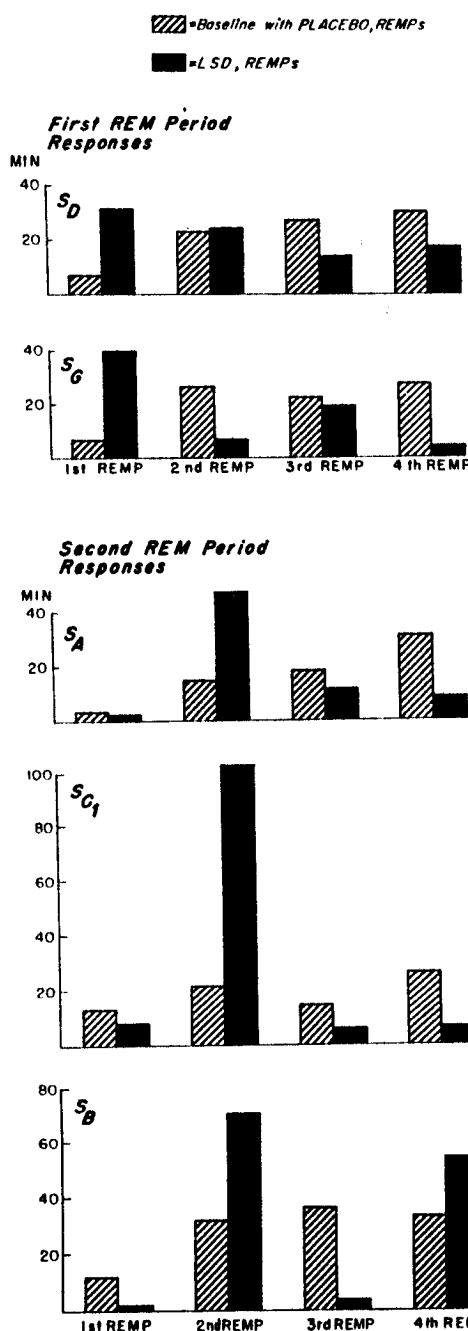
MEAN REMPS FOR BASELINE (PLACEBO) Ns 8
LSD-REACTIVE Ns
Five Subjects

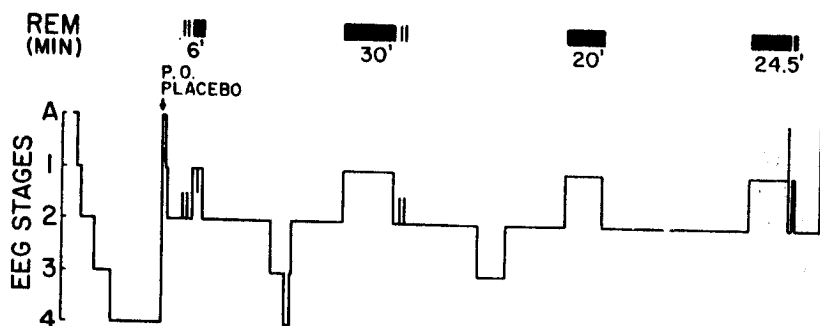
Fig. 4

General tendency towards curtailment of REMS periods subsequent to an LSD-induced prolongation of either the first or second REMS period.

SUBJECT: C₁
22 YEAR OLD ♀

PLACEBO NIGHT (9-22-63)

TSP: 7:14
TST: 7:12
ST. 1 T: 1:20.5
ST. 1 %: 18.6%



d-LSD₂₅ NIGHT (9-23-63)

