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Effects of LSD-25 on the EEG and Photic Evoked Responses

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SINCE the accidental discovery of the psychosomimetic properties of Lysergic acid diethylamide (LSD-25) by Stoll,[1] in 1947, a great amount of work has been carried out to elucidate the behavioral effects and pathophysiological mechanisms of action of this substance. The literature on this topic is steadily growing and contains now more than 1,000 publications.[2]

There are several studies available that report on the electroencephalographic changes resulting from LSD administration to humans as seen by surface recordings [3-9] and there are also some observations on changes in the human depth electrogram.[10-13] It is generally agreed that the amplitude of the EEG decreases, α-rhythms tend to disappear and the tracings become of the low-voltage fast or desynchronized type. Gastaut [4] reported that the average α-frequencies are increased by 0.5 to 4 cycles per second (cps) and Grey Walter [7] noted an increase from 11.6 to 12.7 cps in one subject. Most studies were carried out by simple visual inspection of the recordings except for that by Grey Walter who used toposcopic analysis and that by Goldstein et al,[8] who used Drohocki's integrator. A decrease in energy content and decrease of variability of the EEG as the result of LSD was observed by the latter method. The findings were similar to what was seen in the resting EEG's of chronic schizophrenic patients.

Within recent years electronic equipment has become available that makes it possible to detect responses evoked by sensory stimulation, through the intact skull, in most human beings. The visual system has been studied most extensively in the normal by a great number of authors.[14-19] The somatosensory evoked potential in normals and psychiatric patients was studied mostly by Shagass and Schwartz.[20] These authors reported also, that the intensity response gradients of this potential were not appreciably altered as a result of LSD administration.[21]

Inasmuch as visual changes form a prominent part of the LSD psychosis it was of great interest to ascertain whether the visually evoked potential would be altered in a consistent manner by this drug. The study presented here was undertaken for this reason.

Materials and Methods

Eight healthy young adult male student volunteer subjects participated in the investigation. The experiments were started at 8 AM, and the subjects had not had breakfast. After arrival in the laboratory the pupils were fixed in dilatation by means of cyclopentolate (Cyclogyl). Electrodes were applied in a bilaterally symmetrical manner to the occipital and the parietal areas as well as to the supraorbital regions, in order to record the electroretinogram. The signals were amplified by an electroencephalograph. A bipolar type of electrode montage was employed for the recordings from the occipital and parietal areas. The supraorbital electrodes were

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linked to the ipsilateral ear. The output of the EEG was connected to a five-channel tape-recording system which in turn was connected to a computer of average transients (CAT). The evoked responses were written out on an XY plotter. The subjects reclined in a comfortable chair in a darkened room and had their eyes closed throughout the experimental procedure. Prior to photic stimulation, a ten minute resting record was obtained to determine the basic frequency characteristics of the subject's EEG. Photic stimulation was then carried out by means of a photic stimulator. The light source was 8 inches from the subject's closed eyes. The intensity scale of the stimulator was set at "8." The flashes were delivered in two series: one consisting of 100 flashes repeated at the rate of one flash per second and the other of 200 flashes repeated at the rate of three flashes per second.

After control observations had been obtained, LSD-25 was started by intravenous drip in a dosage of 1μg/kg. In order to detect possible early changes in the evoked response photic stimulation was carried out at the rate of one flash per second throughout the infusion. This lasted usually approximately 15 minutes, subsequently another EEG, without photic stimulation was obtained. Then the two series of 100 flashes at one flash per second and 200 flashes at three flashes per second were repeated. The results of these series are designated "LSD I" in the text. After this, the volunteers were interviewed in regard to their subjective sensations. The mental status was tested and a brief neurological examination was performed. This lasted usually about 20 minutes. The room was subsequently darkened again and the two series of photic stimulations were repeated. At the end of testing another five minutes of resting EEG was obtained. These results will appear in the text as "LSD II."

The subjects were then taken to the neurological ward and kept under observation for the rest of the day. Psychiatric interviews were carried out during this time. One subject who had a profound psychotic reaction was kept overnight on the ward.

The entire EEG data was available on magnetic tape and could subsequently be analyzed in various ways. The basic EEG was subjected to automatic frequency analysis by means of a 2-channel frequency analyzer. For graphic demonstration of the results of frequency analysis a 40-second period of integration was used. The evoked response curves were written out on two different settings. An analysis time of one second which allowed observations on the late components of the evoked response (after rhythm) and an analysis time of 250 milliseconds, which provided the basic information about the main components of the visually evoked response proper, were used.

