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Effects of LSD on Cortex of Cat Correlated with Changes in Vital Signs

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Introduction

In a previous report[15] it was demonstrated that large doses of lysergic acid diethylamide (LSD) had no consistent effect on primary sensory evoked potentials in the cortex of the cat. However, in a recent publication Purpura[21] reported qualitative differences in the effect of LSD on cortical evoked potentials and postulated that these were due to anatomical differences in the termination of afferents in the cortex, some ending on soma and others on dendrites. Sensory afferents end primarily on the soma of cortical neurons.

In contrast, direct electrical stimulation of the cortex produces a predominantly surface-negative wave, which is generally considered to represent the activity of apical dendrites.[5,8,10] Furthermore, it is also thought to be a postsynaptic potential analogous to the postsynaptic potential of motoneurons in the spinal cord.[9] Also, anatomical evidence has been advanced to indicate that callosal fibers terminate primarily on dendrites or as free endings.[18]

The purposes of the present study were to investigate the effects of LSD on the direct response of the cortex and the transcallosal evoked potential and to correlate the effects on cortical activity with changes in the vital signs of the animal.

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Methods

The methods used for preparation of the animal and electrical recording were the same as those described in a previous report.[15]

The direct response of the cortex was obtained by stimulating the surface of the suprasylvian gyrus with bipolar electrodes made from fine strands of insulated steel wire. The interelectrode distance was 0.5 mm. or less. A monopolar recording electrode was positioned on the cortical surface approximately 2 mm. from the stimulating electrodes, and the indifferent electrode was placed on bone surrounding the craniectomy. The transcallosal evoked potential was recorded with a monopolar electrode on the suprasylvian gyrus in response to stimulation of an approximately symmetrical point on the contralateral suprasylvian gyrus.

Square-wave pulses 0.1 msec. in duration were used for cortical stimulation. The stimulus intensity varied from 2 to 8 volts.

The electrocardiogram was recorded on one channel of the Grass ink-writing oscillograph. The femoral artery was catheterized and the blood pressure measured with a Sanborn electromanometer and single-channel D. C. amplifier. Respiratory changes were determined by observation of the animal and by the respiratory excursions which were usually superimposed on the blood pressure records.

Detailed analysis of evoked potential amplitudes was performed in 26 animals, which received a total of 57 injections of LSD. Because it was often impossible to distinguish the shock artifact from the evoked potential in the EEG records, amplitude measurements were made from the cathode-ray oscilloscope (CRO) traces. Using a microfilm reader, 10 consecutive traces were projected onto graph paper, and the peak amplitudes were plotted and measured. The mean amplitude was calculated for each series of 10 traces during the control period and at numerous times after injection of LSD. The postinjection mean amplitudes are ex-

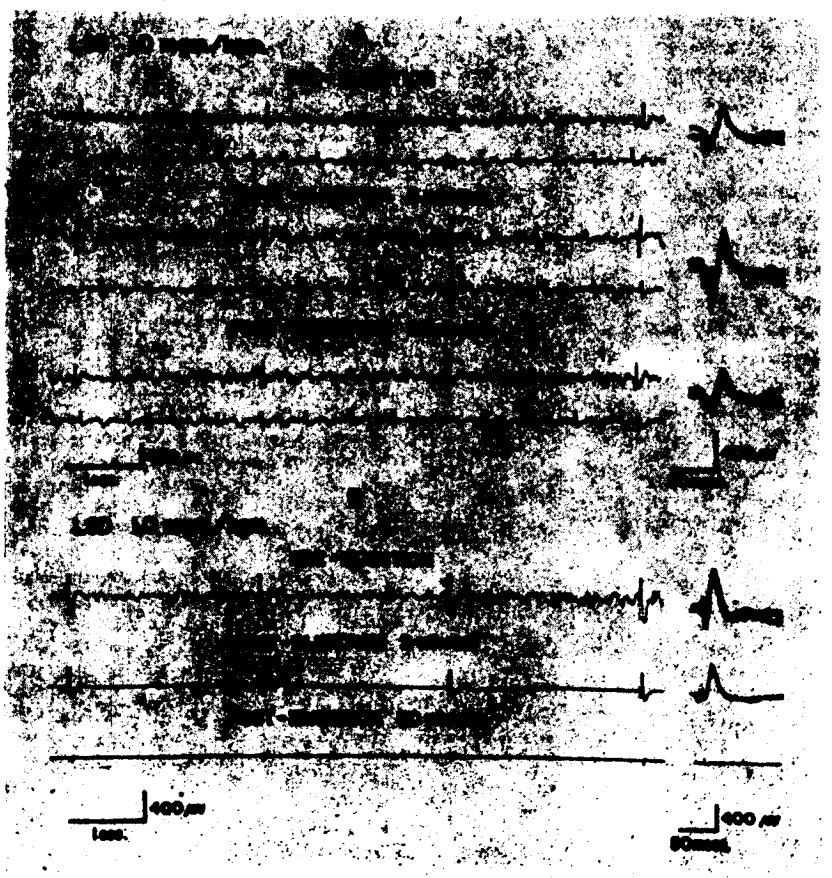
pressed as a percentage of the preinjection mean amplitude in each experiment.

