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# DRUG INDUCED STATES OF CNS EXCITATION: A THEORY OF HALLUCINOSIS

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## I. INTRODUCTION

It is obvious from the discussions during this meeting that evaluation of drug efficacy is difficult. The simplest technique involves administering various doses of a drug and observing the resultant gross behavior. Inherent in this approach is an inbred bias which most observers seem to maintain, namely, that when a subject is less active or lies down and is quiet, he is depressed. Further, if one adds to this the finding that the subject is unresponsive, then one is even more convinced that the subject is depressed. For many years, pharmacologists have utilized this incorrect type of observation and added the loss of the righting reflex as a further indication of depression. We have recently observed that drugs which induce CNS excitation, *i.e.*, cataleptoid and epileptoid states, can likewise induce an appearance of depression with a loss of the righting reflex (Winters and Spooner, 1965*a,b;* Marcus *et al.*, 1967; Winters, 1967) (Fig. 1).

It was obvious that better techniques were required in order for us to assess the state of the CNS following drugs. The technique which we now utilize involves an assessment of brain activity by examining the gross behavior, cortical and subcortical EEG, auditory and visual averaged evoked responses and multiple unit activity in the midbrain reticular formation. Utilizing these techniques, characteristic changes were noted for each control state, *e.g.*, wakefulness, slow wave sleep and rhombencephalic sleep (RPS or paradoxical sleep) (Figs. 2, 3, and 4), and following drug induced states

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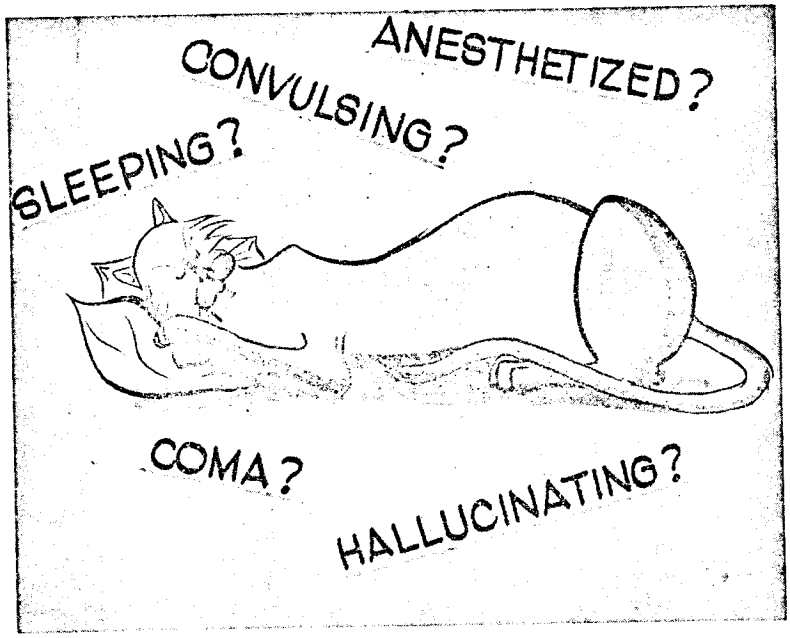


FIG. 1. Cartoon characterization of possible misinterpretations of CNS activity when behavioral manifestations are the only criteria assessed.

of CNS depression and excitation in the chronic cat with brain and muscle electrodes implanted (Winters, 1964; Winters, *et al.*, 1967*b;* Mori *et al.*, 1967).

## II. CONTINUUM OF STATES

On the basis of studies with various CNS excitatory agents, a progression of CNS excitation has been proposed (Winters *et al.*, 1967*a;* Winters, 1968). All the agents examined have the same general initial EEG and behavioral patterns, and differ only in the degree of progression. The least active CNS excitant agents induce only the initial phases of the progression (Fig. 5); for example, 2 to 8 mg/kg of *d*-amphetamine induces only the initial desynchronization and motor excitability; 50 to 100 $\mu$g/kg of LSD-25 induces desynchronization followed by intermittent hypersynchrony; 25 mg/kg of mescaline and 80 to 90% nitrous oxide induce desynchronization, intermittent and then continuous hypersychrony associated with bizarre postures and inappropriate behavior; 10 to 15% diethyl ether similarly induces

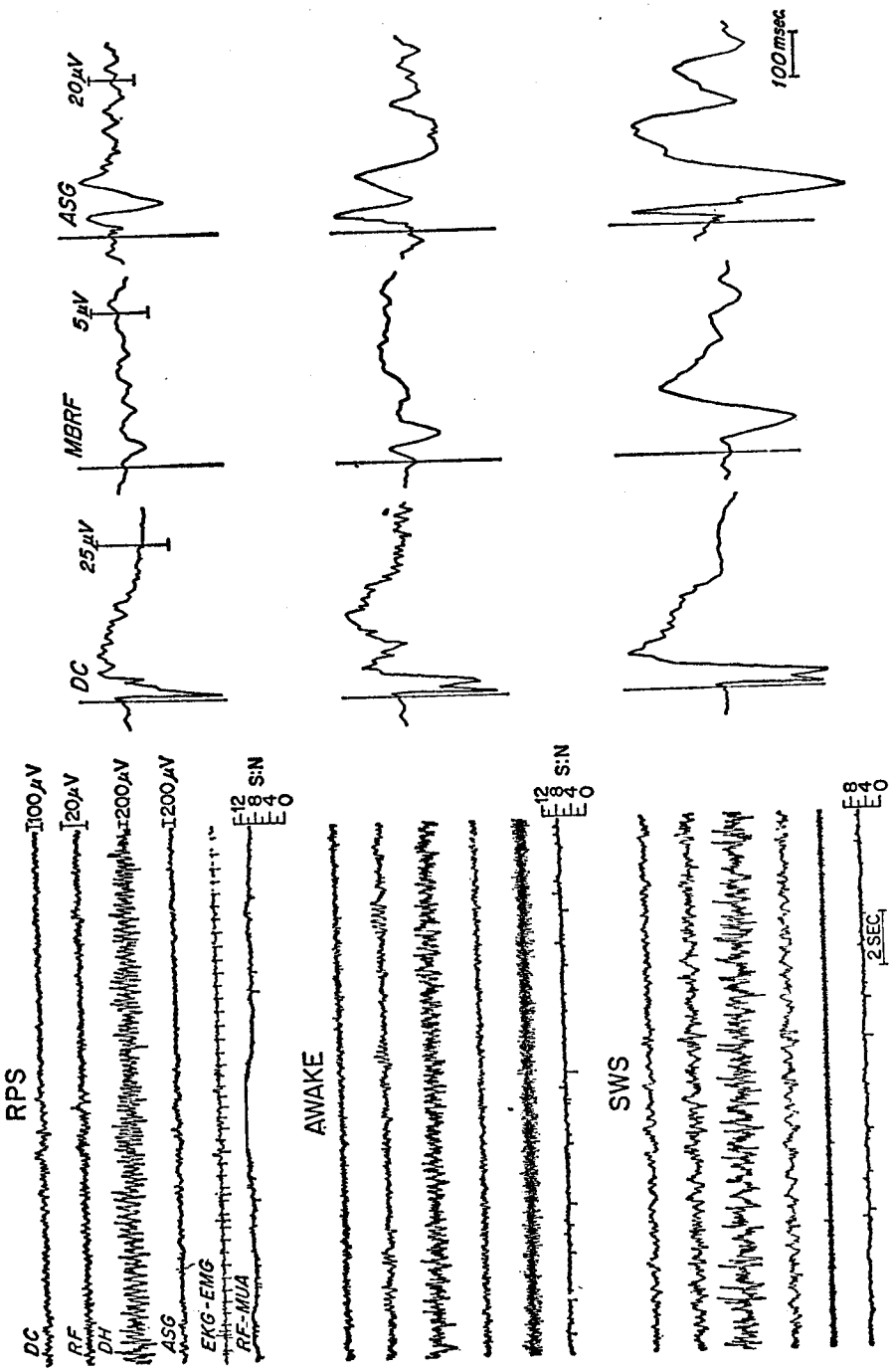


FIG. 2. Comparison of EEG (*A*) and auditory evoked response (*B*) during rhombencephalic sleep (RPS), awake, and slow wave sleep (SWS). The leads are as follows: dorsal cochlear nucleus (*DC*), midbrain reticular formation (*RF*), dorsal hippocampus (*DH*), anterior suprasylvian gyrus (*ASG*), electrocardiogram—electromyogram (*EKG-EMG*), and reticular multiple unit activity (*RF-MUA*). The signal-to-noise level scale (*S:N*) is given in units equal to the level obtained with a 10 K ohm resistor at the input. (From Winters *et al.*, 1967*b*).

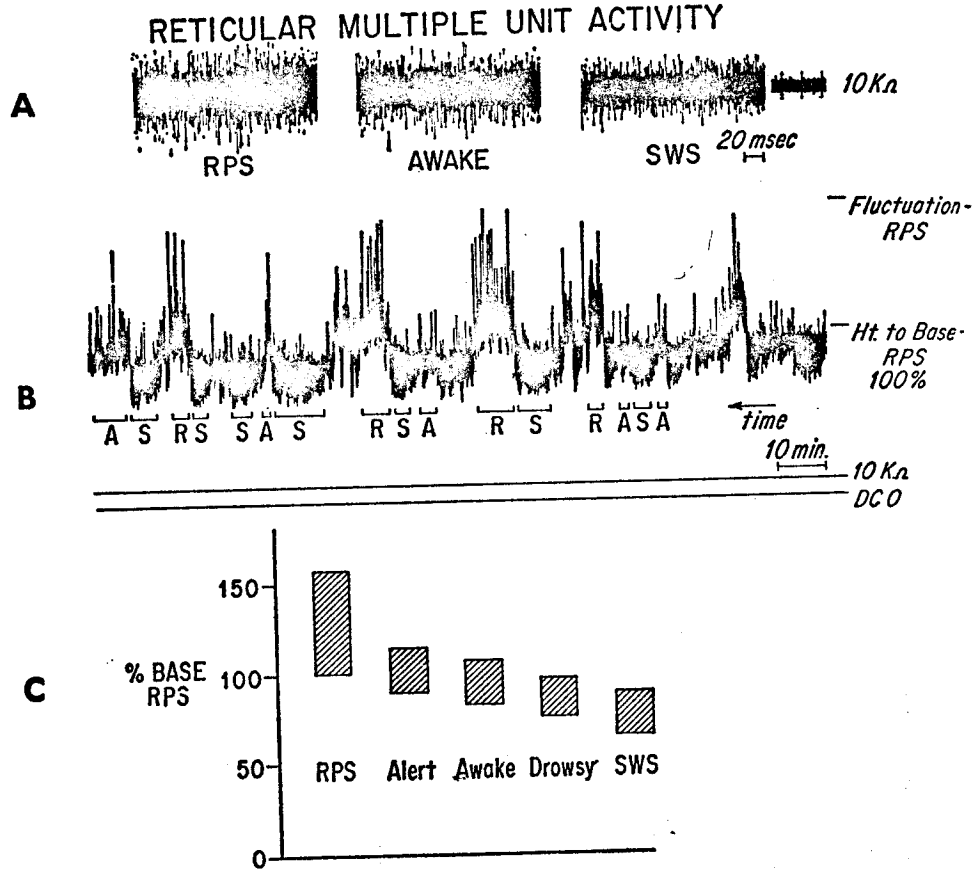


FIG. 3. Comparison of the reticular multiple unit activity during rhombencephalic sleep (RPS in **A** and **C**; R in **B**), awake states (**A** in **B**), and slow wave sleep (SWS in **A** and **C**; S in **B**).