TSP: 7:27.5
TST: 7:14.5
ST. 1 T: 2:16
ST. 1 %: 31.3%

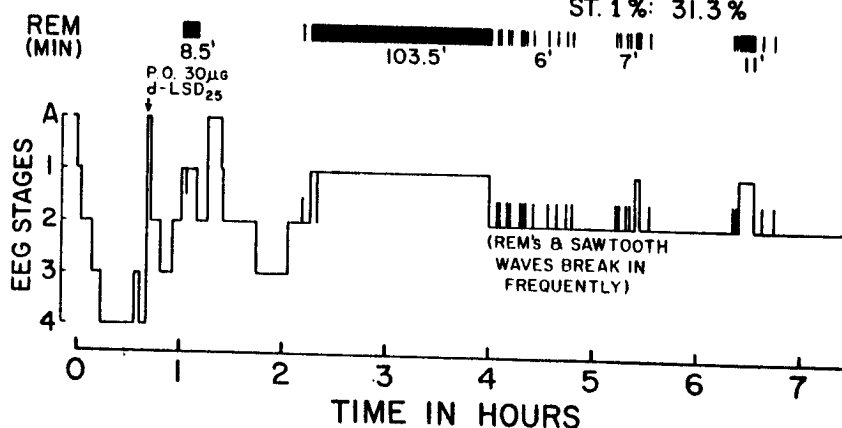


Fig. 5

Nocturnal sleep cycle graphs in a subject on placebo (*top section*) and on LSD administered after onset of sleep (*bottom section*). TSP: total sleep period; TST: total sleep time; St. 1 T: total stage 1 (REMS) time; St. 1 % total percent St. 1 (REMS) sleep in relation to TST.

periods result from direct stimulation of the mechanism underlying REMS or from inhibition of the processes responsible for SWS. In interpreting our data we have tended to assume that LSD potentiates REMS.

There was considerable response variability to orally administered LSD from one subject to another and in the same subject from one series to the other. Why subjects show inconsistent reactions to the drug is a question not answered by this study. Other studies (Klee 1963; Kuramachi and Takahashi 1964) have emphasized a

number of factors capable of influencing the response to LSD in the waking state, among them personality and mood of the subject, environmental setting, absorption rate, and physiological dose requirements. Our results suggest that for a given individual there is a dose range below which no alterations in the sleep cycle are observed, whereas above it arousal occurs. Within this range there is a high probability of prolongation of the early REMS periods.

The data also indicate that the time of action of LSD is determined by the time of administra-

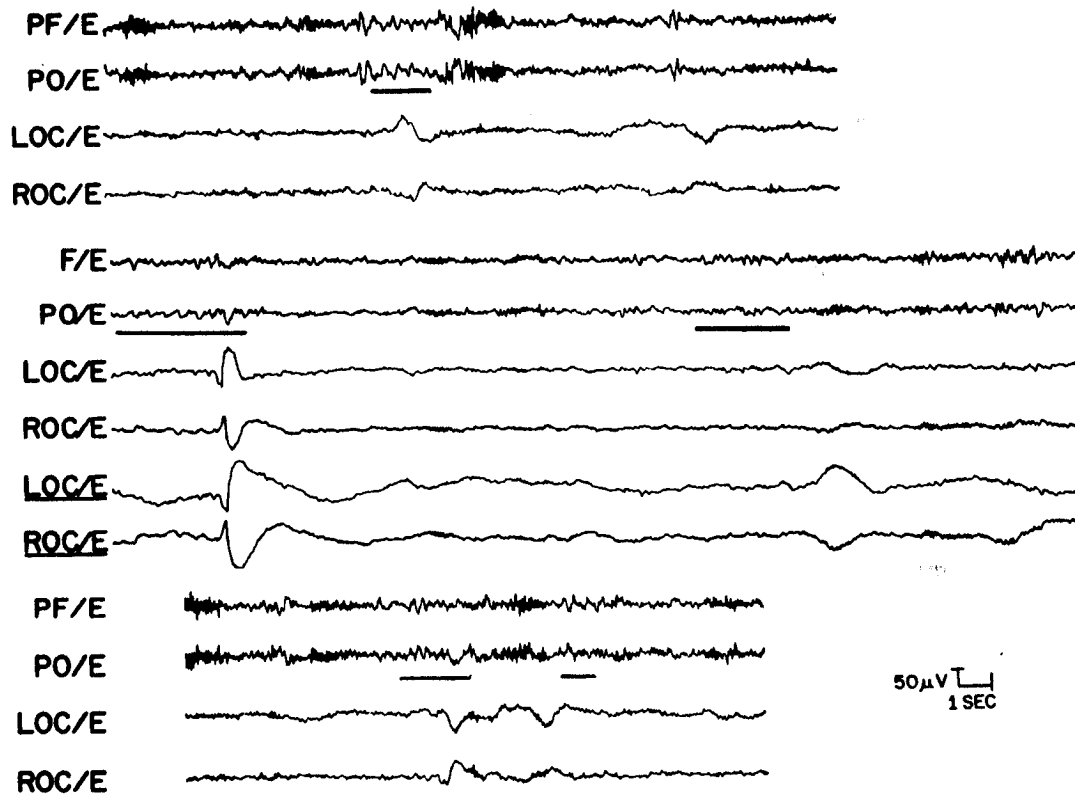


Fig. 6

NREM (stage 2) sleep EEGs (PF/E, PO/E, F/E) and EOGs (LOC/E, ROC/E) in subject on LSD taken from sections of record showing interposition of REMS activity. (Abbreviations and paper speed same as in Fig. 1. Lower two channels of middle trace are EOGs on a longer time constant.) Note the REMs simultaneous with low voltage EEG or "sawtooth activity" interrupting SWS.