Results

Description of Evoked Potentials

The direct response of the suprasylvian gyrus obtained in these experiments was primarily a surface-negative 20-40 msec. wave. Occasionally a small positive wave preceded the large negative wave, and usually there was a second positive wave, which in a few experiments was as large as the negative component. These findings are in agreement with the descriptions of Chang,[5] Bishop and Clare,[2] and Ochs.[19] Chang also identified a second negative wave, which appeared only with strong stimulation. In some of Chang's and Ochs' illustrations this second negative wave follows the initial

Fig. 1.—*A* (Cat 77): Succinylcholine-treated (Anectinized). LSD 1.0 mg/kg.
Each record shows four evoked potentials at 2.5 sec. intervals. To the right of each record are five single-sweep superimposed CRO traces recorded at approximately the same time as the corresponding EEG record. The top EEG channel of each pair records transcallosal evoked potentials; the lower channel, the EKG. Note preferential facilitation of positive wave after LSD.
Calibration 200μv. Time line 1 sec.
B (Cat 50): Anectinized. LSD 1.0 mg/kg.
Note preferential inhibition of the positive wave of transcallosal evoked potential prior to complete inhibition of cortical activity.
Calibration 200μv. Time line 50 msec.



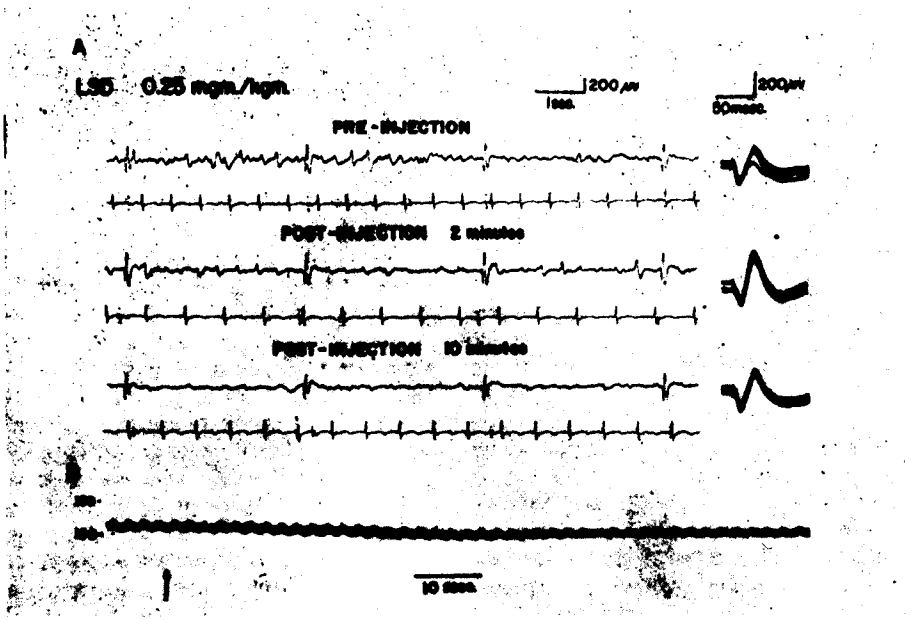


Fig. 2 (Cat 78).—Pentobarbital.
A, transcallosal evoked potentials. LSD 0.25 mg/kg. The lower channel of each EEG pair is the EKG. Description in text.
B, blood pressure record. The figures to the left indicate millimeters of mercury. The arrow indicates injection of LSD 0.25 mg/kg.

negativity without a return to isopotential. In Figure 5 of the present report, two negative peaks can be distinguished in the superimposed CRO traces. In this study interest was focused on the effects of LSD on the primary negative potential.

Transcallosal evoked potentials were recorded in suprasylvian, lateral, and ectosylvian gyri, but the largest and most consistent responses were obtained in the suprasylvian gyrus, a finding which corresponds with those of Chang.[6] Furthermore, the anterior suprasylvian gyrus gave more consistent evoked potentials than the middle or posterior segment, as was also noted by Peacock.[20] Observations on the configuration of the evoked potential in relation to the intensity of stimulation were also similar to those of Chang, i. e., a predominantly surface-negative response with liminal stimulation and a large positive wave with obliteration of the negative component with high stimulus intensities. Most of the evoked potentials used for this study were simple positive-negative responses of 30-50 msec., produced by submaximal stimulation.

Effects of LSD on Transcallosal Potentials

The effects of LSD on transcallosal evoked potentials were studied with doses of 0.2-3.0 mg/kg. In succinylcholine-treated (Anectinized) preparation the results were inconsistent. Doses of 0.5 mg/kg. of LSD had little effect, whereas 1.0 mg/kg. produced significantly varying effects in several animals. These results are illustrated in Figure 1. In *A*, after 1.0 mg/kg. of LSD, the amplitude of the negative component has increased slightly, but there has been preferential increase of the positive wave. Before injection the electrocorticogram showed the typical low-voltage fast activity seen in Anectinized preparations, but at the time of maximum increase of the evoked potentials, marked slowing and an increase in amplitude of the ECG have occurred. This results in greater amplitude variability

among the evoked potentials, which is manifested in this Figure by less precise superimposition of CRO traces. There is also marked bradycardia, which is still present 20 minutes after injection, at a time when the transcallosal potentials have returned to control amplitude.