**A**: Oscilloscope tracing of multiple unit activity. Note the change in the width of the envelope during each state. System noise level (10 K ohm resistor at input) is shown at right.

**B**: Amplitude demodulation of the unit envelope recorded on a strip chart recorder. The lowest line (DC 0) represents the system balanced to zero, the 10 K ohm line represents the system noise level with 10 K ohms at the input. Changes in basal unit activity are measured as the distance from the base of the units tracing to the 10 K ohm line. The fluctuation is the width of the excursion from the basal level to the peaks. Bracketed areas represent states of wakefulness and sleep as verified by EEG and gross behavior.

**C**: Represents the basal height and fluctuation of unit activity as measured from the amplitude demodulated data and expressed as percent of the basal rhombencephalic sleep. (From Winters *et al.*, 1967*b*).

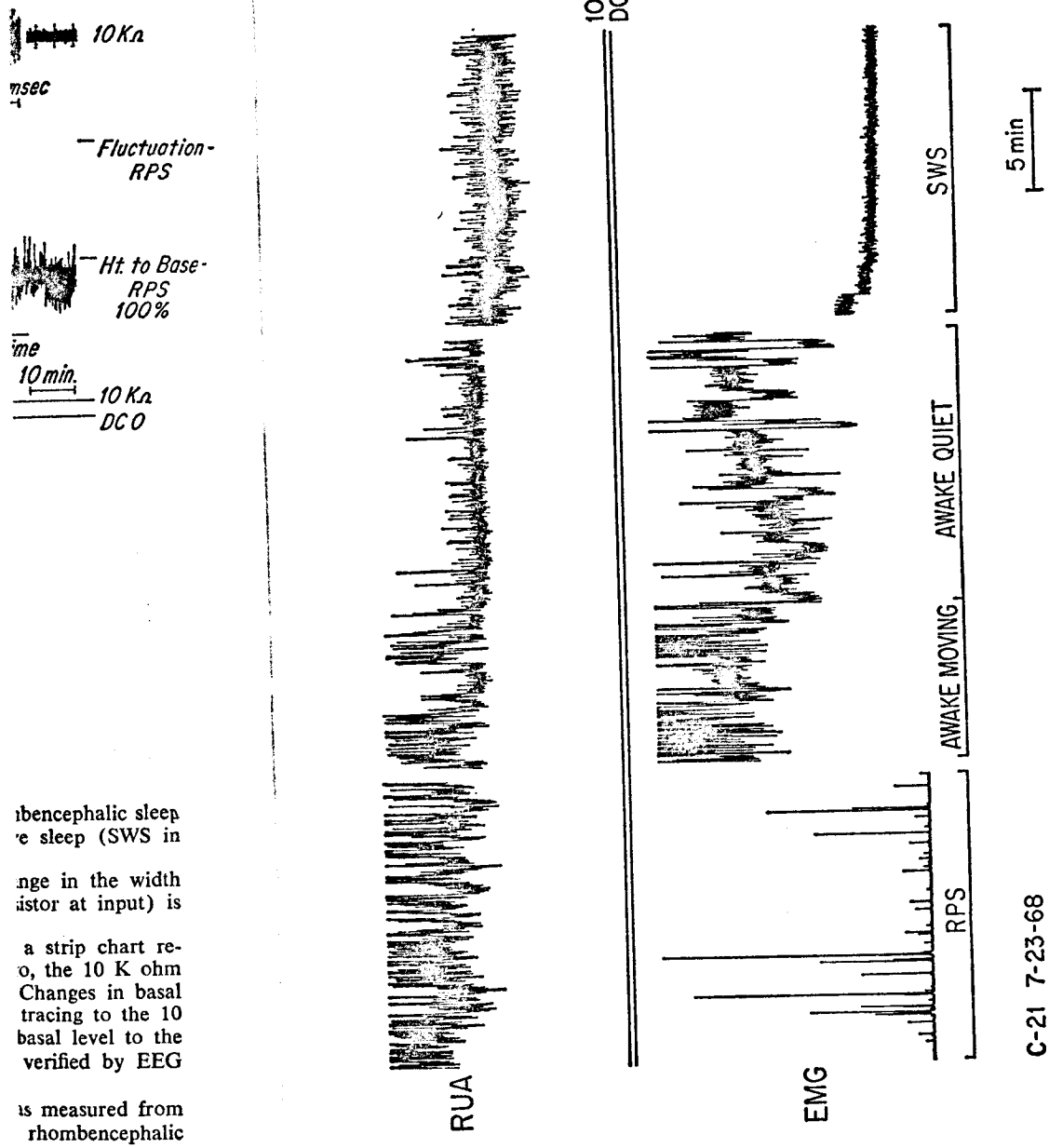


FIG. 4. Recordings of the amplitude demodulated signals of the midbrain reticular formation unit activity (RUA) and EMG. The RUA and EMG are recorded during the control states of RPS, wakefulness, and SWS. See also Figs. 2 and 3.

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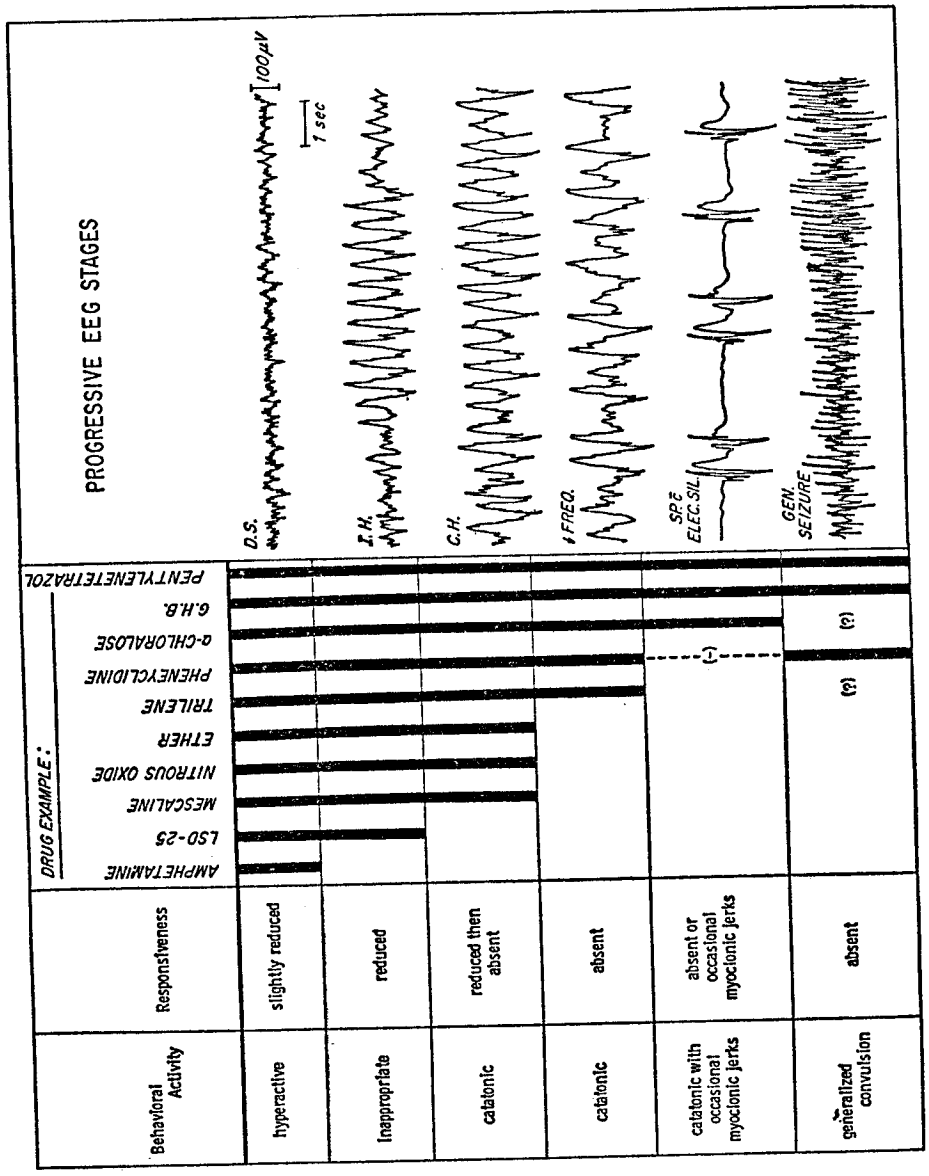


FIG. 5. Behavioral activity, responsiveness, EEG stages following the progression of effects induced by various drugs. Desynchronization (*D.S.*), intermittent hypersynchrony (*I.H.*), continuous hypersynchrony (*C.H.*), reduced frequency of hypersynchrony (↓ *FREQ.*), spikes with electrical silence (*SP. c ELEC. SIL.*), and generalized seizure (*GEN. SEIZURE*). Spikes with electrical silence rarely noted following phencyclidene were not observed in our studies. (From Winters *et al.*, Wisc. Med. J., *66:* 299–303, 1969).

the initial progression up to continuous hypersynchrony and then induces the characteristic EEG and behavioral patterns of anesthesia; 2 to 8 mg/kg of phencyclidine, 500 to 800 mg/kg of gamma-hydroxybutyrate and 20 mg/kg of pentylenetetrazol transcend the initial phases and induce the total progression to generalized seizure.

While the initial state (Fig. 6) is clearly a behavioral and electrical psychomotor stimulation, the next three induced states are less clearly defined. These states are characterized by inappropriate behavior coupled with abnormal postures indicative of "hallucinatory" behavior. Obviously one cannot be certain that this induced state in cats is an hallucinatory phenomenon similar to that which occurs in man; however, this behavior is pronounced in the cat following agents such as LSD, mescaline and psilocybin which induce profound hallucinatory actions in man. In addition to the induction of hallucinatory behavior in man, these agents induce 2.5 to 3 cps hypersynchronous EEG wave patterns during the hallucinatory state in man (Heath and Mickle, 1960). Further, Adey *et al.* (1962) demonstrated that LSD induced an apparent intermittent loss of contact with the environment at the same time that the hypersynchronous 3 cps EEG waves appeared in the EEG of cats performing in a T-maze. Thus, there is strong presumptive evidence that the induced state of intermittent and continuous hypersynchrony, coupled with inappropriate behavior and inappropriate postures, represent an *hallucinoid* state in the cat. For convenience, I would like to refer to these states as hallucinoid with the clear realization that this is entirely speculative in the cat.

