

A Neurophysiologic Study of Ketamine Anesthesia in the Cat

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The effects of ketamine on CNS electrical activities (EEG and multiple-unit activity of the brain-stem core) and gross behavior were studied in cats with chronically implanted electrodes. Ketamine induced three distinct patterns, related to dose. An initial CNS excitation coupled with catatonic behavior was followed by disorganized excitation characterized by a catatonic-anesthetic state and finally, electrographic seizures without clinical correlates. During the initial period multiple-unit activity increased. Following this, the basal level of multiple-unit activity decreased, but the level increased phasically in synchrony with EEG hypersynchrony. During the stage of generalized seizures, the basal level decreased further, while phasic enhancement was not much affected. Comparison of polygraphic findings in the ketamine-induced anesthetic state and during control paradoxical (dream) sleep revealed that there is little or no possibility that ketamine induces dream sleep in the cat. Comparison of ketamine anesthesia and states induced by other hallucinogenic and convulsant drugs, including anesthetics, indicated some possibility that ketamine induces hallucinations. It was concluded that the ketamine-induced anesthetic state is a result of functional disorganization of the CNS rather than CNS depression. (Key words: Ketamine; Brain-stem core; Multiple-unit activity; Slow-wave hypersynchrony; Electrographic seizures; Paradoxical sleep.)

BASED ON MONITORING of gross behavior, EEG, and spontaneous activity of a large population of neuronal units in the midbrain reticular formation, our previous studies demonstrated that pentobarbital and halothane are simple cen-

tral nervous system depressants whose effects are dose-related depression of neuronal firing with flattening of the EEG and quiet behavior, while phenacyclidine, the prototype of ketamine, is an epileptogenic, or CNS stimulant, which produces a preictal hallucinatory state followed by generalized electrographic and behavioral seizures.¹⁻³ Ketamine has been reported to be a "dissociative anesthetic agent" since in the EEG it induced delta-wave activity of the association and somatosensory cortices but did not affect the visual and auditory cortices or the limbic structures. Furthermore, it induced selective depression in the thalamic center-median nucleus but did not affect the midbrain reticular formation.^{4,5} McCarthy *et al.*⁶ and Domino *et al.*⁷ reported that ketamine had both excitatory and depressant actions in the central nervous systems of various species of animals.

The present study was undertaken to study the excitatory and depressant effects of ketamine on the CNS as manifested by changes in the spontaneous firing of neurons in the brain-stem core correlated with changes in EEG pattern and gross behavior. Special attention has been focused on epileptogenic properties, and higher-than-clinical doses were used in some experiments. Since "vivid dreams" in man have also been reported,^{8,7,8} electrographic comparison of ketamine-induced states and the naturally occurring dream-sleep (paradoxical sleep) was attempted.^{9,10} The techniques utilized for these studies were identical to those used in the previous study.¹¹ Some of the results have been presented as a preliminary note.¹²

Methods

Fifteen experiments were performed on six cats weighing 2.6-4.1 kg. Monopolar cortical (the frontal sinus bone used as reference) and bipolar subcortical leads were chronically im-

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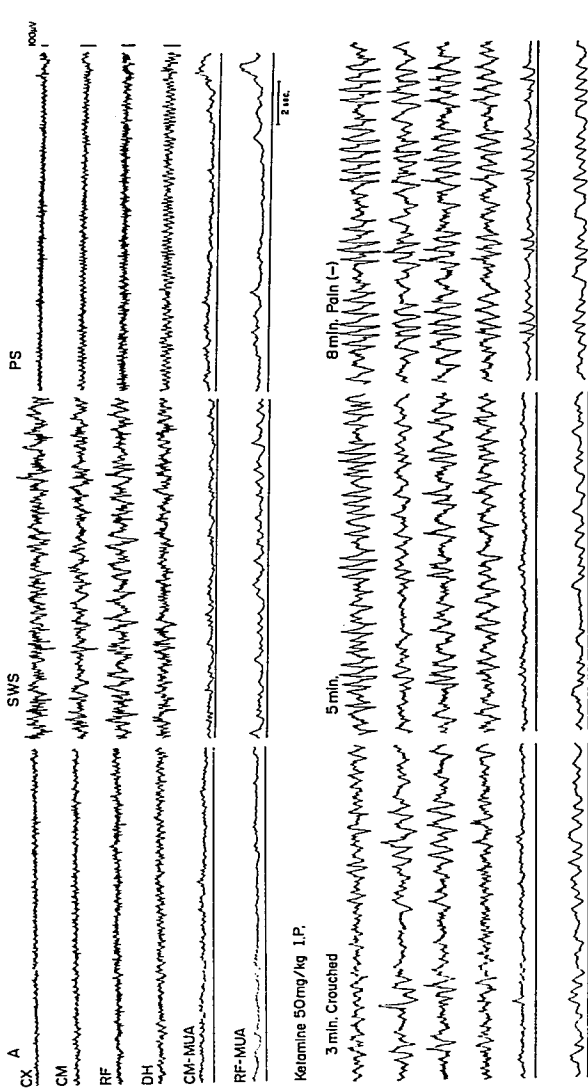