In Figure 1*B*, from another preparation, injection of 1.0 mg/kg. of LSD has been followed by an equally marked, but opposite, effect. In this instance the negative component of the evoked potential has not changed, at a time when the spontaneous activity of the cortex has disappeared and the positive wave of the evoked potential has been markedly depressed. These observations, that the positive component is more affected in both increase and decrease of the transcallosal potential, are not confirmed in other experiments. In fact, after injections in two animals the negative wave was increased two- and threefold, and the positive wave was proportionately decreased.

When LSD was administered to animals under pentobarbital anesthesia, there was a consistent lack of effect on the amplitude of the transcallosal potentials with all doses. In only two instances was there a decrease of 50% or more, and in only one animal was there a significant increase. Figure 2 shows a 40% increase of evoked potentials two minutes after the injection of 0.25 mg/kg. of LSD in a deeply anesthetized animal. An increase of the negative component has occurred without change in the positive wave, the reverse of the effects observed in Figure 1. Figure 2*B* is the blood pressure record from this animal, with superimposed respiratory excursions. There has been a slight decrease in blood pressure, bradycardia, and some reduction in respiratory rate. All of these effects occurred less than one minute after injection. In contrast, Figure 3 shows abolition of the evoked potential, except for a small positive wave, after 1.0 mg/kg. of LSD. Spontaneous cor-

Fig. 3 (Cat 75).—Pentobarbital.
A, transcallosal evoked potential. LSD 1.0 mg/kg.
The lower channel of each EEG pair is the EKG. Note the marked bradycardia at the time of almost complete inhibition of transcallosal potential.
B, blood pressure record. One arrow: injection of LSD 1.0 mg/kg.; two arrows: respirator on. Note the marked arrhythmia. Further description in text.

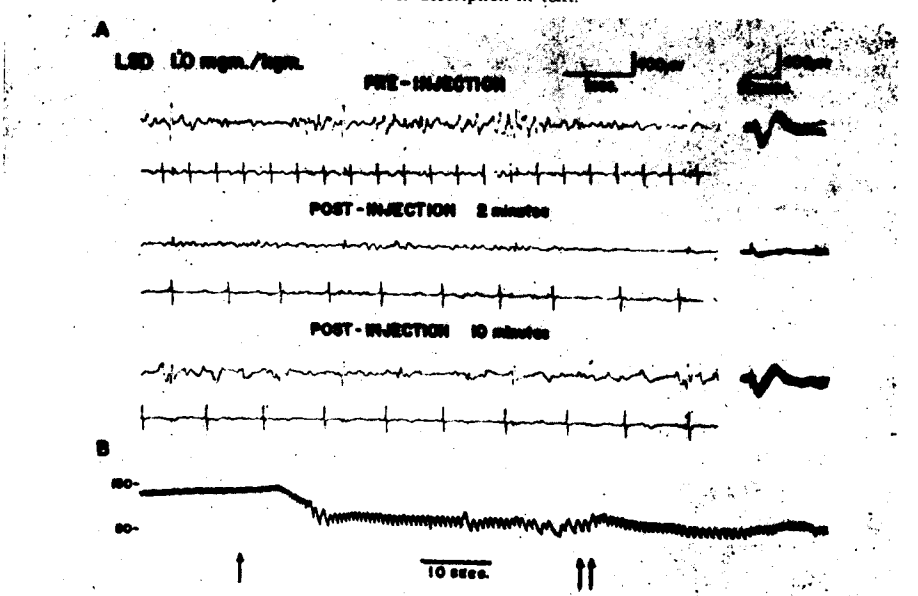


TABLE 1.—*Effect of LSD on the Transcallosal Evoked Potential* *
Succinylcholine (Anectine)

Animal No.	LSD, Mg/Kg.	Postinjection Times, Min. 2	5	10	20	30	60
71	0.1	100	105	105		80	85
73	0.25	95	85	80	85		85
77	0.25	90	90	125	110		145
73 †	0.5	145	110	110	125		140
77 †	0.5	85	90	95	100		70
50	1.0	65	0		0		
76	1.0	95	70	70			
73 ‡	1.0	70	100	95	90		125
77 ‡	1.0	95	200	150	100		155
55	2.0	30	0		0		
73 §	3.0	55		50	100		
77 §	3.0	30	50	80	80		

* Postinjection mean amplitudes are expressed as the percentage of preinjection mean amplitudes.

In those preparations which received multiple injections, † indicates second injection; ‡, third injection, and §, fourth injection.

tical activity is still present, though greatly depressed. There is marked bradycardia and a profound fall in blood pressure, seen in *B*. Respiratory excursions are difficult to detect in this record, but the animal was observed to stop breathing within 10 seconds after the injection. Bradycardia was

TABLE 2.—*Effect of LSD on the Transcallosal Evoked Potential* *
Pentobarbital

Animal No.	LSD, Mg/Kg	Postinjection Times, Min. 2	5	10	20	30	60
70	0.25	110	85	75	85	60	
74	0.25	90	100	90	85		80
75	0.25	95	110	110	90		85
78	0.25	140	125	110	95		100
80	0.25	90	90				
74 †	0.5	65	90	100	100		70
75 †	0.5	105	90	100			110
78 †	0.5	100	110	105	100		100
80 †	0.5	100	60	140	115		
54 †	0.75	85	80	80	85		80
49	1.0	80	80	80		80	
49 †	1.0	110	125	100	60		65
74 ‡	1.0	105	100	120	130		100
75 ‡	1.0	20	70	115			80
78 ‡	1.0	85	110	110	110		110
80 ‡	1.0	95	110	85		75	
79	2.0	80	30	100		120	100
74 §	3.0	100	120	130	115		95
75 §	3.0	95	105	100		110	115
78 §	3.0	90	100	100	100		

* Postinjection mean amplitudes are expressed as the percentages of preinjection mean amplitudes.