LSD usually induced hallucinations in man in which the subject is aware of the experience. Since the EEG (Fig. 7) is characterized by intermittent bursts of hypersynchronous activity during the LSD induced state, the periodic episodes of desynchronization between hypersynchrony may indicate that the subject returns intermittently to an excited, non-hallucinating, alert state. This pattern of alternating hypersynchrony and desynchrony we will refer to as *hallucinatory A* (Fig. 7). The intermittent appearance of the alert EEG may indicate that during LSD, as in the studies reported above by Adey *et al.* (1962), the hallucinating experience is intermittent, thus the subject is unaware of the experience. The EEG pattern during the state induced by mescaline, nitrous oxide, ether and phencyclidine is one of continuous hypersynchrony (Fig. 8) (Winters *et al.*, 1968). The subjects hallucinate following these agents but are apparently not aware that they are in an abnormal state and usually have some later recall; we shall call this state *hallucinatory B* (Fig. 7). We postulate that the unawareness of subjects during this induced state may be a manifestation of the induced continuous hypersynchrony, with no return to the desynchronized EEG patterns as was characteristic following

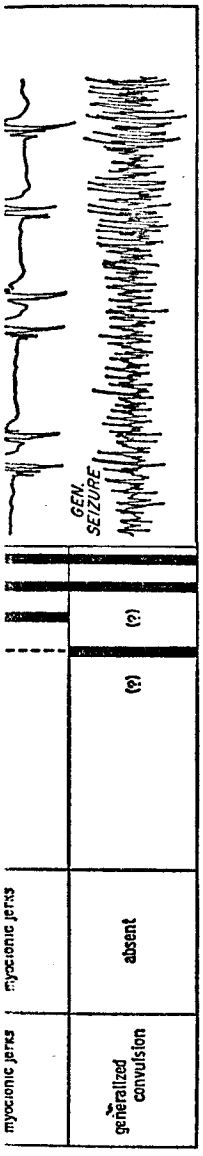


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FIG. 6. EEG records from a cat during rhombencephalic sleep (RPS), wakefulness (AWAKE), slow wave sleep (SWS) and following 50 µg/kg i.p. LSD-25. Medial geniculate (*MG*), median suprasylvian gyrus (*MSS*), pontile reticular formation (*PRF*), dorsal hippocampus (*DH*), median forebrain bundle (*MFBB*) and electrocardiogram/respiration (*EKG*). (From Winters *et al.*, 1967*a*).

EXCITE

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B

PRESEIZU

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SEIZURE

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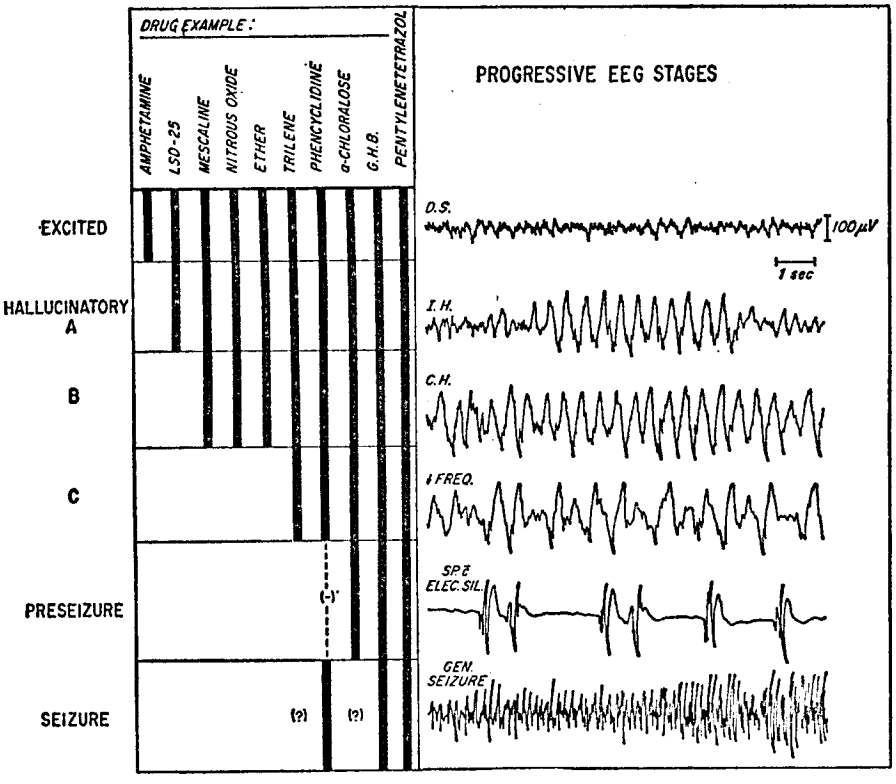



FIG. 7. Representation of the division of the continuum of CNS excitation. (See Fig. 5 for explanations of abbreviations.)

FIG. 6. EEG records from a cat during rhombencephalic sleep (RPS), wakefulness (AWAKE), slow wave sleep (SWS) and following 50 μg/kg i.p. LSD-25. Medial geniculate (*MG*), median suprasylvian gyrus (*MSS*), pontile reticular formation (*PRF*), dorsal hippocampus (*DH*), median forebrain bundle (*MFBB*) and electrocardiogram/respiration (*EKG*). (From Winters *et al.*, 1967*a*).

LSD. During the transition to reduced frequency hypersynchrony induced by phencyclidine, gamma-hydroxybutyrate and pentylenetetrazol, which we refer to as *hallucinatory C* (Fig. 7), the patients apparently are completely unaware that they are hallucinatory, are not rousable and have no recall. Of interest is the finding that the hallucinatory C phase is utilized in anesthesiology as a "pseudo" state of general anesthesia. For example, both phencyclidine and gamma-hydroxybutyrate have been reported to be anesthetic agents (Winters *et al.*, 1967*a*). Our interpretation of this would be that these agents apparently meet the major requirements of an anesthetic agent, *i.e.*, loss of responsiveness and amnesia. It is of interest that both gamma-hydroxybutyrate and phencyclidine traverse the continuum and induce generalized seizures (Winters and Spooner, 1965*a,b;* Winters *et al.*, 1967*a*) in a manner similar to the progression induced by pentylenetetrazol (Fig. 9). The hal-

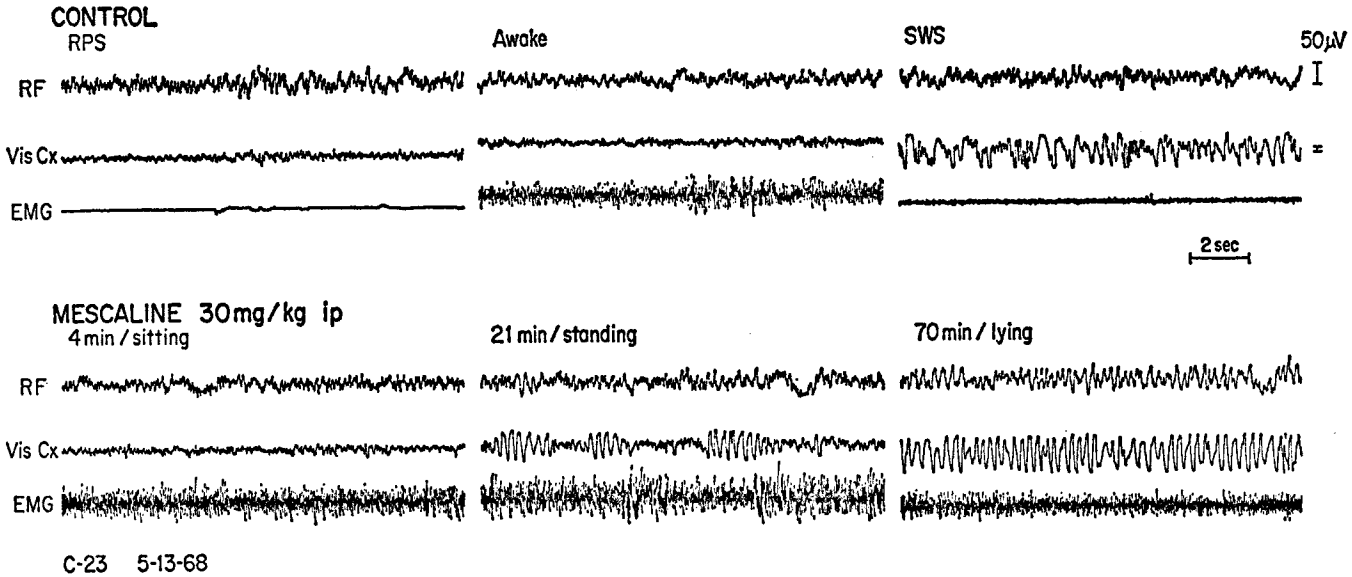



FIG. 8. EEG comparison recorded during control (RPS, Awake, SWS) and following mescaline, 30 mg/kg i.p. *Vis Cx* = visual cortex. (See also Fig. 2.)

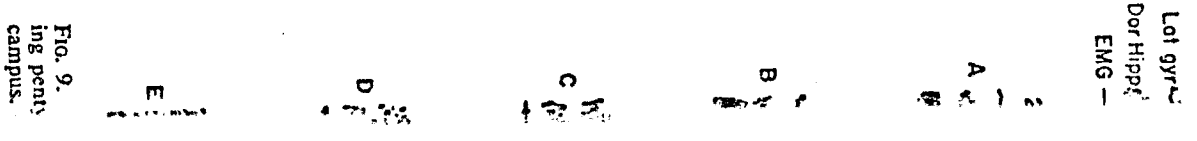



FIG. 9. ing pent campus.

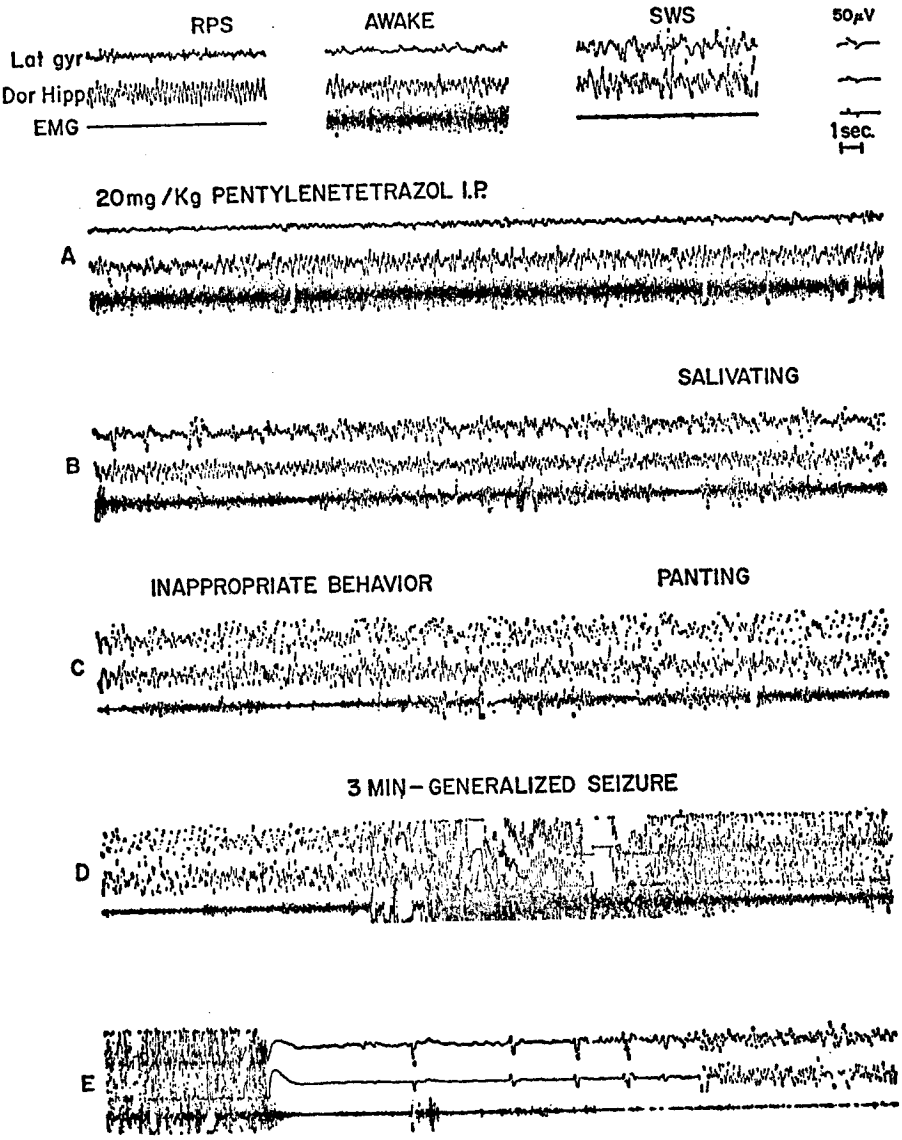



FIG. 9. EEG comparison recorded during control (RPS, AWAKE, SWS) and following pentylenetetrazol, 20 mg/kg i.p. *Lat. gyr* = lateral gyrus, *Dor Hipp* = dorsal hippocampus. (See also Fig. 2.)