Fig. 1. Effects of ketamine on the EEG and on multiple-unit activity. A, control awake; SWS, slow-wave sleep; PS, paradoxical sleep; CX, anterior suprasylvian gyrus; CM, nucleus centrum medianum of the thalamus; RF, midbrain reticular formation; DH, dorsal hippocampus. MUA is expressed by amplitude-demodulated signals. The horizontal straight line beneath MUA represents the system noise level obtained by inserting a 15-k Ω resistor at the input. The larger the distance from the horizontal line to the MUA tracing, the greater the firing rate of the neurons. Three minutes after injection of ketamine, 50 mg/kg ip, sporadic hypersynchrony was observed. Eight minutes after injection, typical intermittent hypersynchrony was recorded, and MUA had greater fluctuation synchronized with hypersynchrony.

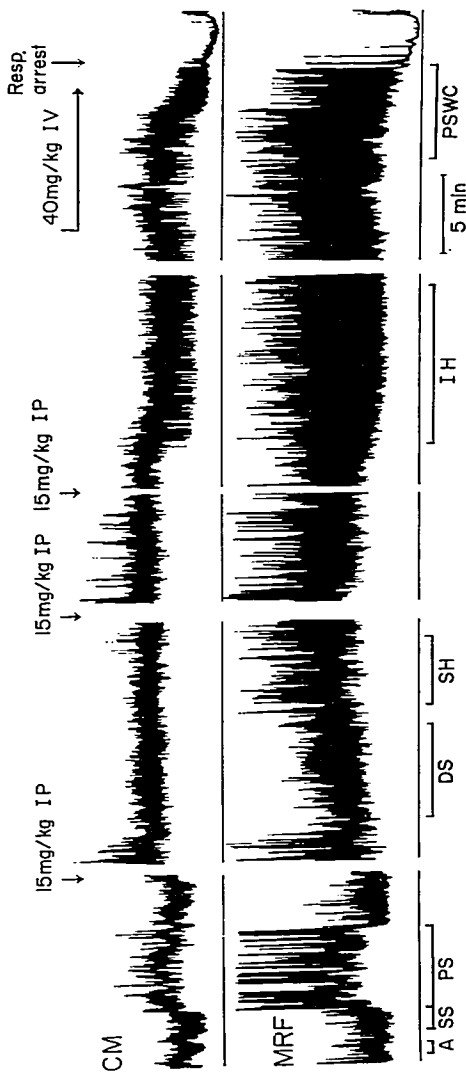


Fig. 2. Effects of ketamine on the multiple-unit activity of the thalamic centrum medianum and the midbrain reticular formation. A, awake; SS, slow-wave sleep; DS, paradoxical sleep; SH, sporadic hypersynchrony; PSWC, intermittent hypersynchrony; PSWC, poly-spike-wave complex. MUA is expressed by the horizontal line beneath NUA tracings represents the system noise level. The firing rate of the neurons. During DS and SH, the firing rate of the neurons is greater than during the stages of A, SS, and SH. Following the stages of SH, the basal level decreased while the fluctuations increased. At the end of the PSWC respiration ceased almost to system noise level. Artificial respiration, however, restored MUA. Time scale is 5 min.