† Second injection.

‡ Third injection.

§ Fourth injection.

followed by cardiac arrhythmia, at which time mechanical ventilation was begun. Ten minutes after injection, at the time of recovery of evoked potentials, the blood pressure had approached the control level.

The effects of LSD on the transcallosal evoked potential are indicated in Tables 1 and 2.

Effects of LSD on the Direct Cortical Response

Effects on Amplitude.—The effects of LSD on the amplitude of the direct response were no more consistent than those observed on the transcallosal potentials. In Anectinized animals abolition of all cortical activity, with failure to recover, occurred in three animals, two of which received 0.5

TABLE 3.—*Effect of LSD on the Direct Response of the Suprasylvian Gyrus* *
Succinylcholine (Anectine)

Animal No.	LSD, Mg/Kg.	Postinjection Times, Min. 2	5	10	20	30	60
71 †	0.1	100	135	135		125	200
58	0.25	115	115	85		110	105
59	0.25	125	115	100	90		85
57	0.5	80	0			0	
63	0.5	115	165	170	165		225
57 †	0.5	60	0			0	
59 †	0.5	100	90	125	90		85
63 †	0.5	110	110	110	110		95
64	1.0	100	0			0	
71 ‡	1.0	90	90	75	100		95
63 ‡	2.0	85	120	115	110		85

* Postinjection mean amplitudes are expressed as the percentages of preinjection mean amplitudes.

† Second injection.

‡ Third injection.

mg/kg. of LSD. In two other preparations, which received 0.1 and 0.5 mg/kg., respectively, there was a gradual increase to two times the control amplitude at the end of an hour. These data are presented in Table 3. Figure 4 shows a slight increase in amplitude of the direct response, which undoubtedly is not significant. A slight but distinct bradycardia has occurred and also, in *B*, a transient increase in blood pressure. The excursions of the respirator are clearly seen on the blood-pressure tracing. In Figure 5 the amplitude of the direct response has gradually increased during the 60 minutes after injection. Also, there has

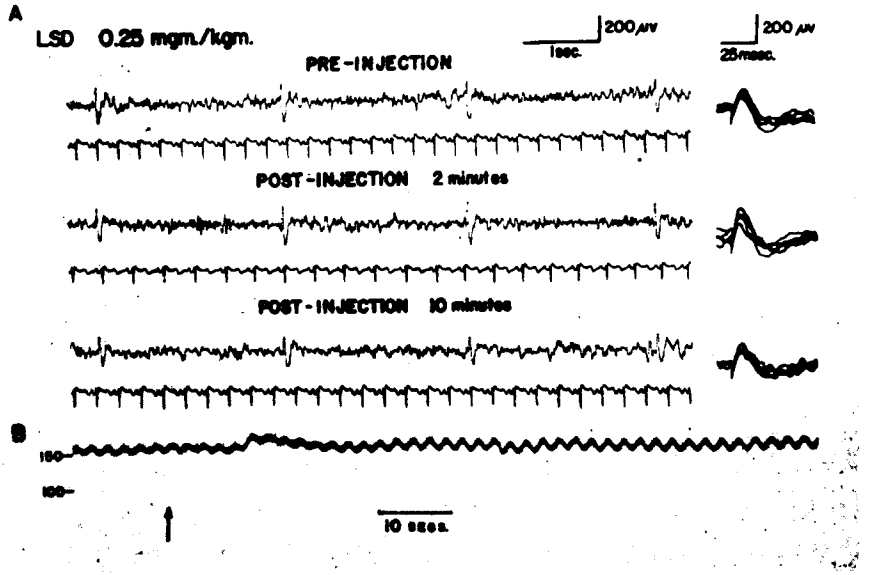
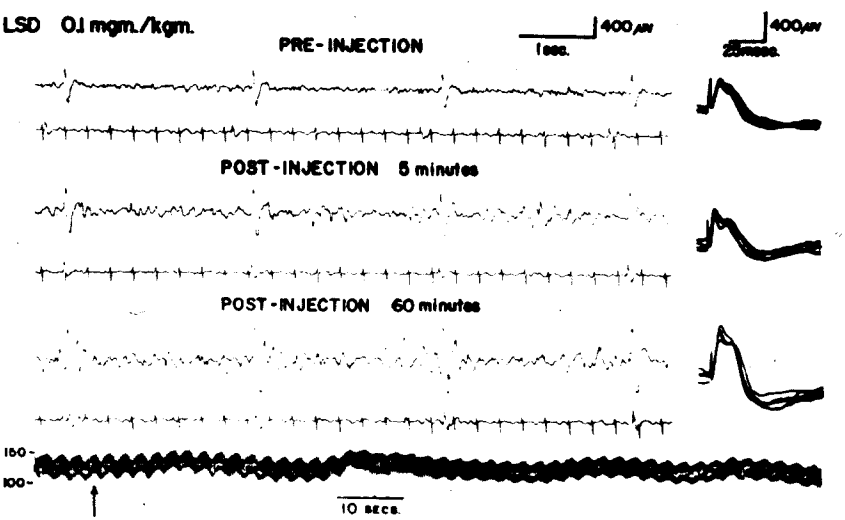


Fig. 4 (Cat 59).—Anectinized.
A, direct cortical response. LSD 0.25 mg/kg.
The lower channel of each EEG pair is the EKG.
B, blood pressure record. Arrow: injection of LSD 0.25 mg/kg. Description in text.