FIG. 8. EEG comparison recorded during control (RPS, Awake, SWS) and following mescaline, 30 mg/kg i.p. *Vis Cx* = visual cortex. (See also Fig. 2.)

lucinoid activity preceding the generalized seizure activity induced by these convulsant agents may be similar to the aura noted clinically prior to pentylenetetrazol or spontaneous grand mal seizures.

## III. A THEORY OF HALLUCINOSIS

A neuropharmacological approach to the problem of studying the basic etiology of psychosis would be to utilize drugs which induce a state identical with the clinical disease. Thus far the search for suitable drugs has been deemed unsuccessful since hallucinogenic agents like LSD induce mainly visual aberrations, whereas psychotic episodes usually involve auditory or multisensory hallucinations.

In an attempt to develop a working hypothesis of psychosis the relationship between the auditory and visual system during acute drug induced states of "hallucinatory" activity was examined. The basic question asked was: "How are the electrical responses of various brain areas altered by hallucinatory drugs, and is there a unifying theory capable of explaining these phenomena?"

We will focus attention mainly on the intermediate states of excitation described in our continuum model characterized by hallucinoid activity.

Some of the agents which induce hypersynchrony in our studies have a history of psychedelic usage; some since the early 1800's, *i.e.*, ether (frolics) and nitrous oxide (laughing gas parties), mescaline since the late 1800's, while LSD and phencyclidine have been utilized within the past few years.

### *A. Auditory system*

Comparison of the auditory evoked response (AER) during the natural states of wakefulness and sleep (Fig. 2) demonstrates that the potential recorded at the dorsal cochlear nucleus, midbrain reticular formation and the association cortex is largest during slow wave sleep (SWS), smaller when the animal is awake and smallest during RPS. A comparison of the reticular unit activity with these findings indicates an inverse correlation, *i.e.*, the level of unit activity is lowest during slow wave sleep and highest during RPS. Since the level of reticular neuronal activity is directly correlated with the level of arousability, *i.e.*, wakefulness and sleep, it appears likely that this level of neuronal activity is likewise related to the degree of modulation which the reticular system exerts on the auditory sensory input system

(Winters *et al.*, 1967*b*). The model states that when reticular unit activity is reduced there is less modulation exerted at the peripheral input system; therefore, the transmitted sensory signal is larger; thus the evoked response is larger. Conversely, when the animal is highly alert, reticular unit activity is elevated, modulating activity is elevated, the transmitted sensory input signal is reduced and the evoked response is smaller.

Those drugs which induce desynchronization, intermittent hypersynchrony and early continuous hypersynchrony (*i.e.*, amphetamine, LSD, nitrous oxide, mescaline and moderate doses of gamma-hydroxybutyrate, phencyclidine or pentylenetetrazol) all induce a slight fall in the amplitude of the evoked responses as compared with the awake control. During this activity the reticular unit activity is high, the animals are markedly aroused and sensory modulation is increased; thus, there is an apparent reduction in the amplitude of the sensory input, and evoked responses are reduced.

During the later phase of the hypersynchronous activity, the animal does not arouse either electrically or behaviorally, the evoked potentials are slightly larger than controls and the basal level of unit activity begins to fall, but the units appear to fire in synchronous bursts. Since the arousal response disappears at the same time that this intermittent bursting of units occurs, it appears that the reticular unit activity has undergone a partial functional disorganization (Schlag and Balvin, 1963; Winters and Spooner, 1966), and while highly excitable, it exerts a reduced control over the level of arousal and sensory modulation (Figs. 10 and 11). As this functional disorganization becomes more profound, the EEG pattern changes to the spiking phase, and the bursting pattern of unit activity becomes more pronounced. At this time there is a more profound loss of reticular modulation, the sensory input becomes markedly elevated and the evoked response in all brain areas is enlarged (Fig. 12).

Reviewing the action of agents on the auditory system during the hallucinatory phase of action, it appears that those drugs which induce only intermittent hypersynchrony, *i.e.*, LSD, result in a reduction in the auditory evoked response, whereas the agents which induce a progression of action to continuous 2.5-1.5 cps hypersynchrony, *i.e.*, mescaline, nitrous oxide, ether, phencyclidine and gamma-hydroxybutyrate, can induce an augmentation of the auditory evoked response. This augmentation appears when the modulation of auditory input is reduced due to the functional disorganization of the reticular system (Fig. 10). Thus it appears that agents inducing 2.5-1.5 cps hypersynchronous activity may be useful tools for investigating states of auditory aberration more closely associated with the clinical symptoms of the psychotic hallucination.

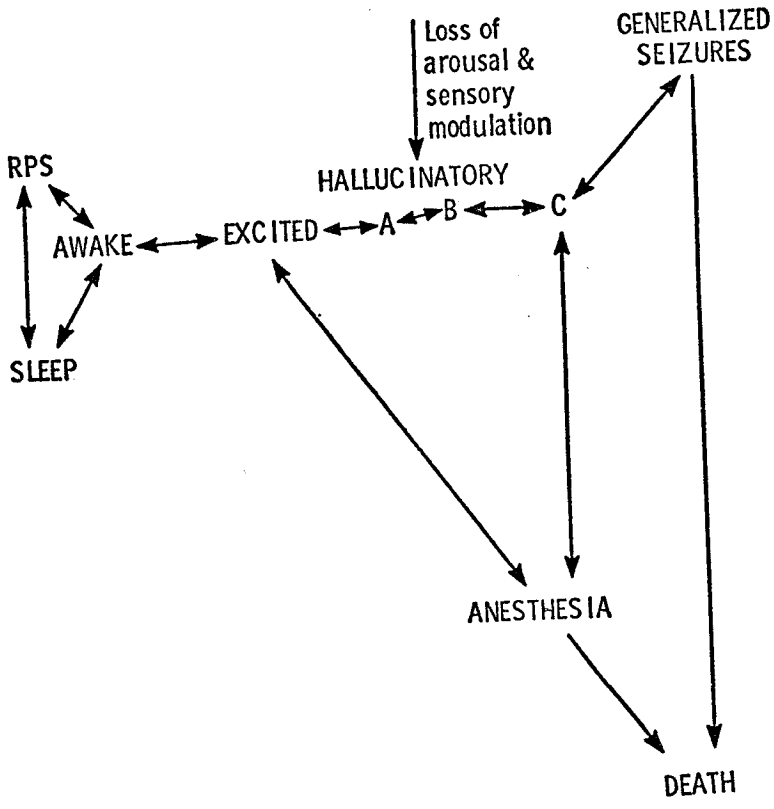



FIG. 10. A simplified representation of the continuum of states of CNS excitation and depression demonstrating the approximate position at which the loss of reticular control occurs.

GAMMA HYDROXYBUTYRATE
600 mg/kg ip

### *B. Modulation of sensory systems*

In order to clarify the dichotomy between drug induced hallucinatory states and those found in psychotic patients, the modulation control of various sensory inputs was examined during spontaneous and drug induced states, and a model was postulated (Winters and Spooner, 1965*a,b;* Winters, 1967; Winters, 1968). The model is based on the assumption that sensory inputs are directly controlled by a subcortical modulating system located in the midbrain reticular formation, and that the reticular system varies the level of modulation in accordance with the regulation of the state of arousal. The

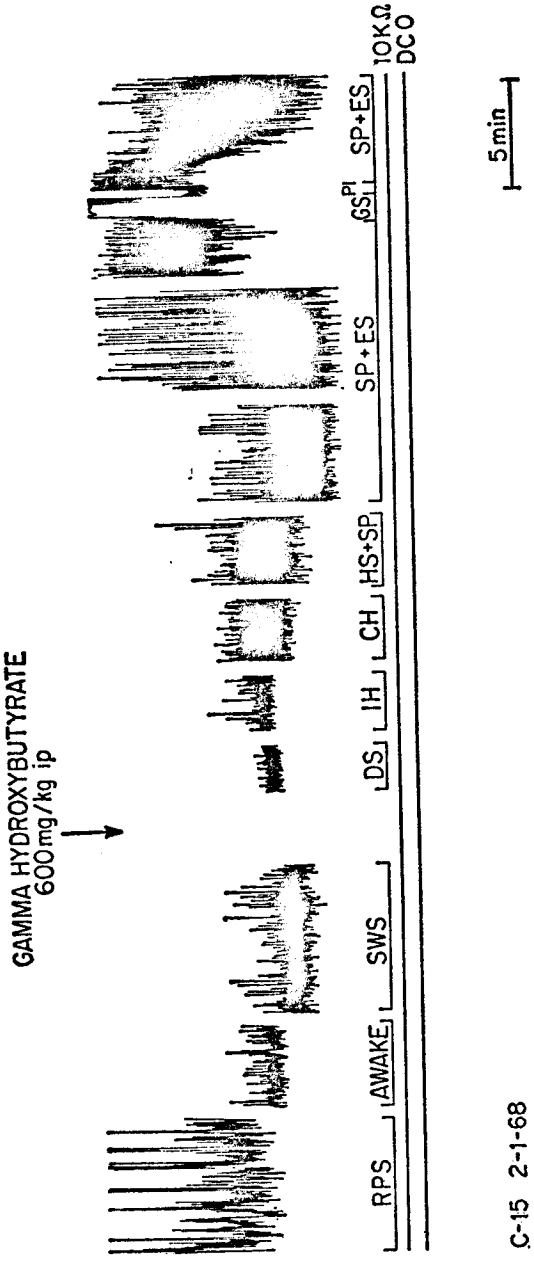



FIG. 11. Multiple unit activity of midbrain reticular formation recorded during the control states of RPS, AWAKE, and SWS, and following gamma-hydroxybutyrate, 600 mg/kg i.p. Desynchronized (*DS*); intermittent hypersynchrony (*IH*), continuous hypersynchrony (*CH*), hypersynchrony with spikes (*HS* + *SP*), spikes with electrical silence (*SP* + *ES*), generalized seizure (*GS*), postictal depression (*PI*). (See also Fig. 3.)
Hallucinatory *A*, *B* and *C* occur during *IH*, *CH*, and *HS* + *SP*, respectively.