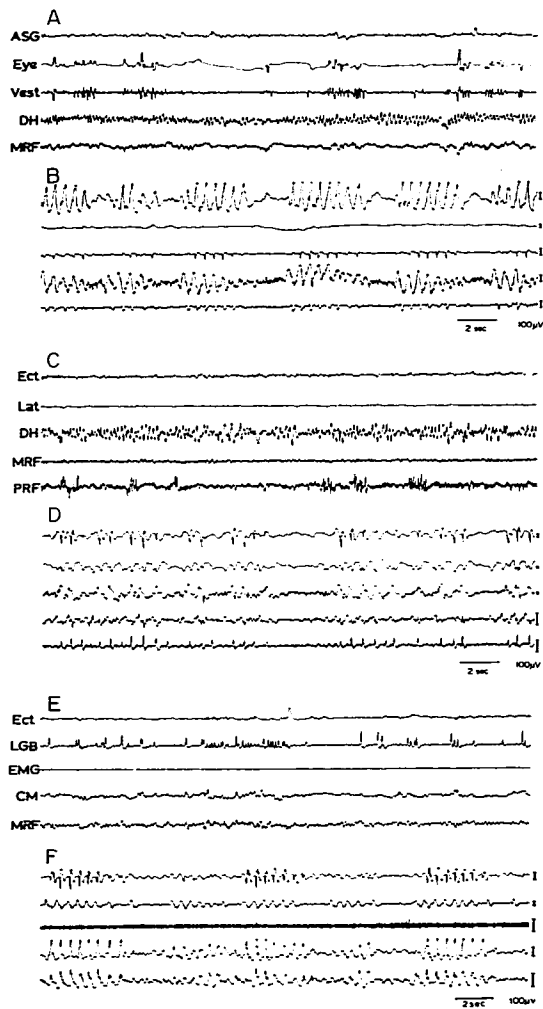


FIG. 3. Comparison of EEG's during paradoxical sleep and ketamine-induced states. A, C, E, records of control paradoxical sleep of three cats; B, D, F, 20 minutes after ketamine, 40 mg/kg ip. ASG, anterior sigmoid gyrus; Eye, electrooculogram; Vest, lateral vestibular nucleus; DH, dorsal hippocampus; MRF, midbrain reticular formation; Ect, middle ectosylvian gyrus; Lat, lateral gyrus; PRF, pontine reticular formation; LGB, lateral geniculate body; EMG, neck-muscle electrogram; CM, nucleus centrum medianum of the thalamus. During paradoxical sleep, spikes, which are either isolated or occur in trains of four or five events, are observed in the lateral vestibular nucleus, pontine reticular formation, and lateral geniculate body. Following ketamine, solitary sharp waves are observed in the lateral vestibular nucleus and pontine reticular formation but not in the lateral geniculate body. During paradoxical sleep, there is complete silence of neck-muscle EMG, while following ketamine it showed moderate activity.

planted. Electrical activities were recorded from the anterior suprasylvian gyrus, anterior sigmoid gyrus, middle ectosylvian gyrus, pos-

terior lateral gyrus, midbrain reticular formation (MRF), thalamic centrum medianum (central nucleus of the thalamus) (CM), pontine