Fig. 5 (Cat 71).—Anectinized.
A, direct cortical response. LSD 0.1 mg/kg.
The lower channel of each EEG pair is the EKG. Note the second negative peak in the CRO traces.
B, blood pressure record. Arrow: injection LSD 0.1 mg/kg.



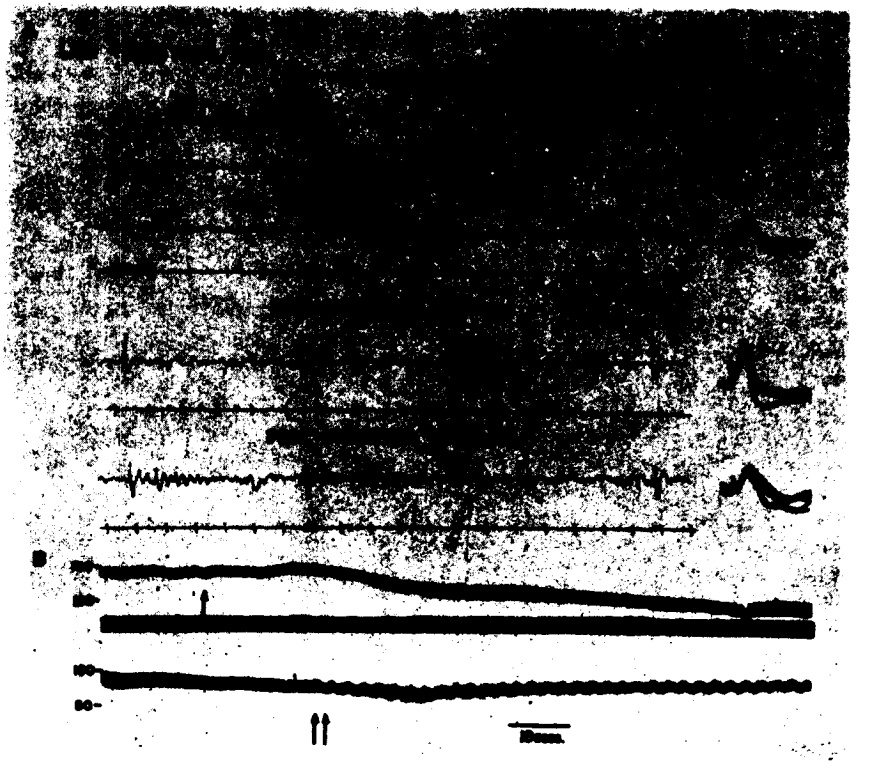
been a progressive increase in a positive wave following the primary negative deflection. It appears unlikely that LSD was responsible for a gradual increase over such a long time, since this was observed in only two animals. A possible explanation is a gradual change in the pressure of contact of the electrode with the cortical surface. On occasion, marked changes in the size of the shock artifact occurred in association with abolition of cortical activity and marked cardiovascular depression after large doses of LSD. This may have resulted in decreased volume of the brain and decreased contact of the electrode, which increased the resistance. In contrast, since it has been shown that the positive wave in Figure 5 has a higher response threshold

TABLE 4.—*Effect of LSD on the Direct Response of the Suprasylvian Gyrus* *
Pentobarbital

Animal No.	LSD, Mg/Kg.	Postinjection Times, Min. 2	5	10	20	30	60
70 †	0.1	115	130	80		80	65
70 ‡	0.1	75	95	85	75		65
68	0.25	95	50	145			90
69	0.25	70	30	30	45	55	60
69 †	0.25	45	0			0	
53	0.5	95	80	80	90	85	85
65	0.5	130	70	0		0	
66	0.5	110	135	140		120	105
67	0.5	80	0	50	95	95	90
68 †	0.5	145	150	115		115	90
68 †	0.5	100	0			0	
54	0.75	125	125	120	120		115
67 †	1.0	90	115		130		105
54 ‡	4.0	100	105	115	115	115	

* Postinjection mean amplitudes are expressed in percentages of preinjection mean amplitudes.
† Second injection.
‡ Third injection.

Fig. 6 (Cat 68).—Pentobarbital.
A, direct cortical response. LSD 0.25 mg/kg.
The lower channel of each EEG pair is the EKG. Description in text.
B, blood pressure record. Arrow: injection of LSD 0.25 mg/kg. Note cessation of respirations after injection.



than the preceding negative wave,[5] the increase of the former in this experiment may be explained on the basis of more effective contact between the electrode and the cortex.

Table 4 lists the data for the effects of LSD on the direct response in animals anesthetized with pentobarbital. Complete abolition of evoked potentials and 50% increase are seen in different preparations. In Figure 6 there is a 50% decrease, followed by an equally marked increase and then recovery, after 0.5 mg/kg. of LSD. In this animal severe respiratory depression occurred within a few seconds following injection, as shown in Figure 6*B*. Artificial ventilation was not used, and the animal remained apneic for four minutes. At this time respirations began again spontaneously; the blood pressure increased, and the evoked potentials regained control amplitude. The evoked potentials then increased to 145% of the control and one hour after injection had returned to normal.