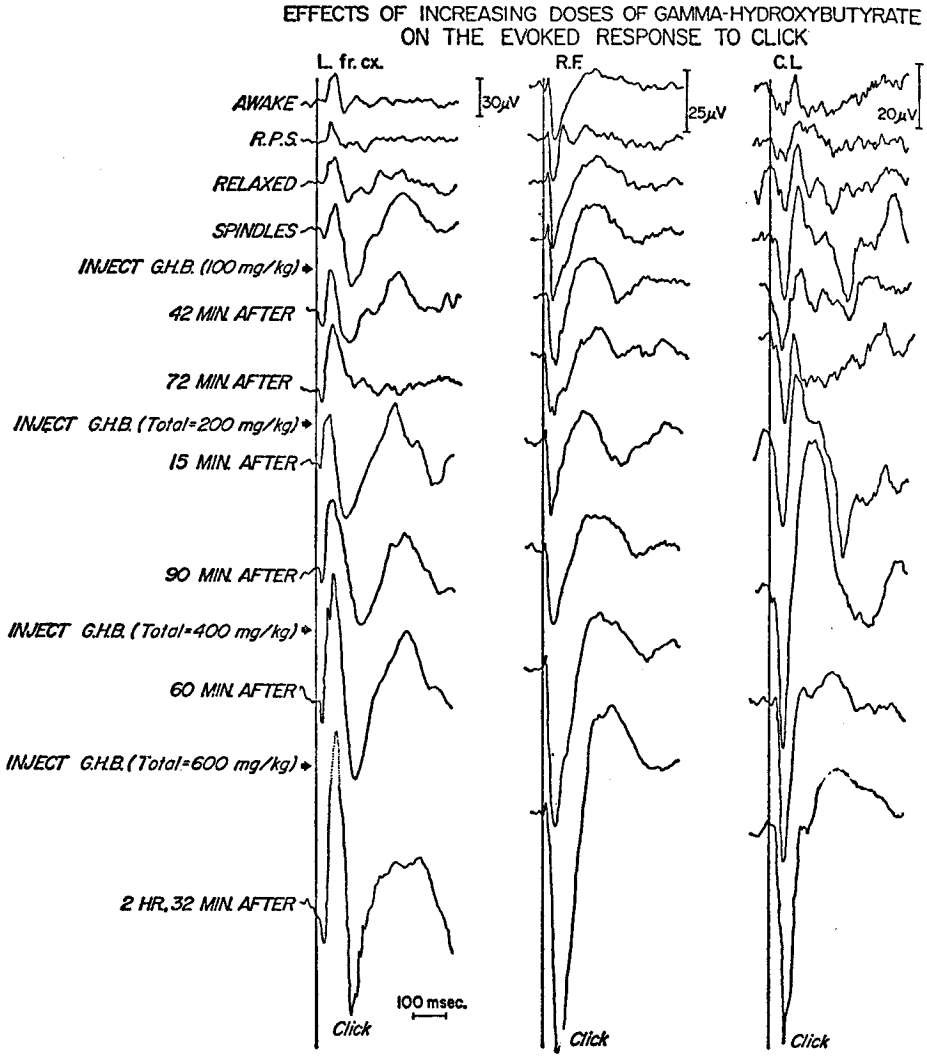



FIG. 12. Computed average of 40 clicks during increasing doses of gamma-hydroxybutyrate (G.H.B.). Frontal cortex (*L. fr. cx.*), midbrain reticular formation (*R.F.*), and centralis lateralis (*CL.*). The amplitude of the response markedly increases in all of the above leads as the dose of gamma-hydroxybutyrate is increased. (From Winters *et al.*, 1965*a*).

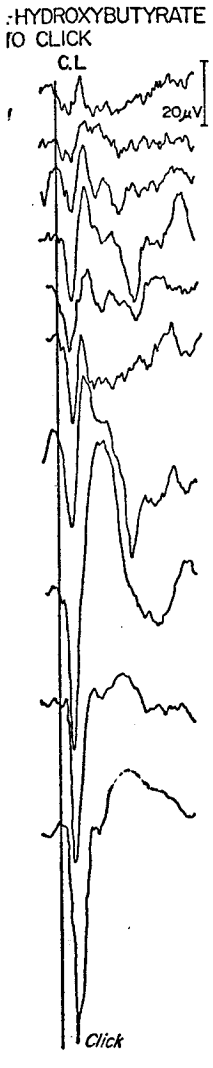
existence of an inhibitory system in the reticular formation which acts on the first synaptic relays within each of the classical afferent systems has been postulated previously. Killam and Killam (1958) suggest that this inhibitory system filters incoming information in order to control the priority level of incoming information. Scheibel and Scheibel (1962) have demonstrated that reticular neurons bifurcate and send ascending branches into the diencephalon and cortex and descending branches caudal as far as the receptors and spinal cord. Therefore, there appears to be anatomical evidence for the proposed modulatory system.

### C. Visual system

To understand better the role of LSD action on the visual system, studies paralleling those described for the auditory system were performed. Apter and Pfeiffer (1957) reported that the visual system activity induced by LSD starts in the retina and travels through visual pathways up to the visual cortex. They also describe clinical studies indicating that LSD does not induce hallucinations when administered to patients whose optic nerves were severed.

Visual hallucinations can be postulated to result from an abnormally large number of visual stimuli entering the CNS which overload the visual system, thus resulting in bizarre sensory manifestations. Evidence in favor of this premise is noted by the studies of Purpura (1956*a*, 1965*b*) which demonstrated an increase in the visual evoked response (VER) in both the lateral geniculate and cortex following LSD at the same time that the AER was reduced. Preliminary studies in our laboratory demonstrate that the VER is largest during wakefulness, smaller during SWS and smallest during RPS (Figs. 13 and 14). These findings are in agreement with Granit (1955) who demonstrated that reticular activation induces facilitated responsiveness of retinal cells. Thus the cat appears to demonstrate an *inverse* relationship between the level of reticular neuron activity and that of the auditory system activity, but a *direct* relationship between the visual system and the reticular system level of activity. The exception to this is noted during RPS since both auditory and visual responses are reduced during this state. It appears that during sleep the cat is an "auditory animal," while when awake he is a "visual animal," and during RPS both auditory and visual inputs are markedly reduced.

Following amphetamine, and during the initial desychronous activity induced by the more potent CNS excitant agents (*i.e.*, LSD, mescaline, nitrous oxide, ether, phencyclidine, gamma-hydroxybutyrate and pentylene-

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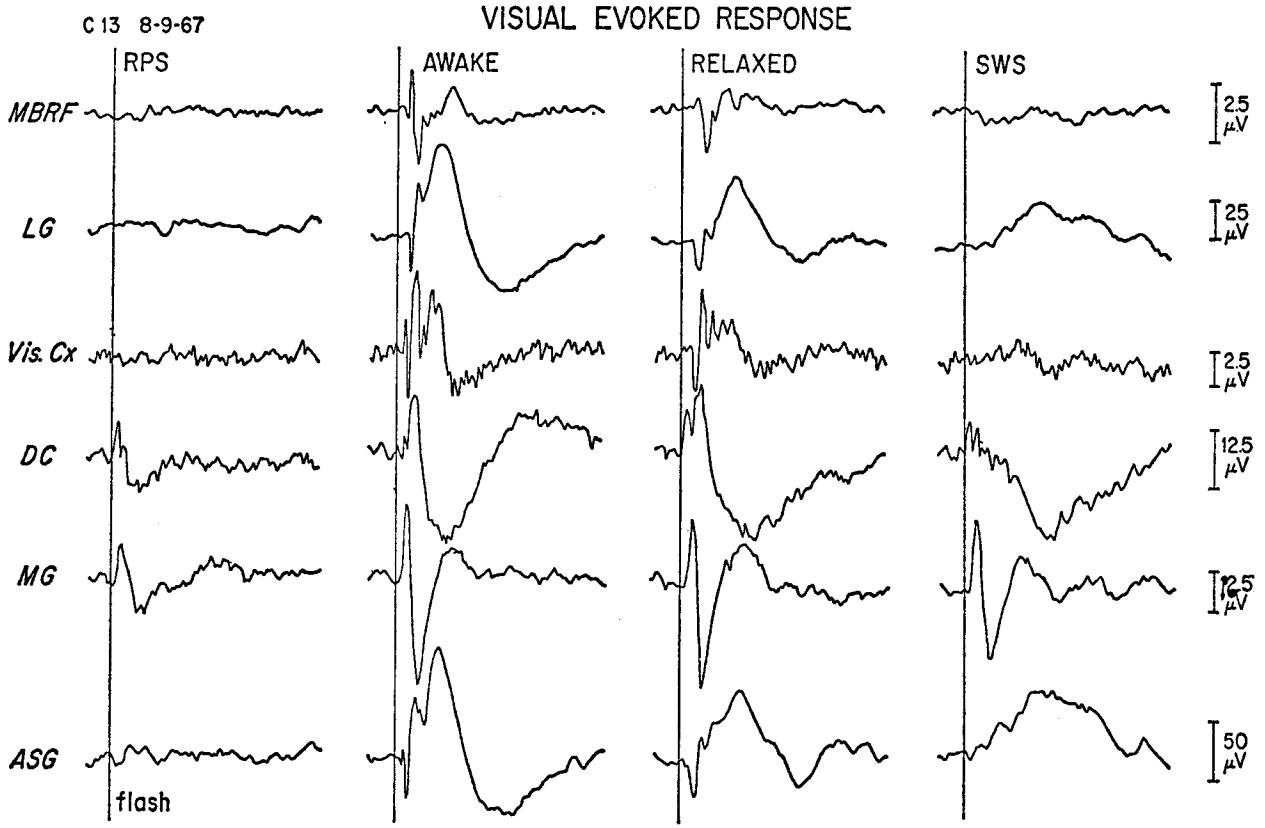


FIG. 13. Averaged visual evoked response recorded during the control states of RPS, AWAKE, RELAXED and SWS. Midbrain reticular formation (*MBRF*), lateral geniculate nucleus (*LG*), visual cortex (*Vis. Cx.*), dorsal cochlear nucleus (*DC*) medial geniculate nucleus (*MG*), and anterior suprasylvian gyrus (*ASG*). (See also Fig. 2.) (From Winters, 1968).