tion of the drug. In our study the responses were observed 1.5–2.5 h after oral intake, when the drug's activity was at its peak. Moreover, we have some evidence that LSD administration a number of hours before sleep may result in an earlier onset of the first REMS period. The same effect may also be produced by larger doses, or routes of administration which provide quicker access to the CNS than the oral route.

There is evidence that certain subcortical regions may be discharging in REMS as they do in awake individuals under the influence of LSD; humans (Monroe *et al.* 1957), monkeys (Monroe and Heath 1961) and cats (Adey *et al.* 1962) show "paroxysmal" or "seizure-like" theta patterns in the hippocampus (propagated to surrounding areas). The similarity between these LSD-induced hippocampal rhythms during

waking and hippocampal theta during REMS suggests that a relationship may exist between the hallucinatory phenomena of the LSD "state" and that of dreaming.

It is important to know whether subjects whose sleep was altered by LSD were experiencing typical dreaming or some other more bizarre hallucinatory activity during the protracted REMS intervals. Since our primary interest was to observe LSD influence on the all night sleep cycle, we attempted no awakenings during prolonged REMS, or during brief bursts of REMS. However, subjects who showed protracted REMS periods on LSD infrequently volunteered any information about prior dreaming during spontaneous arousals or on the next morning and, when they did, the dream reports did not seem atypical.

There are only two other reports known to us concerning the effect of LSD on sleep in man. In a single case, Toyoda (1964) observed an increase in restlessness and total REMS following the administration of 25 μ g of LSD, and Green (1965) reported similar findings for 2 nights in an alcoholic who received 300 μ g of the drug 12 h prior to the first night's sleep. In both studies, however, unmonitored sleep was allowed between control and drug nights.

Hobson (1964) reported on the effects of LSD on the sleep cycle of cats. Intraperitoneal administration of doses of 20, 2, and 1 μ g/kg resulted in disturbed sleep and reduction in mean REMS, though the findings were less dramatic with the smaller doses. He also found that differentiation between REMS and SWS based on EEG and EMG criteria was not always clear following administration of LSD. The time of onset of the first REMS phase was apparently doubled but the SWS pattern became mixed with lower voltage fast activity 20 min after onset of sleep. This phenomenon may be similar to the LSD-induced occurrence of brief REMS bursts interrupting SWS found in our study.

There have been other attempts designed to induce alterations in the nocturnal sleep cycle. One technique involves the selective deprivation by repeated awakenings of stages 1 (REMS) or 4 (SWS). Following the deprivation of a given stage, the amount of the same stage greatly increases as compared to control nights if uninterrupted sleep is allowed (Agnew *et al.* 1964; Dement 1964). Post-deprivation REMS periods have a much earlier onset and last several hours (Dement 1964). Moreover, total and partial sleep deprivation results in lengthened REMS and increased percentage of REMS in the post-deprivation period (Johnson *et al.* 1965; Webb and Agnew 1965).

Pharmacological agents have been used to produce quantitative alterations of REMS and slow wave sleep. Atropine suppresses the REMS in cats (Jouvet 1962), whereas gamma butyrolactone, gamma hydroxybutyrate (Jouvet 1965), sodium butyrate (Matsuzaki *et al.* 1964), and eserine (Jouvet 1962) increase the amount of REMS. In humans, amphetamines (Oswald and Thacore 1963; Rechtschaffen and Maron 1964) and barbiturates (Oswald and Priest 1965)

reduce the amount of REMS. LeGassick *et al.* (1965) have shown that tranlycypromine (Par-nate), a potent MAO inhibitor, suppresses REMS.

A hypothesis concerning the mediation of REMS has been advanced by Jouvet (1962) and Dement (1964). In their view, the cyclic recurrence of REM periods is the effect of an endogenous neurohumoral substance which triggers and maintains the REMS until the substance falls below the threshold level. Following this, an interval of SWS ensues while the mediator reaccumulates to threshold for another REMS phase. "Deprivation" of REMS would provoke overaccumulation of the mediator. When eventually allowed to act, the mediator would sustain the protracted REMS found following experimental REMS suppression.