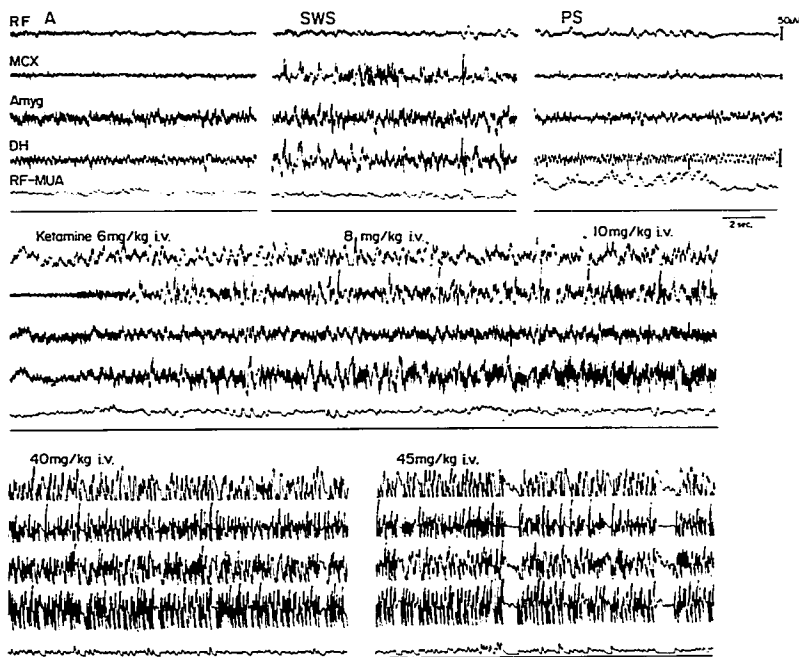


FIG. 4. Effects of rapid intravenous administration of a high dose of ketamine on the ongoing EEG and reticular MUA in the gallamine-immobilized cat. At a dose of 6 mg/kg iv, sporadic hypersynchrony appeared. At 40 mg/kg iv, a multiple-spike-wave complex appeared. At 45 mg/kg iv, typical postictal depression of short duration, which is typical of generalized seizures, occurred.

reticular formation (PRF), lateral geniculate nucleus, lateral vestibular nucleus, basilar amygdaloid nucleus, and dorsal hippocampus. EEG activities from all these areas were recorded and multiple-unit activities (MUA) from the CM, MRF and PRF were recorded. Movement of the eyes was recorded bipolarly through stainless steel screws drilled into the orbital bone through the frontal sinus (electro-oculogram). Neck-muscle EMG activity was recorded bipolarly. Techniques of recording the electrical activities of the brain have been described.¹¹ A preamplifier of the polygraph was modified to pick up MUA. The peak frequency response was set at 1,300

Hz, with 3-db decreases at 600 and 2,500 Hz. Thus, the waveforms in the EEG frequency range were considerably reduced, whereas fast action potentials of neurons adjacent to the tip of the electrode could be recorded. Since the conventional ink-writing oscillograph could not follow the high-frequency activity obtained through this amplifier, it was fed into a rectifier, where it was rectified and smoothed (average-integration). The smoothing time constant of the rectifier was set at 50 msec for both increasing and decreasing phases. The output of the rectifier was entered into the DC stage input of another preamplifier and recorded simultaneously with the EEG. Thus,

these amplitude-demodulated signals consisted in fluctuations of DC level: the higher the DC level, the greater the firing rate of a population of units. At the completion of each experiment the system noise was tested utilizing a dummy plug containing a short and a 15-k Ω resistor. The signal-to-noise ratio exceeded 3 to 1. To demonstrate the long-term changes during natural sleep or anesthesia, the amplitude-demodulated signal was recorded on a slow moving straight-writing oscillograph (Sanei 8s-11-3-A) with a paper speed of 5 mm/min. Thus, MUA was expressed by two means, *i.e.*, basal level and fluctuation. Basal level was measured as the distance from the base of the unit tracing to the 15-k Ω resistor line, and fluctuation was measured as the width of the excursion from baseline to peak.

Ketamine was administered either intravenously or intraperitoneally in doses ranging from 2 to 50 mg/kg iv or 5 to 50 mg/kg ip. The interval between successive administrations of drug to any cat was at least 14 days. Rapid intravenous administration of high doses (0.3 mg/kg/sec for a total dose of 20-50 mg/kg) was given to gallamine-immobilized cats and to cats which previously had received anesthetic doses of ketamine ip. When respiration was depressed, the trachea was intubated and artificial respiration with room air was instituted (tidal volume 13 ml/kg at a rate of 30/min).

In each experiment, polygraphic recordings were obtained while the cats were awake, during slow-wave sleep, during paradoxical sleep, and after drug administration.