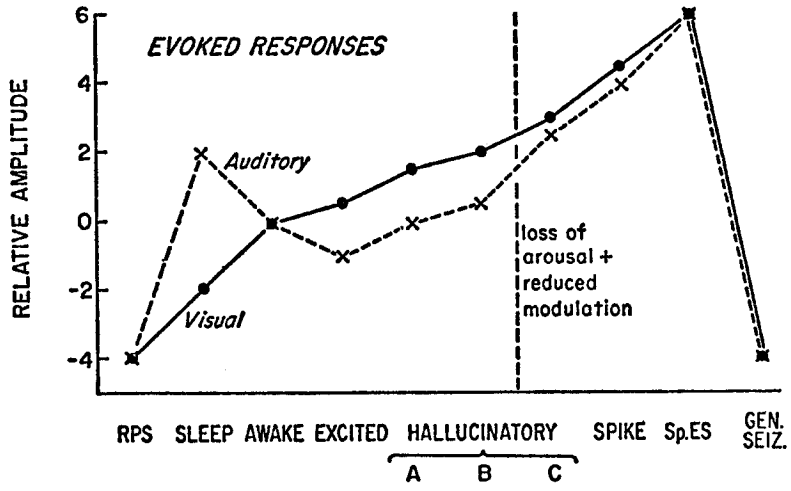


FIG. 14. Representation of the relative amplitude of the auditory and visual evoked response utilizing the effect of gamma-hydroxybutyrate as an example. The amplitude of the responses were normalized such that both auditory and visual responses are zero during the awake state. There is a loss of the arousal response and a reduction in modulation during the hallucinatory *B-C* stage. The modulation action is progressively reduced as the functional disorganization of the reticular formation progresses during spikes, spikes with electrical silence (*SP. ES*) and generalized seizure (*GEN. SEIZ.*).

tetrazol), the visual evoked response increases in size over the awake control. During the intermittent hypersynchronous activity (hallucinatory A), the visual evoked response is further enhanced, apparently to the point that abnormal amounts of visual information are transmitted within the CNS, resulting in the visual hallucinations. This state is characterized by an enlarged evoked response, elevated reticular unit activity and intermittent 2.5 cps hypersynchronous EEG bursts.

Following mescaline, nitrous oxide, ether, phencyclidine and gamma-hydroxybutyrate, and during the progression of increasing reticular functional disorganization (*i.e.*, 2.5-1.5 cps hypersynchrony, hallucinatory C) to spikes with electrical silence, there is a progressive increase in the VER reaching markedly enlarged response amplitudes during the latter phases.

It appears that the visual system, which has a high priority of action during the awake state, can be excessively activated to the point of disruption by overloading the input system during states of increased excitation induced by LSD. As the CNS excitation continues to the point of inducing a functional disorganization of the reticular formation modulation system, other sensory systems, such as the auditory system, begin to become functionally disrupted

FIG. 13. Averaged visual evoked response recorded during the control states of RPS, AWAKE, RELAXED and SWS. Midbrain reticular formation (*MBRF*), lateral geniculate nucleus (*LG*), visual cortex (*Vis. Cx.*), dorsal cochlear nucleus (*DC*) medial geniculate nucleus (*MG*), and anterior suprasylvian gyrus (*ASG*). (See also Fig. 2.) (From Winters, 1968).

due to a reduction in the modulation of these sensory systems; thus multisensory aberrations are induced.

Three points are relevant regarding the relationship of visual and auditory systems to reticular formation modulation of input signals (Fig. 14): (1) As evidenced by the amplitude of the evoked response, the asleep cat is an auditory animal and the awake cat is a visual animal. (2) As one progresses through the continuum as outlined, the AER is reduced and the VER is progressively increased through hallucinatory A and B. (3) During hallucinatory C the animal is no longer arousable, the AER begins to enlarge, and both AER and VER are markedly enlarged during the pattern of spiking with electrical silence. The increase in size of the AER during hallucinatory B and C and the loss of the arousal response correlates with the progressive increase in RUA. The pattern of firing during hallucinatory B begins to lose functional organization, and during hallucinatory C is essentially functionally disorganized, thus sensory inputs are no longer modulated and the AER increases.

Since the psychotic hallucination involves more than one modality, *i.e.*, auditory, visual, somatosensory, etc., perhaps an abnormality in the general modulation system in the reticular formation exists during this disease. The psychotic hallucination may be triggered by abnormally large numbers of sensory stimuli entering the CNS which would normally be inhibited at the peripheral sense organ. In psychosis or after LSD these stimuli can enter the CNS and overload one or more sensory systems, resulting in bizarre sensory experiences.

## IV. SUMMARY

To recount, we have postulated:

1. That there is a continuum of CNS excitatory states.
2. That hallucinatory activity is a part of this continuum, falling between motor excitation on one side and either general anesthesia or convulsions on the other.
3. That visual hallucinations occur prior to multisensory aberrations, presumably due to the higher priority of the visual system during states of increased excitation.
4. That hallucinations are manifestations of abnormally increased amounts of sensory input.
5. That multisensory aberrations probably occur as a result of a loss of reticular modulation of these sensory systems.
6. That psychosis may be a disorder of modulation control.

The psychotic state appears to fall in the general range of hallucinatory B. As the modulatory control of the prepsychotic becomes increasingly more disrupted, the total environment of the patient becomes more and more bizarre. Thus the lack of a clean symptomatology in schizophrenic states may be a function of the patient's individuality, past experiences and rate of change in sensory control.

It should be noted that the theories proposed above represent only a working hypothesis which serves as an aid in the design and performance of studies of these phenomena. Our strategy has been to test various aspects of the model in the cat, relate the conclusion to man and alter the model as necessary. This process will continue until a final model arises that can pass all of the critical tests and improve our understanding of the basic processes involved in disease states and the therapeutic rationale of effective controlling agents.

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## *DISCUSSION*

DR. DEMENT: Is the multiple unit absolutely foolproof? How do you know that you really are dealing with anatomical units?

DR. WINTERS: We can't say we are recording only unit firing. What we say is that the biological activity which we are assessing has a band pass between 500 cycles and 2.5 KC.

DR. DEMENT: And so, it might just be some curious condition that is *not* necessarily related to many units firing.

DR. WINTERS: We don't know any more than the electrophysiologist who puts a microelectrode into a cell. We probably know a little less, but all we can say is that the spikes have a one msec duration. They look very much like a spike which one sees with microelectrode techniques. It's related to biological activity because it disappears when we poison the animal with anesthetic agents, and it has a relation to behavioral states.

DR. GESSNER: In terms of your working model here, as I understand it, pentylenetetrazol does not cause hallucinations in man.

DR. WINTERS: Yes it does. Pentylenetetrazol induces a profound hallucinatory phase with intermittent and continuous EEG hypersynchrony followed by hypersynchrony of reduced frequency prior to the generalized seizure.

DR. GESSNER: If you administer it to man there is no record of it being hallucinatory?

DR. WINTERS: My understanding is that pentylenetetrazol seizures are preceded by a hallucinatory aura.

DR. DIAMOND: I would support that. Metrazol produces significant psychic changes in subconvulsive doses. These auras of terror, confusion and sense of doom are frequently so intense that psychiatrists appear to have grown much more hesitant to use the drug.

A VOICE: Operationally what you are calling the hallucinatory phase is EEG hypersynchrony. Was it intermittent to continuous hypersynchrony picked up in different brain areas?

DR. WINTERS: Yes.

A VOICE: That's all you really know about hypersynchrony?

DR. WINTERS: We see intermittent hypersynchrony associated with the behavioral syndrome which is associated with inappropriate posture and behavior in the animal, and we call it hallucinatory behavior.

We fully realize the fact that one cannot prove that a cat is hallucinating, but behaviorally he certainly looks as if he is. This behavior always appears when we see the electrical phenomena described. On the basis of the behavioral and associated electrophysiological records, we postulate the existence of three states, hallucinatory A, B, and C.

A VOICE: Would the changes in amplitude noted for the visual evoked response occur at the receptor level?

DR. WINTERS: The modulation is probably mainly at the receptor level.

DR. TEUBER: You mean there is no control over the pupil in these experiments?

DR. WINTERS: That's right. The eyes are closed when the animal is asleep. We are just reporting the phenomenon as it occurs.

DR. TEUBER: It might reflect changes in the pupils, eyes, or in general muscle tension.

DR. WINTERS: Right.

DR. DOMINO: Would you agree that the change is peripheral?

DR. WINTERS: Yes. I think it is mainly peripheral, but induced via a central control mechanism.

DR. DIAMOND: What is the magnitude of the visual stimulus as compared to the auditory?

DR. WINTERS: The auditory stimulus is 10 db above noise; we have not quantitated it.

DR. DIAMOND: A global stimulus?

DR. WINTERS: Yes. The visual and auditory stimuli were set arbitrarily at levels which enabled us to obtain responses which were above threshold and which changed significantly with changes in state.

DR. UNGER: You don't think these stimulus parameters affect the magnitude of the auditory or visual response? Do you think that you can just make a flat statement that this is an auditory animal, not a visual one, independent of parameters of the input?

DR. WINTERS: I'm not sure that it is possible to equalize two different input systems in a meaningful way. However, the data in Fig. 14 were normalized such that the amplitudes of the evoked response were the same when the animal was awake. I don't see why it is so difficult to assume that when an animal goes to sleep his auditory system is a more protective sensory input system for him than is his visual system, and that when he is awake his visual system is a more protective sensory system than is his auditory system.

DR. UNGER: On what basis do you infer that LSD induces mainly visual hallucinations? Which cat experiment showed this? We can get auditory hallucinations with LSD.

DR. WINTERS: I was referring to clinical studies and trying to explain the clinical data on the basis of our model and data obtained in the cat. My impression is that LSD induces mainly visual hallucinations in man.

DR. UNGER: On occasion, auditory hallucinations under LSD do occur, if you want to call them hallucinations. However, man appears to be a visual animal.

DR. DOMINO: Dr. Winters, you have stuck your neck out, but frankly I am glad you did. You have taken a great deal of very complex electrophysiological data and tried to make some sense out of it. I might disagree here and there with your scheme; still, you have been very courageous and I personally

would like to say thank you for doing it, because you are making me do a lot of thinking about what is going on.

For example, a subject on LSD who has a hallucinogenic episode develops theta waves. That seems to fit with your cat story.

DR. WINTERS: I might mention that fifteen years ago Heath recorded similar types of EEG patterning with electrodes implanted in brains of men, *i.e.*, hypersynchronous activity following psilocybin, LSD, and mescaline. This was associated with hallucinatory behavior. He reported further that schizophrenics during acute exacerbations have hypersynchronous activity and septal spiking, whereas, during regression, this activity subsides. These studies were looked upon with distrust for a long time. However, studies of two schizophrenic patients with implanted electrodes at U.C.L.A. have confirmed Heath's findings.

DR. DOMINO: I was a little surprised that you would take the position that the decreased response in the visual system during slow wave sleep was a strictly peripheral phenomenon. Do you have data to support that?

DR. WINTERS: I didn't say it was strictly peripheral. I didn't want to get into an argument about the cat's eyes being closed, thus there is less illumination on the retina, and so on. More important is the finding that going from the point of wakefulness up the continuum of CNS excitation, reticular activation facilitates unit firing of the retina, and would indicate a central control of the input system such that arousal induces facilitation (Granit, 1955).

DR. STEIN: Could we return to someone's previous question about where dreaming fits into your scheme?

DR. WINTERS: We obviously don't have any evidence as to whether cats dream during RPS[1] or not. They certainly look like they are sleeping and dreaming, but I suppose I am not to be permitted the same clinical observation that one is permitted in the case of man.

DR. WEST: If they can hallucinate, they can dream.