Effects on Peak Time of Initial Negative Wave.—Changes in evoked potentials other than an increase or decrease in amplitude, e. g., changes in configuration, latency, or duration, may occur as manifestations of a drug effect. It has been noted that a second negative peak was seen occasionally in the direct cortical response (Fig. 5). In one animal injection of LSD was followed by obliteration of the second negative wave without a change in amplitude of the initial negative wave. Ten minutes following injection it had reappeared but did not regain preinjection amplitude.

Attempts to measure the latency of the direct cortical response were unsuccessful because of difficulty in controlling the amplitude of the shock artifact. However, in a series of 10 injections measurements were made of the time between the beginning of the shock artifact and the peak of the negative wave, immediately before and several times after the administration of LSD. Initial negative peak times varied from 9.7 to 17.0 msec., but within a series of 10 consecutive sweeps the variation was usually less than 10%. Following LSD, changes in peak time were dependent on changes in amplitude, prolongation of conduction time occurring with a decrease in mean amplitude of 50% or more. The maximum increase in peak time was 4.4 msec. and occurred when there was a 75% decrease in amplitude of the evoked potentials. Following two injections there was an increase in amplitude of the evoked potentials, associated with a decrease in peak time of 3.4 and 1 msec., respectively.

Cardiovascular Effects of LSD

The cardiovascular change most commonly observed after LSD was bradycardia. This occurred uniformly after all doses except 0.1 mg/kg. Furthermore, in most experiments the bradycardia outlasted whatever changes occurred in cortical activity. With large doses there was frequent cardiac arrhythmia, which at times progressed to brief periods of asystole. However, in none of the experiments did LSD cause death of the animal, despite profound cardiovascular and respiratory effects. Marked variation was seen in blood pressure re-

TABLE 5.—*Mean Arterial Blood Pressure in All Animals with Inhibition of Evoked Potentials of 50% or More*

Animal No.	LSD, Mg/Kg.	Control	Postinjection Times, Min. 2	5	10	20	60
		Succinylcholine					
57	0.5	125	35				170
57 *	0.5	135	85	100			
50	1.0	160	50		50		
54	1.0	135	0	55	20		
55	2.0	130		30	50		
73 †	3.0	145	85	165	165		165
77 †	3.0	100	55	110			
		Pentobarbital					
68	0.25	150	80	100	130		
69	0.25	165	80	105	110	110	140
69 *	0.25	115	85	145	160		
65	0.5	140	20	60	70		
67	0.5	150	40	80	90	100	
75 ‡	1.0	130	60	95		130	120
79	2.0	120	45	60	60	120	

* Second injection.
† Third injection.
‡ Fourth injection.

TABLE 6.—*Incidence of Severe Respiratory Depression Following LSD*

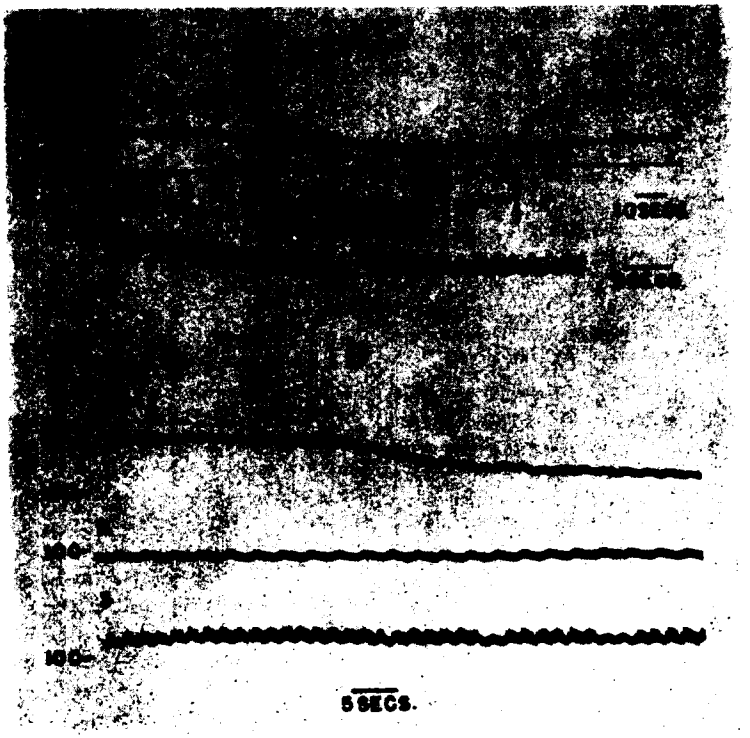
LSD, Mg/Kg.	No. of Injections	Respiratory Depression	Respirator	Recovery
0.05	6	0	--	--
0.01	4	2	1	2
0.25	9	4	3	4
0.5	6	3	3	3
1.0	3	2	2	2
2.0	1	1	1	1
3.0	1	1	1	1

sponses. As shown in Figure 6*B*, the blood pressure was reduced to shock levels by 0.25 mg/kg., but in other experiments 1.0 mg/kg. produced only transient hypotension.

An attempt was made to correlate blood pressure changes with alteration in cortical activity following LSD. Table 5 lists the mean arterial blood pressures of all animals in which there was at least a 50% decrease of evoked potentials after injection of LSD. In each instance there was a significant fall in blood pressure, and after 9 of 14 injections the pressure was decreased to 60 mm. Hg or less. However, after five injections the blood pressure was reduced to 60 mm. Hg, but the evoked potentials were not markedly inhibited.