Results

Changes in the EEG pattern following various doses of ketamine correlated with changes in gross behavior and levels of MUA in the brain-stem core. There was essentially no difference between the directions of changes in MUA in the three areas of the brain. The progression of changes can be delineated according to a classification of EEG changes which we have used previously.³ The higher the dose, the more severe were the changes induced. However, the durations of the stages differed according to the dose of ketamine, *e.g.*, the initial stage of EEG desynchronization was longest after 10 mg/kg ip, shorter

after 40 mg/kg ip, and shortest during rapid intravenous administration of high doses.

DESYNCHRONIZATION

Doses less than 10 mg/kg ip induced the stage of EEG desynchronization only, and doses above 10 mg/kg ip induced this stage during the initial period after drug administration. The EEG was characterized by sustained desynchronization in the neocortical and subcortical leads and continuous rhythmic theta activity in the dorsal hippocampus (hippocampal arousal pattern). The basal level and the fluctuation of MUA showed moderate increases above corresponding values in the control awake period (fig. 2, DS). The cat was restless, with slow nystagmus, and apparently was excited, but was less responsive to pin-prick stimulation.

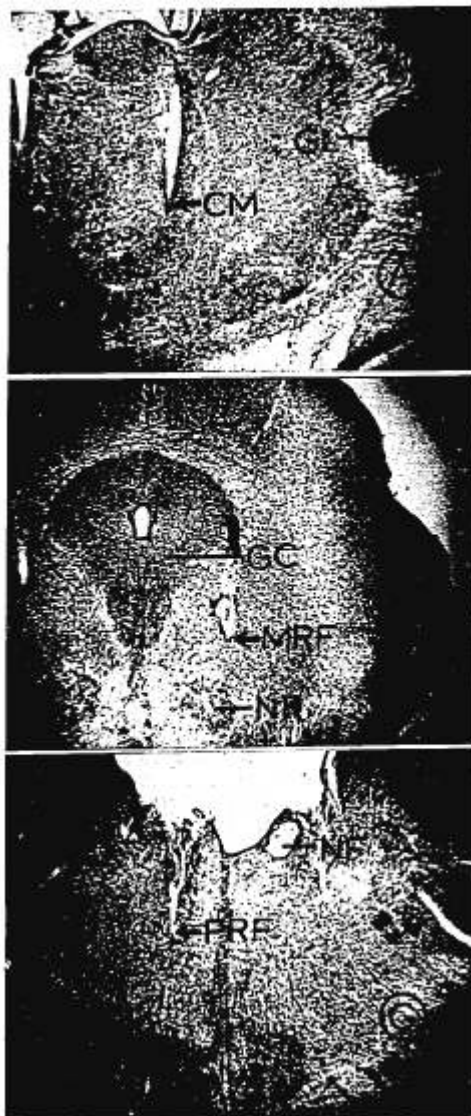
SPORADIC HYPERSYNCHRONY

Following doses greater than 10 mg/kg ip, some sporadic slow-wave hypersynchrony of 2 Hz appeared in the EEG of the neocortex and the brain-stem core (fig. 1, 3 min). This stage always followed the stage of desynchronization. The dorsal hippocampus showed either theta activity or desynchronization, and slow waves appeared less frequently. Brain-stem MUA increased further, approaching the level of control paradoxical sleep in the basal level, but the fluctuation was less than during paradoxical sleep (fig. 2, SH). Moderate salivation, continuous licking, bizarre swinging of the head, nystagmus, and loss of the righting reflex were observed. Respiration appeared to be stimulated, and usually the cat panted. The pupils were dilated maximally, eyes were wide open, and the nictitating membrane was completely retracted. The cat appeared to be excited but could not move because of severe ataxia.

INTERMITTENT HYPERSYNCHRONY

Doses of 20 to 50 mg/kg ip induced intermittent hypersynchrony after the two EEG stages mentioned above. The EEG showed intermittent slow-wave hypersynchrony (2 Hz) of 2-3 sec duration interrupted by short periods of desynchronization. The cortical hypersynchronous waves had some low-amplitude positive sharp wave components which

FIG. 5. Histologic verification of electrode placement. A and B are frontal sections at 7 and 2 of the stereotaxic coordinate, and C is a section of pons at genu of the facial nerve about 30 degrees posterodorsal to the frontal plane. CM, right centrum medianum; GL, right lateral geniculate body; GC, substantia grisea centralis; MRF, midbrain reticular formation; NR, right nucleus ruber; NF, right genu of the facial nerve; PRF, left pontine reticular formation (nucleus reticularis pontis caudalis).