That an exogenous substance such as LSD can prolong some REMS periods may indirectly support the hypothesis of a neurohumoral agent responsible for REMS. In light of this hypothesis, the enhancing effect of LSD on REMS might be explained by the following possibilities: (1) that it possesses a chemical structure similar to the endogenous mediator and contributes to its action (the structural resemblance of LSD to serotonin (5-HT) may be of interest in this regard), or (2) that it may enhance the formation, stimulate the early release, or block the inactivation of the mediator. Following an LSD-induced REMS prolongation, subsequent REMS periods may be curtailed because of: (1) insufficient repletion of available mediator, or (2) partial refractoriness of reactive sites to the mediator.

L-Tryptophan loading has been found to cause early onset of REMS in normal humans, and a 100% prolongation of the sleep onset REMS period in narcoleptics (Oswald 1965). Mandell *et al.* (1965) suggest that intravenous 5-HTP increases REMS in humans. It is noteworthy that methysergide, a 5-HT blocking agent, prevents the reaction to tryptophan in both normal subjects and narcoleptics (Oswald 1965). These findings have been interpreted as suggesting that a possible link exists between brain 5-HT levels and REMS activation. On the contrary, it has been shown in cats that 5-HTP potentiates SWS while suppressing REMS. MAO

inhibitors act similarly (Vimont-Vicary 1965).

Despite the fact that the effects of 5-HTP on REMS in humans and cats are somewhat contradictory, the possibility of a 5-HT-REMS relationship should be contemplated. Reserpine, which depletes the brain of 5-HT and other brain amines, has both an early and a sustained action on REMS in cats. It induces spike discharges, but not typical REMS, in the pons, lateral geniculate and occipital cortex (phasic phenomena of REMS) for as long as 40 h after drug administration (Delorme *et al.* 1965), but the spiking is then reduced for 4 days, accounting for diminished REMS during that period (Matsumoto and Jouvet 1964). Lengthened periods of REMS soon after i.v. reserpine were observed by Khazan and Sawyer (1964) but a later curtailment was not looked for.

LSD increases 5-HT levels in the intraneuronal granular moiety (probably a 5-HT storage site), and results in faster repletion of intraneuronal 5-HT after reserpine pre-treatment (Freedman and Giarman 1962). The fact that LSD responses are heightened after acute reserpine treatment (Isbell and Logan 1957; Freedman 1963) seems to indicate that lower levels of serotonin might potentiate LSD action. However, it is also suggestive that the action of LSD may depend on mobilizing 5-HT or other free brain amines. Since LSD mobilizes 5-HT *into* and reserpine mobilizes 5-HT *out of* intracellular storage sites, the possibility deserves further study that both agents may cause temporary increases in free 5-HT at active sites and thereby briefly affect the REMS mechanism.

Our findings are that LSD stimulates REMS or arousal depending on dosage. Grastyán and Karmos (1961), and Jouvet (1962) have shown that it is possible to induce REMS with moderate electrical stimulation of the reticular formation, but arousal results when there is stronger stimulation. Accordingly, there may be only quantitative rather than qualitative differences between the two states. In view of experimental interruptions in cats of the ascending limb of the midbrain-limbic circuit (the proposed REMS pathway) which do not prevent REMS above the lesion (Carli *et al.* 1963; Hobson 1965), Jouvet's (1962) hypothesis that a distinct pathway exist for REMS is questionable. Thus, the possibility

remains that REMS and arousal mechanisms both operate via the reticular activating system.

SUMMARY

1. Thirty-six LSD doses of 0.08–0.73 $\mu\text{g/kg}$ (6–40 μg total dose) were administered orally to humans either just prior to sleep or 1 h after onset of sleep. All night EEGs and EOGs were recorded on control nights, on nights when LSD was administered, and frequently on nights following those in which the drug was given.

2. On 21 nights following administration of LSD a prolongation of either the first or second REMS period was observed. Additional alterations were: (a) occurrence of brief REMS bursts interrupting phases of SWS; (b) general curtailment of REMS periods subsequent to a prolonged REMS period; (c) increased body movements and arousals frequently occurring in relation to REMS.

3. Certain neurophysiological similarities during LSD induced awake hallucinatory activity and "dreaming" sleep (REMS) are reviewed. The possible relationship of LSD neuropharmacological action to the hypothetical neurohumoral mechanism underlying REMS is considered.