Fig. 7.—*A* (Cat 84), pentobarbital. The top trace is the blood pressure record. Note the cessation of respiratory excursions after LSD 0.5 mg/kg. At the point midway between the arrows on the right the respirator was turned on. Prior to this, slight spontaneous respiratory excursions have begun. Lower traces: enlarged (× 3) segments of top tracing (indicated by arrows) to show more clearly the respiratory pattern.

B, (Cat 85), pentobarbital. *1*, injection of LSD 0.05 mg/kg., indicated by arrow; *2*, 2 minutes after injection; *3*, 10 minutes after injection. Note the decrease in respiratory rate at 2 minutes and return to normal at 10 minutes.



The Respiratory Effects of LSD

Table 6 lists the incidence of severe respiratory depression following various doses of LSD.

Respiratory changes following approximately half of the injections without a significant relationship of dose to effect except that they were not observed in any animal given 0.05 mg/kg. In Figure 7*A* cessation of respiratory movements followed 0.5 mg/kg. of LSD. The lower inserts are enlarged segments of the same record to demonstrate more clearly the changes which occurred immediately after the drug was given and at the time artificial ventilation was begun. It is evident that prior to starting the respirator slight spontaneous breathing had returned. After two injections (Table 6) apparent apnea occurred and artificial respiration was not used. In both instances natural respirations returned within five minutes. The results for one of these animals are illustrated in Figure 6. Table 6 also shows that there were no deaths from respiratory depression irrespective of whether or not the animals were artificially ventilated.

Figure 7*B* illustrates the observation that changes in respiratory rate frequently followed small doses of LSD. In this animal the rate has been reduced by one-half following the administration of 0.05 mg/kg. of LSD.

Effects of Succinylcholine and Tubocurarine on Cortical Activity

It is undesirable to give additional pharmacological agents to animals which are used to evaluate the effect of a given drug, but in the majority of experimental designs this is unavoidable. In these experiments every animal received either pentobarbital or ether and succinylcholine. The influence of pentobarbital on the action of LSD was included in the study, and it was assumed that the effect of ether could be disregarded two hours after cessation of anesthesia.

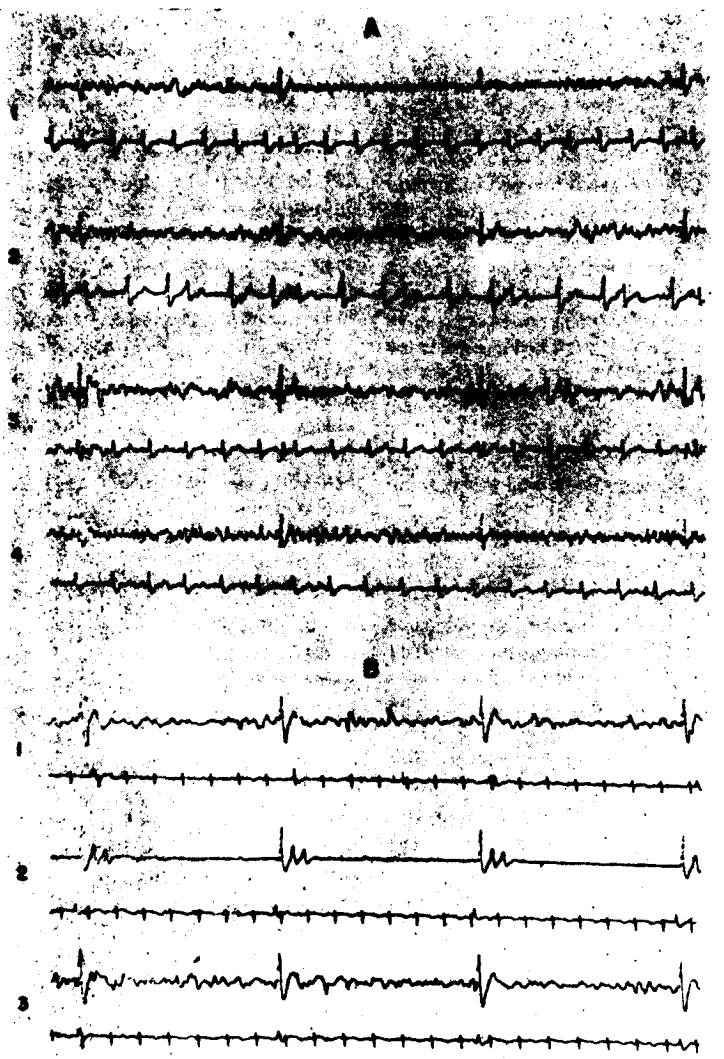
In a majority of the animals EEG records were obtained during the injection of succinylcholine. After injection of 20 mg., the dose used for immobilization of the animal, some effect on either cortical activity or the EKG was noted in about one-fourth of the animals. These effects were always transient, rarely lasting more than two minutes. In rare cases profound changes in both the EKG and cortical activity were observed, as illustrated in Figure 8*A*. In this animal, after the intravenous injection of 20 mg. of succinylcholine chloride, marked cardiac arrhythmia occurred within 20 seconds without a significant change in cortical activity. Forty-five seconds after injection the amplitude of the transcallosal potential was two times the control amplitude and the cardiac rhythm had returned to normal. Ninety seconds after injection both records show normal activity.