were followed by slow waves (fig. 1, 8 min). These hypersynchronous bursts appeared in the limbic structures also. During the short periods of cortical desynchronization between the slow-wave bursts, the dorsal hippocampus showed either desynchronization or rhythmic theta activity. In the subcortical leads the slow waves were more spiky, especially in the pontine reticular formation and the vestibular nucleus (fig. 3, B, D). These pontine and vestibular sharp waves were smaller in amplitude than the spikes observed during paradoxical sleep. No spike activity was observed in the lateral geniculate nucleus following ketamine (fig. 3, F). Furthermore, there was no train of 6-8-Hz activity ("pseudo-spindle," Jouvett *et al.*¹³) (fig. 3, B, D, F), an essential finding for paradoxical sleep (fig. 3, A, C, E).¹⁴ Neck-muscle activity (EMG) was always present following ketamine (fig. 3, F) but was absent during paradoxical sleep (fig. 3, E). Brain-stem MUA showed a phasic increase in synchrony with the EEG spike component and a decrease concomitant with the succeeding slow-wave component (fig. 1, 8 min). During the desynchronization period, MUA remained a little below the peak of the phasic enhancement. Thus, the basal level decreased, although it was still above that of control slow-wave sleep, and fluctuation increased markedly. During this stage the cat dropped its head and appeared nonresponsive to pinching. The eyes were wide open, with a fixed gaze; the pupils were maximally dilated, and licking continued. Careful observation revealed slight flapping (1-2 mm in distance) of the bilateral earlaps in synchrony with the EEG hypersynchrony. Behaviorally, excitation with profound catatonia was apparent although respiration appeared depressed.

POLY-SPIKE-WAVE COMPLEX (FIGS. 5 AND 2, PSWC)

This stage was induced only by rapid intravenous administration of high doses (30-50 mg/kg, iv). When 6-8 mg/kg iv were administered, the above-described hypersynchrony (2 Hz) appeared in the cortical and subcortical leads. After 20-30 mg/kg iv, the slow-wave hypersynchrony disappeared and multiple-spike-wave complexes appeared in all areas. With the highest dose (40-50 mg/kg,

iv) the bursts of poly-spike-wave complex activity were interrupted by short periods (0.5-2.0 sec) of total electrical silence, the so-called postictal depression. When poly-spike-wave complex activity appeared, the basal level of MUA decreased gradually as dose increased. The pupil size was smaller than that at the previous stage. No convulsion was observed. Respiration almost ceased, and artificial ventilation was necessary.

There was essentially no difference between the EEG patterns and the directions of changes in MUA in nonparalyzed and paralyzed preparations.

Discussion

The so-called EEG activities have frequency ranges of 1/2 to 50-80 Hz. These activities, the durations of the waves of which are 10-500 msec, have been supposed to originate in the neuronal dendrite rather than in the soma or axon. Although there had been no direct evidence, a general conclusion had been drawn from stimulation experiments and behavioral observations that the higher the level of neuronal activity the smaller the amplitude and the higher the frequency of the EEG.^{15, 16} There had been numerous efforts to prove this assumption (see Schlag and Balvin¹⁷ for a historical study of the problem), and finally Schlag and Balvin¹⁷ confirmed it by measuring MUA. The time courses of action potentials of neuronal soma never exceed 1.0 msec. The conventional EEG recording technique, therefore, is not suitable for MUA. MUA can best be measured with an instrument capable of measuring high-frequency responses, such as that used in the present study. Utilizing a similar technique, Halas and Beardsley¹⁸ demonstrated that a specific sensory stimulation induced an increase of MUA in the corresponding sensory system in the CNS, and confirmed the reliability of this method in quantifying the overall level of neuronal firing. The ideal method of measurement of neuronal activity is analysis of single-unit activity. However, when this is applied to the study of drug effects on CNS structures such as the reticular formation, difficulties may arise. The reticular formation has a heterogeneous cell population. The specific function of a given neuron under

observation cannot be identified. Furthermore, for evaluation of whether such a structure becomes more or less active, an accumulation of numerous experimental data and statistical analysis are mandatory, since one experiment can provide information from only one neuron both during the control period and during anesthesia. When the technique of MUA measurement is employed, it is easy to determine at least whether a population of neurons is firing more or less actively as a whole.