The authors gratefully acknowledge the editorial and secretarial assistance of Miss M. Pleasant, and Miss B. Holloway, R. N., of the New York State Psychiatric Institute. LSD-25 was provided by Sandoz Laboratories, Hanover, N.J.

REFERENCES

- ABRAMSON, H. A., JARVIK, M. E., GORIN, M. H. and HIRSCH, M. W. Lysergic acid diethylamide (LSD-25): XVII. Tolerance development and its relationship to a theory of psychosis. *J. Psychol.*, **1956**, *41*: 81–105.
- ADEY, W. R., BELL, F. R. and DENNIS, B. J. Effect of LSD-25, psilocybin, psilocin on temporal lobe EEG patterns and learned behavior in the cat. *Neurology (Minneapolis)*, **1962**, *12*: 591–602.
- AGNEW, H. W., WEBB, W. B. and WILLIAMS, R. L. The effects of stage four sleep deprivation. *Electroenceph. clin. Neurophysiol.*, **1964**, *17*: 68–70.
- ANDERSON, E. W. and RAWNSLEY, K. Clinical studies of lysergic acid diethylamide. *Mschr. Psychiat. Neurol.*, **1954**, *128*: 38–55.
- BERCEL, N. A., TRAVIS, L. E., OLINGER, L. B. and DRUKURS, E. Model psychoses induced by LSD-25 in normals. I. Psychophysiological investigations with special reference to the mechanism of the paranoid. *Electroenceph. clin. Neurophysiol.*, **1966**, *21*: 313–324.