DR. WINTERS: Cats hallucinate begrudgingly, though. My concept is that there are two general types of hallucinations. The type that was seen with these drug-induced states of increased excitability represents a reduction in modulation of sensory input, so that more information from a given stimulus impinges upon the nervous system. As a result, the learned relationships are lost and bizarre representation of the stimulus occurs. The second type is represented by dreaming, and perhaps also sensory deprivation represents an endogenous dream state characterized by a reduction in exogenous sensory

[1] RPS = rhomboencephalic phasic sleep, the phasic component of REM; however, in this case, the term is used interchangeably with REM. (Ed.)

input. For example, during RPS, the auditory and visual responses are markedly reduced. It would appear that peripheral sensory inputs are reduced, and it is like a state of sensory deprivation. Now, what the mechanism for the hallucination in this state is, I don't know.

DR. STEIN: So on your chart it goes before sleep, rather than in hallucination through excitation?

DR. WINTERS: Yes, I regard RPS as an entirely different phenomenon, and it is not in the CNS continuum. I don't know where to put RPS, but it is off to the side somewhere. On the basis of unit activity and PGO spikes, RPS represents CNS excitation, not deep sleep. On the basis of evoked responses, responsiveness to stimuli, and EEG, it is like a deep sleep.

DR. UNGER: What about hypersynchrony?

DR. WINTERS: I have never seen 2.5 to 3 cps hypersynchrony in RPS sleep. I have seen theta activity in the frequency range of 5 to 7 cps which is localized only in the hippocampus but does not appear in other areas, except in something like the rat which has a very thin cortex. You can often get theta activity reflected on the surface of the posterior cortex in the rat.

DR. UNGER: As I understood you before, the sort of hypersynchrony observed was the operational index for what you called hallucinations. Now, if you don't see hypersynchrony in REM (RPS) sleep, then, in your use of terms, I think one would conclude there are no hallucinations during REM sleep.

DR. WINTERS: As I just stated, there appears to be a difference between the hallucination of the excitatory state which appears to be characterized by hypersynchrony as opposed to dreaming and the hallucination of sensory deprivation. I have not studied the electrophysiology of sensory deprivation.

DR. MANDELL: If you move to man, you can't see the hippocampal theta activity in depth electrode studies of sleep, not even with the aid of a computer.

DR. UNGER: Regarding this hypersynchronous period which you call hallucinatory A, B, and C, if you left out "hallucinatory," I think we could communicate more effectively in an objective data-level language and then discuss the interpretation of these phenomena separately.

DR. WINTERS: You can call it anything you wish.

DR. UNGER: Well, why not first stick to describing the phenomena which you are actually observing?

DR. WINTERS: I call it on the basis of the phenomenon which I have observed. I am using hallucinatory drugs. These are drugs which produce hallucinations in man.

DR. UNGER: Well, but that is perhaps an arguable point.

DR. WINTERS: The point being what?

DR. UNGER: The point being that many investigators have found that *true* hallucinations (with loss of insight) are rare occurrences after the administration of this class of drugs. Hence, it's been a somewhat confusing and prejudicial kind of presumption to have labeled these drugs hallucinogenic.

DR. WINTERS: I am unaware of this group of people and their argument. Whatever the effect is in man and whatever you want to call it in man, something similar to this seems to occur in our animals.

DR. KOPIN: Another question relates to the effect of cutting off the efferent impulses to the sensory organs. Would you expect to have a continual state of hallucination, or would you expect that LSD and other hallucinogens would not work?

DR. WINTERS: I have not studied this. You are pulling me into sensory deprivation experimentation.

DR. KOPIN: I did not mean cutting off incoming signals, but outgoing ones to the sensory organs. If you had cut off these sensory efferents by destruction of the pathways, would you then expect that LSD would no longer have an effect, or that there would then be a continual state of hallucination?

DR. WINTERS: I would guess that there would be a continual state of hallucinations.

DR. KOPIN: Would this be a continual state? If the reason hallucinations are caused is that there is a diminished amount of efferent control of the receptor, then if this were cut off completely there would be a continual state of hallucination.

DR. MANDELL: I don't want to talk for Dr. Winters, but I don't think he implied purely efferent receptor modulation, but rather a more complex, integrative type involving sensory collaterals, the reticular formation, and perhaps more anterior structures, such as the midline thalamic nuclei.

DR. KOPIN: Originally I had asked about the receptor, and his answer was that yes, he did think it was at the receptor.

DR. WINTERS: I think there is a modulation at the receptor, and the geniculate is very important in terms of the visual system. The main responsibility for modulation of sensory input systems probably lies within the control of the reticular formation. We have the idea that psychosis is a state in which modulatory control of input is disrupted, and this is why multisensory aberrations are observed in this disease.

DR. KOPIN: Modulation can occur at any level. The question is, where is it occurring? I think Roy John has demonstrated that you can shift the site of modulating control from one area to another. This is part of the feedback mechanism of the brain. The primary modulating control of sensory input may

be from the reticular formation down to the peripheral sense organ, but there are also ways of modulating impulses at many levels.

DR. TEUBER: How many of these effects might be in a strict sense peripheral, so that they are due to those well-known mechanisms for modulating input, even mere changes in the directions of the head and eyes relative to a visual stimulus, etc. These are questions that have plagued this field for quite a number of years now. But to assure Dr. Domino, I did not mean to say that if we admit these peripheral components we have thereby excluded the central ones; of course not. Unfortunately, all these analyses are still in a rather primitive state. As we begin to investigate these regulations with more refined tools, going from massive stimulation of midbrain (and watching what happens in the retinal pathway) to actual microelectrode recordings, say during certain phases of sleep and REM sleep, for instance, you find that in the cat you do have a presynaptic inhibition at the lateral geniculate nucleus. This effect during rapid eye movements in the dark was discovered by Emilio Bizzi (*J. Neurophysiol. 29:* 1087–1095, 1966). But when Bizzi tried the same thing in the monkey he could not find this particular geniculate interaction during REM sleep, and I do think we are closer to the monkey than to the cat. So this, you see, is one of the many reasons why it is easy to get discouraged at times in looking at these phenomena.[2]

DR. WINTERS: I can't say anything about the monkey in terms of sensory input-output systems. I could add, though, that the pharmacological effects that we observed were also observed in the chimpanzee, which is really a young primate, in the rat, and for some of them, in the chick.

DR. KORNETSKY: I do not think the question whether or not cats or dogs hallucinate or dream is really the relevant question. That is, can you observe and measure physiological and behavioral changes after certain drugs in infrahuman species that are similar to those seen in man when he is dreaming? The question of dreaming in animals is an interesting one. Since animals do not have language, dreaming may be functionally quite disrupting for them. We can use language to test to distinguish reality from non-reality of a dream against the reality of others. How does an animal do this? If an animal dreams as we do and it dreamed that he had eaten, he would be put in immediate conflict when he awakened. He would feel hungry, but would have a memory of eating. I think this would be functionally quite difficult for the animal.

DR. KOPIN: I would think he would have just as much trouble remembering how long ago he ate. If he were hungry he could be hungry again.

DR. DEMENT: That is an interesting point, whether the confusion that

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[2] References for all parts of Dr. Teuber's comments of Session III appear at the end of this discussion.

arises is based upon memory or not. Part of the judgment is made by comparing the dream to reality in terms of spatial configuration and so forth. If you don't remember doing something, is the need still satisfied? How much is remembering part of the really essential aspect of fulfillment?

A VOICE: He would believe in his stomach rather than his memory.

DR. DEMENT: Yes, but for subjects that were not related to his stomach, there could be a traumatic experience.

I would like to pose a question: If someone had a traumatic experience and was amnesiac for this experience; and the memory of the experience came back first in a dream, would it then be experienced as if it had been experienced for the first time, and would the emotional consequences be what they were the first time?

DR. FREEDMAN: What they could have been the first time?

DR. DEMENT: If you have repressed the experience, will eventual recall be as if it were the first time it had happened?

A VOICE: Generally speaking, no. The closest experimental approach to this is in hypnosis and hypnotic amnesias, but a number of experiments show that while a person may claim that he is experiencing the repressed materials, and that he does not remember at all the information that has been blotted out by hypnotic association which is presumably related at least to the mechanism of the traumatic amnesia—I assume emotionally traumatic amnesia is what you are describing—the kind that would come back first in a dream and then little by little as a person could tolerate.

Anyhow, these hypnotic experiments I think may go back in time, and in subtle ways the person reveals that he is aware of the information and behaves in some fashion accordingly.

DR. FREEDMAN: That is not the condition he described—not the subtle way with which he would monitor the behavior and so the amnesia. But with war casualties—we have seen this clinically, I don't know about experimentally—traumatic dreams or sudden confrontations, sudden breaks in the amnesia occur. I think you see this sometimes in LSD. A break of the barrier can be very traumatic.

DR. WEST: From a theoretical view point, wouldn't it be proper to say that the material that began to come back, first in dreams and then in bits and fragments of recollection, was something the person was now psychologically more capable of recalling, more prepared to integrate at a conscious level?

DR. FREEDMAN: You are speaking of adaptive processes in dreams, and they are there.

QUESTION: What if you have a break?

DR. WEST: With sodium amytal you do break into it.

DR. FREEDMAN: Or with LSD.

DR. WEST: I have never known a case where the dream of a normal person, recalled by him, posed a problem that he was so unable to face that he disorganized on account of it.

DR. LEHRER: You talk about a break after a period of amnesia. I wonder if the recall is the equivalent of the original experience or if it may have been amplified, added to or modified in the meantime?

DR. FREEDMAN: Obviously this is possible. That may be the definition of the condition under which a person disorganizes. He doesn't have the option, the alternatives, the feedback from reality—all the things that you might need to have a sort of gyroscope that keeps you going. I think that's probably what we are defining.

DR. STEIN: Isn't the question of whether or not a break occurs separate from the discussion of what processes are involved in retrieving traumatically repressed memories? The retrieval may or may not cause a break. I would like to second Dr. Freedman's idea that the retrieval in narcoanalysis may be similar to the kind of retrieval that occurs in sleep. In both states, the drug state and the dream state, and perhaps in fatigue states as well, one is in a condition of lowered inhibition (lessened activity of the periventricular mechanism). Under these conditions of low inhibition, the forbidden retrieval is more likely to occur.

DR. WEST: I would like to say one more thing about this, if I might, in response to a point Dr. Dement brought out.

I think there are two different kinds of circumstances in which material reappears in a dream that might be pertinent; one augurs well, and the other augurs ill.

If a person is in a state of psychological improvement and is now able to deal with information he couldn't manage before, it might start to appear in dreams as manifest dream content even before he recalled it during wakefulness. This is what you may see in a person who is routinely reporting his dreams during psychotherapy, perhaps following recovery from a psychotic break, and is now being followed along.

However, the opposite significance would hold in the case of a person who is beginning to disintegrate psychologically, and is not able any longer successfully to repress previously unconscious material or process ideation. This previously repressed material may start appearing in dreams as a harbinger of what is soon going to appear even in the waking state. In that respect it would be a sign that things were getting worse.