Inasmuch as it is well known that there are considerable variations in the photic evoked responses of normal individuals it can become difficult to determine what the effects of a given agent are on the various components of the response. In order to obtain this information the evoked response curves of all the 8 subjects were added on the CAT computer. This was done separately for the one flash per second and the three flashes per second recordings. It reduced markedly the complexity of the curves and provided one single curve for each of the various experimental conditions. It allowed immediate comparison between evoked responses obtained prior to the drug administration and the conditions designated as "LSD I" and "LSD II." In order to compare the condition of one flash per second and three flashes per second the first 100 flashes were used of the three flashes per second series and all the results presented here will deal with the responses to 100 flashes only. Because of technical difficulties involving magnetic tapes the electroretinographic curves could be added for six subjects only.

The method of adding various individual curves to form one summed response contains, however, a potential source of error especially in a small sample. It is possible that one or two individuals with unusual responses may induce characteristics which are quite striking but represent only a small fraction of the population. In order to avoid this hazard the individual curves of the subjects were also compared in detail in regard to the various components of the responses.

Results

Clinical Observations.—All subjects experienced striking changes in their mental and emotional functions as a result of drug administration. The symptoms usually started towards the end of the infusion period but were delayed in one subject to one hour after drug administration had been discontinued. The maximum effect occurred usually about one to two hours after the infusion. The earliest manifestations were autonomic and consisted of flushing, respiratory irregularity, dizziness, and tingling of toes and fingers. These were followed by visual changes in seven of the subjects and were reported as the flashing light (photic stimulation) becoming brighter, more intense, and more colorful. Visual distortions were also noted when the subjects had the eyes opened and consisted mostly of magnification of details, for instance in the grain of a door or of the brush strokes on a painted wall. Body image disturbance with depersonalization, derealization, and estrangement were next in sequence and of long duration. The sensation of detached self-observation occurred

frequently. Mood was predominantly euphoric and the entire experience was considered pleasurable. Only one student had a true psychosomimetic response with panic and then paranoid development. The terror was still present 24 hours later. The fact that only one subject had an adverse experience was probably determined by our use of isolation and protection from sensory overloading. As one student said, "I wanted to be alone but at the same time certain that someone was there." All subjects reported distortions of time sense and these occurred in the direction of both slowing and quickening.

Serial 7 subtractions were performed slowly and haltingly with the subjects demonstrating marked difficulty in maintaining a set of ideas. Proverb interpretation remained abstract.

The clinical neurological examinations were unremarkable except for slight cog wheel rigidity in the shoulder girdle musculature of three subjects and the deep tendon reflexes, especially in the upper extremities, became somewhat sluggish in three.

Sensory testing did not reveal any evidence for either decreased or increased sensation. Vibratory sense appreciation was neither prolonged nor shortened and two point discrimination remained likewise normal. Graphesthesia tended to be impaired but this was due to inattention on the part of the subjects and not a loss of function because it could be brought to normal when attention was maintained.

Electroencephalographic Observations.—A. Frequency Analysis: The outstanding feature in the resting records was a progressive desynchronization. The records became lower in voltage and α-rhythm decreased. The progressive decrease in output of electrical energy under the various test conditions is shown in Fig 1. The curves represent the mean values of analyzer pen deflections for the various frequencies measured in millimeters. They are a composite of all eight individuals. It can be seen that the energy output is progressively reduced for all frequencies sampled but least

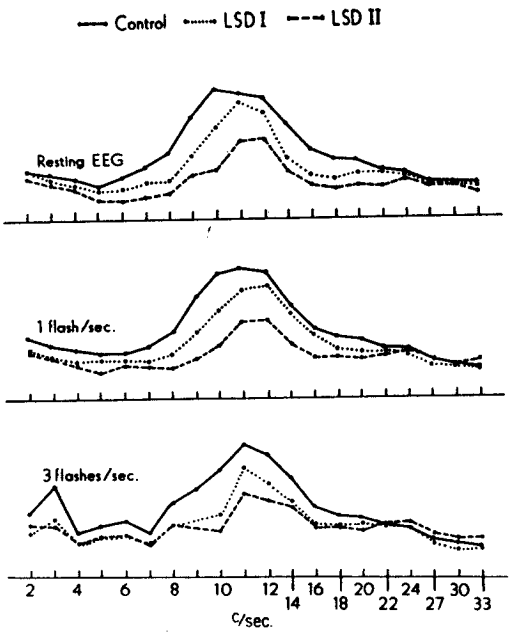

Fig 1.—Effects of LSD on EEG frequency analysis (mean of eight subjects) in resting state and during photic stimulation. Note the progressive decrease of energy output in most frequency bands except for fast activity which is unaffected. The photic driving response at 3 flashes/second is also reduced.