The progression of events induced by ketamine in the present study implies that three distinct stages of effects were introduced, *i.e.*, an initial CNS excitation followed by a cataleptic-anesthetic state and finally by nonconvulsive generalized electrographic seizures. This progression of changes was similar to those induced by other epileptogenic agents except for the presence (gamma-hydroxybutyrate and phencyclidine²) or absence (diethyl ether¹¹) of behavioral convulsions. During the initial CNS excitation, brain-stem MUA increased tonically. The second stage, which began with the onset of sporadic hypersynchrony, was characterized by inappropriate behavior such as swinging of the head, maximal pupillary dilatation, and continuous licking. Following administration of ketamine to man, some psychic reactions, such as changes in mood and affect, hallucination of body image, and dysfunction of equilibrium sensation, have been reported.⁷ The relationship between slow-wave hypersynchrony and the hallucinatory state has been discussed by us previously.³ Various hallucinogenic agents, including LSD, psilocybin, and nitrous oxide, induce slow-wave hypersynchrony in the cat.^{1-3, 19} Adey *et al.*¹⁹ demonstrated that LSD-25 induced an apparent loss of contact with the environment simultaneously with the appearance of slow-wave hypersynchrony in the EEG's of cats in a T maze. Thus, although it cannot be demonstrated that this state in the cat is the same hallucinatory phenomenon that occurs in man, the hypersynchronous EEG coupled with inappropriate behavior suggests a hallucinatory state, as discussed by us previously.³ The spiky or sharp waves observed in the vestibular nucleus might be responsible for the dysfunction of equilibrium to some extent. It has also been reported that in man

ketamine induces a dream-like state, described as "vivid dreams" (Domino *et al.*⁷), "vivid dreams and/or hallucination" (Corssen *et al.*⁸), or "lucid dreams" (Virtue *et al.*⁸). All these reports have been based on the patients' complaints after recovery from ketamine anesthesia. Since "dream," which is a physiologic phenomenon, is known to occur during the paradoxical phase of sleep,⁹ a polygraphic comparison of physiologic dream-sleep and the states induced by ketamine was made. During paradoxical sleep spike activities in the pontine reticular formation, lateral geniculate nucleus, and vestibular nucleus were recorded; these together are called "pontogeniculo-occipital activity" or "PGO" (Jouvet¹²). In the present study, however, even though some spiky or sharp waves appeared in some of these areas after administration of ketamine, they were absent in the others. Furthermore, these ketamine-induced spiky waves were entirely different in amplitude and mode of appearance from those observed during control paradoxical sleep, *e.g.*, following ketamine there was no tendency to form "pseudo-spindles." Neck-muscle EMG activity, the disappearance of which is characteristic of paradoxical sleep, was present at all times after ketamine. All these data imply that there is very little or no possibility that ketamine induces dream-sleep in the cat. Thus, the "vivid dream" following ketamine in man might be a drug-induced hallucination rather than a "dream" experience.

The third stage, that of the EEG polyspike-wave complex, was somewhat different in quality from the generalized seizure that follows phencyclidine, *i.e.*, the prototype of ketamine. During the preictal period following phencyclidine, the basal level of reticular MUA showed a sustained increase, with marked phasic enhancement in synchrony with the EEG spike component. Maximum enhancement was observed during the generalized seizure, with concomitant behavioral convulsions.^{2,3} On the other hand, following ketamine, only phasic enhancement was observed, while the basal level of MUA decreased both during the period of intermittent hypersynchrony and during generalized electrographic seizures. We reported previously that diethyl ether, which also has hallucino-

genic effects during stage II anesthesia, induced a purely electrographic generalized seizure without clinical correlates.¹¹ During ether-induced seizures no enhancement in the neuronal firing of the reticular core was observed, while seizures which produce electrographic and clinical evidence of convulsions cause the maximum increase in the firing of reticular neurons.³ However, the reason for the absence of clinical convulsions during ether- and ketamine-induced electrographic seizures is still unclear, since the failure of neuronal firing to increase maximally in the brain-stem core alone cannot explain this dissociation of EEG and behavior.