DR. DEMENT: Well, the trouble is that we remember so few of our dreams. If you could have the experience of being awakened every time a dream occurs night after night, it might get to be confusing just on its own terms; that is, there would be so many dream memories that you might easily

have trouble sorting them out from real experiences. We are protected from this by not remembering; but in terms of what a recall experience is and what it should do to the organism, if dreams are real at the time—and they certainly seem to be when you remember them vividly—how do we separate them, really, from our waking experience? How is that memory barrier accomplished?

When you add up two hours a night, night after night, that is a lot of experience. Where does it go?

DR. STEIN: Perhaps there are two mechanisms for separating dreams from real experiences. One of them is simply forgetting the dream, and that may account for some of it. The other is labeling a dream as a dream. When I see a motion picture I don't pool these events into my own set of experiences. I remember that they occurred in a movie. And I see no reason why the events that occur in dreams couldn't somehow be labeled and remembered as dreams.

DR. DEMENT: I am only telling you that if you remember all of your dreams, you don't do that so well. You start saying, "Gosh darn it, did that happen in the dream or didn't it?" You can't tell.

DR. STEIN: That may be why we forget some of them.

DR. DEMENT: We don't want to do this too much on a continuing basis.

DR. FREEDMAN: In response to that problem, we have to interpose another step in experiences of vividness and reality. Anything experienced really can't be denied reality. The question is how do you locate it; which order of reality do you locate the "real" experiences in?

DR. OSMOND: I think that schizophrenic patients often attempt to cope with their peculiar and unfamiliar experiences by looking upon them as a dream, or perhaps, more exactly, as a nightmare. When they begin to recover, some patients are very much afraid that the waking nightmare will recur. It is only as they become more confident of their recovery that some of them become much concerned to know what "really" happened to them; then they need help to categorize strange, even bizarre happenings which they can recall with various degrees of reality. They must be helped to distinguish what "really" happened, as perceived by others, from what they experienced, from what might have happened and what never happened. Some people have great difficulty in doing this; some have very little.

DR. DEMENT: I think that the only animal who could get confused is the human. I could give you a whole list of reasons for saying this. I think humans are the only ones for whom dreams and reality are the same. I don't think cats see the real world in REM sleep, and I don't think, with rare

exceptions, that monkeys do either. What I am saying is that the internal stimuli of REM sleep are not capable of replicating the real world in cats, but that they are in humans.

DR. HOLMSTEDT: Why do you say that?

DR. DEMENT: You are asking for a 10 minute discourse. Let me mention just one kind of data relevant to this issue. If you give cats *p*-chlorophenylalanine (PCPA) and follow them while the brain 5-HT level drops to virtually zero, you will see in the waking state of the cat electrophysiological (PGO spike) phenomena which are usually seen only in REM sleep; you can't tell the difference. You can, however, tell that the cat is not in REM sleep. He is, in a sense, in two states at the same time, REM sleep and wakefulness. In this condition, he doesn't act as if he is seeing formed activity. When REM events occur, he acts only as if expecting to see something, or as if you made a click. The cat never seems to be seeing a mouse and then reacting to that appropriately. Never does he ever do anything that would confirm there is a real honest-to-goodness image out there.

The monkey, when given PCPA, falls somewhere in between on the hallucination scale. Most of his behavior is nondescript, like the cat, but every once in awhile—infrequently—you see him do something that could only occur in response to complex stimuli. For example, when you approach the monkey's cage, he bares his teeth and makes threatening motions. Occasionally, he will do that in the PCPA state when no one is there.

The human, from what I have read in the literature, can have continuing complicated hallucinations when treated with PCPA.

But at any rate, this and some other things make you suspect that the cat simply doesn't see in REM sleep what he sees when he is awake, and likewise with monkeys. Human beings are the only animals that really duplicate the real world in REM sleep in most of its properties.

DR. LUDWIG: I would just like to cover a couple of clinical observations which may resolve some of what has been said—perhaps even make it more complex in a way. We are asking the question what is real in terms of dreaming or the waking state? When a man is dreaming he is doing something more than dreaming, since on some level of consciousness he often is aware that he is dreaming. And in many dreams which are disturbing, for example, he can tell himself that he is dreaming, and can go back to the dream and try to resolve it. Is this reality if something is very vivid for him? Well, it is reality plus the additional knowledge that he is dreaming.

For example, under a drug state, such as LSD, things are real, but by the same token the person is often aware that what he is experiencing is due to the drug; it's real but it isn't real at the same time. The really scary part comes when he's no longer aware that he is dreaming or under the influence of drugs.

DR. DEMENT: There is one other aspect of that. Many people have had the experience of knowing that they are dreaming when they are presumably dreaming; at least so they say. But there is another quality: being impelled along and not having time to stop and really contemplate the events; for example, you look at something, it's a person you know perfectly well is dead, or it's writing you know you shouldn't understand, or you are playing a piano. You know full well you didn't take lessons. You don't seem to be able to stop and reflect on the improbability of that—you are on to the next event. So I think that there is some aspect that is missing in this state that is present in wakefulness.

DR. FREEDMAN: Dr. Dement, the Lord was merciful; in view of some of our dreams perhaps he was making sure we were impaired during that state.

A VOICE: Dr. Teuber, what happens in the split-brain preparation in the course of subjective experiences?

DR. TEUBER: I can't speak much about that, having seen only one case, but certainly they don't seem to be very different with respect to the things we are now discussing. Each hemisphere, apparently, can process and store sensory impressions, but only one hemisphere can talk about them. What may be more relevant is another clinical condition, namely, post-traumatic amnesia, not in the sense of hysterical repression but of apparently genuine forgetting due to a cerebral trauma. Following a concussion, as you all know, there may be this inability to recall events immediately preceding the blow, as if some crucial stage in the processing of material had been disrupted. You see particularly severe retrograde effects of this sort after certain surgical assaults upon the brain, as in bilateral hippocampectomy. We have had the privilege of seeing the famous Scoville-Milner case, patient H. M., in our laboratory on several occasions (Scoville and Milner, *J. Neurol. Neurosurg. Psychiat. 20:* 11–21, 1957; Milner, Corkin and Teuber, *Neuropsychol. 6:* 215–234, 1968), and one is certainly struck by the retrograde effect of the operation in this case (he apparently has a gap of more than a year preceding the hippocampal removal); the anterograde amnesia is very severe. This man lost his father about two years ago. We dare not ask him about that, because he has forgotten the event so completely that if you inadvertently bring it up, you get the complete bereavement reaction all over again, as if he heard the news for the first time. Note that this can happen only because his earlier attachment is still there; he does recall the time he spent with his father up to the operation, except for the last 18 months or so before surgery.

In trying to come to grips with these forms of amnesia, one has to assume that some crucial step in the categorizing of ongoing events is missing after these mesial temporal lobectomies (and, transiently at least, after certain lesions in the upper brainstem; cf. Milner, Corkin and Teuber, *Neuropsychol.*

6: 215–234, 1968). Events are perceived but not put into the form in which they can be stored and retrieved.

The difficulty we experience in recalling dreams may be quite similar, and perhaps so is the trouble in retrieving childhood events as well. It is certainly paradoxical: children learn such a great many things, including language and all sorts of complicated motor skills, but the recall for events of one's early childhood is quite poor; this or that incident resurfaces, often in a manner similar to the notorious "islands of memory" that surface from a sea of forgetting in the post-traumatic amnestic state. Some functional level on which we transform individual experiences into a more permanent store is not reached by the child, even though he is extremely competent in acquiring implicit rules (as in first-language learning). To come back, finally, to the unanswerable question, Dr. Winters, of whether cats are dreaming: I am much more ready to concede them their dreams than to assume they could ever give us their autobiography![2]

DR. WINTERS: The point I was making was that gamma-hydroxybutyrate is one example of an agent which induces an epileptoid progression, yet is used clinically in Europe and Asia and is in clinical trial in this country as an anesthetic agent. If you check the clinical literature, there are many clinical statements of the efficacy of the agent, and on the basis of the neurophysiological effect on the cat—and I hasten to add on the chimp, monkey, rat, and chick—one would assume that this agent induces epileptic activity, and the only criteria which we can come up with to understand how this agent can be used clinically is that this drug induces a state of unresponsiveness and amnesia, so that the surgeon can perform his surgery and the subject will not recall the events.

DR. FREEDMAN: The reason you can't use the term catatonic is that the catatonic with waxy flexibility is monitoring very clearly what goes on and doesn't really have amnesia.

A VOICE: There is a fascinating discussion going on here about dreams and the reality thereof, and I wonder if I might address myself to this concept: that is, that people who have experienced psychedelic drugs appeared later to revise for a time thereafter their concept of what is real. I think this is the meaning in which this should be discussed.

DR. MANDELL: I think it would have been of interest to invite to this conference Kenneth Kesey, who has done in addition to his novel writing some informal clinical research in this area. He was the one, you remember, who wrote *One Flew Over the Cuckoo Nest.* He drove a psychedelic bus with a

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[2] References for all parts of Dr. Teuber's comments of Session III appear at the end of this discussion.

rock band and had a hobby of dropping LSD into the punch at parties without telling anyone. I have talked to two people who were at such parties and what resulted is similar to what Dr. Dement is talking about. The unknowing acid takers began to experience their aberrations within the context of normality without the "drug-taking" set. Is this what the REM-deprived person with a high REM deficit experiences? Is the capacity for reflection against reality necessary to make a dream a dream and not reality without the knowledge of the drug ingestion?

Perhaps Hoffman's original experiment with LSD and his initial subjective "psychosis" (not "drug experience") may be another example of the need a person has to have an actual reality against which to reflect an induced reality. These kinds of drug experiences (sans set) add considerable substance to the issue Dr. Dement introduced.

DR. FREEDMAN: Hoffman noticed the difference. He noticed the difference and took certain behavioral measures, such as going home and not working.

DR. WASER: He felt sick!

DR. MANDELL: The second time he knew better.

DR. WEST: Kenneth Kesey is an author who isn't driving his psychedelic bus around anymore because he was jailed for possession of marihuana, and has subsequently withdrawn to recover on a farm in Washington. His case history appears in a recent book by Tom Wolfe entitled *The Electric Kool-Aid Acid Test.*

DR. JULESZ: I have one book I would like to recommend, *The Mind of a Mnemonist* by Luria (Basic Books) translated a year ago from Russian to English. There is a strange, abnormal man whose problem is that he *cannot* forget. He does not have childhood amnesia, and so on. He doesn't have the next process which we have, namely, he just doesn't have symbolic thinking. Probably in this man the ability for symbolic processing did not develop; for instance, he could not imagine the notion of "nothing." For him "nothing" meant a gray cloud, whereas "something" was a cloud of another color. In his childhood he would sometimes forget to go to school because he so vividly visualized that he was going to school. He was already "at school" when his father said, "Oh, why didn't you wake up?" So maybe the sense of reality is something that operates on a higher level.

DR. TEUBER: May I add one footnote to what Dr. Julesz just said? The book is an amazing account of a "hyperamnestic" rather than amnestic condition. Yet with all these tremendous accomplishments of memory, this man had a remarkable and selective difficulty in recognizing faces. I just want to underscore this. We are utter primitives in dealing with these phenomena. To think that we have a single word, *memory,* for such a tremendous diversity

of behavioral achievements! The term *memory* is one of the main barriers that keeps us from coming to grips with the question of basic mechanisms.

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