A variety of effects occurred in other animals, but the most commonly observed change was cardiac arrhythmia. When profound EKG changes were observed, there were parallel changes in the blood pressure. Usually this consisted of a very rapid fall in pressure, which was never great, followed by a rise to control level within a few minutes.

In a few animals, 3.0 mg/kg. of tubocurarine U. S. P. was given intravenously in order to compare its effects on the cortex with those of succinylcholine. Direct cortical potentials were investigated, and the response illustrated in Figure 8*B* was observed after most of the injections. There was abolition of the electrocorticogram two minutes after injection, but no change in the amplitude of the direct response was observed at any time. Recovery of spontaneous cortical activity was slow, but one hour following injection of the drug it had returned to normal. The waves following each evoked potential (*B2*) were also observed occasionally during marked cortical depression following LSD. These may be analogous to the rhythmic after-discharges observed by Chang[4] in sensory cortex. He found that these were more clearly discerned in animals with cortical depression

from pentobarbital (Nembutal). However in another publication[6] he noted that after discharges were not seen in association with the transcallosal evoked potential, which is more closely related to the direct response than are cortical sensory potentials.

Fig. 8.—(Cat 77). *A*, Anesthetized cat. Succinylcholine chloride 20 mg.
Transcallosal evoked potentials. *1*, preinjection; *2*, postinjection, 20 seconds. Note the marked cardiac arrhythmia. *3*, postinjection, 45 seconds. Note the increase of the transcallosal evoked potentials. *4*, postinjection, 90 seconds. Further description in text.
B.—(Cat 77). Anesthetized cat; tubocurarine U. S. P. 3.0 mg/kg.
Direct cortical response. *1*, preinjection; *2*, postinjection, two minutes. Note the waves, suggesting after-discharge. *3*, one hour after injection.



Comment

The effect of LSD on the transcallosal evoked potential and the direct cortical response were no more consistent than the effects of LSD on sensory cortex.[15] Occasionally 0.25 mg/kg. produced complete abolition of cortical activity, whereas in another animal 4.0 mg/kg. produced no detectable effect. In general, profound depression of all cortical activity occurred more frequently than in the previous study.

These results differ from those of Marrazzi and Hart,[16,17] who reported decrease of the negative component of the transcallosal evoked potential following intracarotid doses of LSD as small as 0.008 mg/kg., and of Purpura,[21] who found that 0.025 mg/kg., injected intravenously, decreased the suprasylvian-striate response, which is also considered to be a cortical dendritic potential. Marrazzi and Hart used pentobarbital-treated (Nembutalized) animals exclusively, whereas Purpura's animals were unanesthetized. In the present investigation, differences in the effect of LSD on evoked potentials in anesthetized and Anectinized animals were considered too variable to be significant.

The cardiovascular and respiratory effects observed are in general agreement with the findings of Cerletti.[3] In cats anesthetized with chloralose and urethan, hypotension and respiratory depression were seen after 0.04 mg/kg. of LSD. Bradycardia was also seen uniformly, and Cerletti states that, in his experience, tachycardia has not occurred in any pharmacological preparation after LSD. With rather small intracarotid doses, Ingvar and Söderberg[13] reported an increase in blood pressure and increased cerebral vascular resistance.

In several animals in the current study marked depression of cortical activity and blood pressure followed 1.0 mg/kg. or less of LSD, but subsequent injections of 1.0, 2.0, or 3.0 mg/kg. produced only slight changes. Although the number of examples is small, these results suggest that tolerance to the drug has developed. In these experiments multiple injections were given no less than one hour apart. There have been few comments on the development of tolerance to LSD in acute animal preparations, but several investigators have shown that daily doses of approximately 0.001 mg/kg. administered to human subjects resulted in tolerance to the psychotomimetic effects of LSD after seven days.[1,7,14]

In two series of experiments[15] we have failed to find a significant effect of LSD on several different cortical evoked potentials, and changes in the natural activity of the cortex occurred only with large doses. On the basis of these experiments it might be concluded that the cortex is relatively insensitive to LSD, and, therefore, it is unlikely that the psychotomimetic effects in man are caused by an action of LSD on the cortex. However, there is a paucity of information on the neurophysiological signs of both drug-induced and functional disturbances of the mind.[12] Therefore, it seems more likely that these results reflect the inadequacy of present electrophysiological techniques in evaluating drugs that affect behavior, and that they do not necessarily eliminate the cortex as a site of action of LSD.

Summary and Conclusions

The effects of LSD on the transcallosal evoked potential and the direct cortical response were investigated in 26 cats. Doses from 0.1 to 4.0 mg/kg. were administered intravenously.

There was a marked inconsistency in the effects of LSD on the evoked potentials. Occasionally, 0.25 mg/kg. produced inhibition of all cortical activity, but in several animals 3.0 mg/kg. had no detectable effect on the amplitude of the evoked potentials.

Prolongation of conduction time occurred in association with a marked decrease of the initial surface-negative wave of the direct cortical response.

In a majority of the animals a decrease of evoked potentials of 50% or more occurred only in association with bradycardia,

arrhythmia, marked hypotension, and, in the anesthetized animals, respiratory depression.

The effects of succinylcholine and tubocurarine on cortical activity were investigated in several animals.

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