McCarthy *et al.*⁶ and Domino *et al.*⁷ indicated not only that ketamine was less potent on a mg/kg basis than phencyclidine, but also that its central excitatory action was much less than its CNS depressant action, based on behavioral criteria. The present study definitely confirmed their behavioral findings of CNS excitation at low doses and CNS depression contaminated by some electrographic excitation at higher doses.

Corsen *et al.*⁵ reported electrographic dissociation of the neocortical system from the limbic structures and also of the thalamocortical system from the midbrain reticular formation. Our study did not confirm these findings. A similar and much more profound dissociation was found during cyclopropane anesthesia.^{20, 21} It seems likely that Corsen *et al.* used the term "dissociative" because they considered that EEG slow waves represented decreased activity of neuronal elements. However, the situation is not so simple. Several reports by us^{1-3, 11, 21} and others¹⁹ indicate that two types of slow waves are induced by various neurotropic agents. One consists of irregular slow waves induced by simple CNS depressants such as pentobarbital and halothane, and the other of so-called slow-wave hypersynchrony. The latter is induced by hallucinogenic agents (LSD-25 and mescaline), hallucinatory or epileptogenic anesthetics (nitrous oxide, ether, cyclopropane, alpha-chloralose, gamma-hydroxybutyrate, and phencyclidine), and CNS excitants (pentylentetrazol and bemegride). Thus, slow-wave hypersynchrony may well imply some disorganized CNS ac-

tivity, but it does not imply simple CNS depression.

Since the dissociation of the EEG pattern is not restricted to ketamine but is common to several general anesthetics, we suggest that "dissociative anesthetic" is not a precise term. It can be concluded that the ketamine-induced anesthetic state is not a CNS depression but rather a functional disorganization similar to those following other excitant anesthetics.^{2, 11, 21}

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Drugs and Their Actions

DIGITALIS AND PULMONARY VASCULATURE The effects of acute digitalization on pulmonary blood volume (PBV) and pulmonary vascular distending pressure (P_d) were studied in 23 adults during simultaneous right and left heart catheterization. Digitalization with acetylstrophantlidin (1.1-1.3 mg intravenously) was achieved over a 9-13-minute period. The subjects were divided into two groups according to the responses of left ventricular end-diastolic pressure (LVEDP) to digitalization. Group I (11 patients in whom digitalization reduced LVEDP 5 mm Hg or more) included five patients with ischemic heart disease, five with aortic valve disease (including two with aortic insufficiency), and one with mitral stenosis. Group II (12 patients in whom digitalis did not reduce LVEDP by more than 1 mm Hg) consisted of three patients with ischemic heart disease, six with aortic valve disease (including four with aortic insufficiency), two with mitral stenosis, and one normal patient.

In Group I, digitalis decreased the heart rate by 11 beats/min, increased the cardiac index from 2.39 ± 0.19 to 2.60 ± 0.19 l/min/m², and decreased LVEDP from 23.6 ± 3.2 mm Hg to 12.1 ± 2.7 mm Hg. Left atrial mean pressure dropped from 24.6 ± 1.7 to 13.1 ± 2.1 mm Hg, while mean pulmonary arterial pressure dropped from 28.1 ± 2.3 to 18.5 ± 2.3 mm Hg. The calculated pulmonary vascular resistance did not change (control, 123 dyne-sec cm⁻⁵; after digitalization, 120 dyne-sec cm⁻⁵). A decrease in the pulmonary distending pressure P_d from 27.8 ± 2.2 to 16.8 ± 2.3 mm Hg was observed, and was the result of the decline in both LA and PA mean pressures, since P_d is calculated by averaging mean LA and PA pressures.

Pulmonary blood volume, calculated by multiplying mean transit time from PA to LA by the cardiac index, decreased from 317 ± 27.6 to 262 ± 23.0 ml/m² after digitalization. A graph of pulmonary blood volume vs. pulmonary distending pres-

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