- reaction. *Arch. Neurol. Psychiat. (Chic.)*, 1956, 75: 588-611.
- CARLI, G., ARMENGOL, V. and ZANCHETTI, A. Electroencephalographic desynchronization during deep sleep after destruction of midbrain-limbic pathways in the cat. *Science*, 1963, 140: 677-679.
- DELORME, F., JEANNEROD, M. et JOUVET, M. Effets remarquables de la réserpine sur l'activité EEG phasique ponto-géniculo-occipitale. *C.R. Soc. Biol. (Paris)*, 1965, 159: 900-903.
- DEMENT, W. C. Experimental dream studies. In J. MASSERMAN (Ed.), *Science and psychoanalysis*. Grune and Stratton, New York, 1964, 7: 129-184.
- DEMENT, W. C. and KLEITMAN, N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *Electroenceph. clin. Neurophysiol.*, 1957, 9: 673-690.
- FORRER, G. R. and GOLDNER, R. D. Experimental physiological studies with lysergic acid diethylamide (LSD-25). *Arch. Neurol. Psychiat. (Chic.)*, 1951, 65: 581-588.
- FREEDMAN, D. X. Psychotomimetic drugs and brain biogenic amines. *Amer. J. Psychiat.*, 1963, 119: 843-850.
- FREEDMAN, D. X. and GIARMAN, N. J. LSD-25 and the status and level of brain serotonin. *Ann. N.Y. Acad. Sci.*, 1962, 96: 98-107.
- GRASTYÁN, E. and KARMOS, G. A study of a possible "dreaming" mechanism in the cat. *Acta physiol. Acad. Sci. hung.*, 1961, 20: 41-50.
- GREEN, W. J. The effects of LSD on the sleep-dream cycle: an exploratory study. *J. nerv. ment. Dis.*, 1965, 140: 417-426.
- HOBSON, J. A. The effect of LSD on the sleep cycle of the cat. *Electroenceph. clin. Neurophysiol.*, 1964, 17: 52-56.
- HOBSON, J. A. The effects of chronic brain-stem lesions on cortical and muscular activity during sleep and waking in the cat. *Electroenceph. clin. Neurophysiol.*, 1965, 19: 41-62.
- ISELL, H. and LOGAN, C. R. Studies on the diethylamide of lysergic acid (LSD-25). II. Effects of chlorpromazine, azacyclonol, and reserpine on the intensity of the LSD-reaction. *Arch. Neurol. Psychiat. (Chic.)*, 1957, 77: 350-358.
- JOHNSON, L. C., SLYE, E. S. and DEMENT, W. Electroencephalographic and autonomic activity during and after prolonged sleep deprivation. *Psychosom. Med.*, 1965, 27: 415-423.
- JOUVET, M. Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. *Arch. ital. Biol.*, 1962, 100: 125-206.
- JOUVET, M. Étude de la dualité des états de sommeil et des mécanismes de la phase paradoxale. In *Aspects anatomo-fonctionnels de la physiologie du sommeil*. Colloq. Int. C.N.R.S., Paris, 1965: 397-449.
- KHAZAN, N. and SAWYER, C. H. Mechanisms of paradoxical sleep as revealed by neurophysiologic and pharmacologic approaches in the rabbit. *Psychopharmacologia (Berl.)*, 1964, 5: 457-466.
- KLEE, G. D. Lysergic acid diethylamide (LSD-25) and ego functions. *Arch. gen. Psychiat. (Chic.)*, 1963, 8: 461-474.
- KURAMOCHI, H. and TAKAHASHI, R. Psychopathology of LSD intoxication. *Arch. gen. Psychiat. (Chic.)*, 1964, 11: 151-161.
- LEGASSICKE, J., ASHCROFT, G. W., ECCLESTON, D., EVANS, J. I., OSWALD, I. and RITSON, E. B. The clinical state, sleep and amine metabolism of a tranlycypromine ("Parnate") addict. *Brit. J. Psychiat.*, 1965, 111: 357-364.
- MANDELL, M. P., MANDELL, A. J. and JACOBSON, A. Biochemical and neurophysiological studies of paradoxical sleep. In J. WORTIS (Ed.), *Recent advances in biological psychiatry*. Plenum Press, New York, 1965, 7: 115-122.
- MATSUMOTO, J. et JOUVET, M. Effets de réserpine, DOPA et 5-HTP sur les deux états de sommeil. *C. R. Sec. Biol. (Paris)*, 1964, 158: 2137-2140.
- MATSUZAKI, M., TAKAGI, H. and TOKIZANE, T. Paradoxical phase of sleep: its artificial induction in the cat by sodium butyrate. *Science*, 1964, 146: 1328-1329.
- MONROE, R. R. and HEATH, R. G. Effects of lysergic acid and various derivatives on depth and cortical electrograms. *J. Neuropsychiat.*, 1961, 3: 75-82.
- MONROE, R. R., HEATH, R. G., MICKLE, W. A. and LLEWELLYN, R. C. Correlation of rhinencephalic electrograms with behavior. *Electroenceph. clin. Neurophysiol.*, 1957, 9: 623-642.
- OSWALD, I. Some psychophysiological features of human sleep. In K. AKERT *et al.* (Eds.), *Progress in brain research. Vol. 18. Sleep mechanisms*. Elsevier, Amsterdam, 1965: 160-169.
- OSWALD, I. and PRIEST, R. G. Five weeks to escape the sleeping-pill habit. *Brit. med. J.*, 1965, 2: 1093-1099.
- OSWALD, I. and THACORE, V. R. Amphetamine and phenmetrazine addiction, physiological abnormalities in the abstinence syndrome. *Brit. med. J.*, 1963, 2: 427-431.
- RECHTSCHAFFEN, A. and MARON, L. The effect of amphetamine on the sleep cycle. *Electroenceph. clin. Neurophysiol.*, 1964, 16: 438-445.
- RINKEL, M., DESHON, H. J., HYDE, R. W. and SOLOMON, H. C. Experimental schizophrenia-like symptoms. *Amer. J. Psychiat.*, 1952, 108: 572-578.
- ROFFWARG, H. P., MUZIO, J. N. and DEMENT, W. C. Ontogenetic development of the human sleep-dream cycle. *Science*, 1966, 152: 604-619.
- SCHWARZ, B. E., BICKFORD, R. G. and ROME, H. P. Reversibility of induced psychosis with chlorpromazine. *Proc. Mayo Clin.*, 1955, 30: 407-417.
- TOYODA, J. The effects of chlorpromazine and imipramine on the human nocturnal sleep electroencephalogram. *Folia psychiat. neurol. jap.*, 1964, 18: 198-211.
- VIMONT-VICARY, P. *La suppression des différents états de sommeil*. Thèse de Médecine, Université de Lyon, 1965.
- WEBB, W. B. and AGNEW JR., H. W. Sleep: effects of a restricted regime. *Science*, 1965, 150: 1745-1747.
- Reference: MUZIO, J. N., ROFFWARG, H. P. and KAUFMAN, E. Alterations in the nocturnal sleep cycle resulting from LSD. *Electroenceph. clin. Neurophysiol.*, 1966, 21: 313-324.