so in the high frequencies. The seeming increase in fast activity on inspection of the EEG tracings is therefore, in most instances, not a result of an actual increase in fast frequencies but due to a decrease of the slower frequencies which allows fast activity to appear more prominent. An actual increase in fast activity could be demonstrated by frequency analysis in three subjects only. The photic driving response

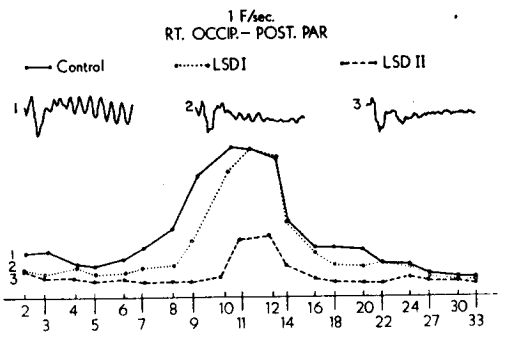

Fig 2.—Effect of LSD on frequency analysis and occipital evoked response. The rhythmic after discharge of the visually evoked occipital potential disappears as the EEG becomes progressively desynchronized. The events occurring within one second after the flash are shown in the top traces.

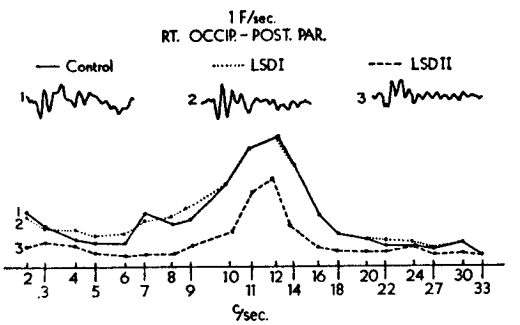

Fig 3.—Effect of LSD on frequency analysis and occipital evoked response. Example of "improvement" of rhythmic after discharge resulting from LSD administration. Frequency analysis shows slower components in the δ- and θ-range have decreased markedly leaving a single α-peak.

as shown by the amount of 3 cps activity is clearly reduced at that flash rate. This can be seen in the bottom segment of the figure. An important aspect of these observations is that LSD showed its most marked effects on the EEG about half an hour after the infusion had been stopped.

B. Visually Evoked Responses: 1. "After Rhythms." The late events following a single flash have been variously designated as "after discharge," "ringing phenomenon," or "after rhythm." Figure 2 presents an example of the effects of LSD on this phenomenon and places it also in relationship to the frequency analysis of the basic EEG. It is apparent that the rhythmic activity appearing at about 300 milliseconds after the flash is progressively reduced as a result of LSD administration. It parallels the decrease in energy output of the basic EEG. This progressive decrease in after rhythm was observed in six of the eight subjects tested. The after rhythm did not change appreciably in one and it actually improved somewhat in another. This was due to the fact that it had contained a considerable amount of slow activity prior to the LSD administration. These slower components disappeared and the rhythms in the α-frequency range became relatively more prominent, Fig 3.

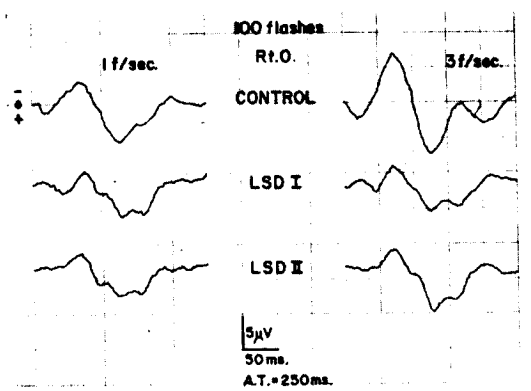

Fig 4.—Example of LSD effect on occipital evoked response. There is no pronounced change when 1 flash/second is used but a reduction in amplitude of the potential can be noted with 3 flashes/second.

2. Visually Evoked Response Proper. As can be seen from Fig 2 and 3, the early components of the evoked response tended to show a reduction in amplitude. This is seen somewhat better, however, when only those events which occur within 250 milliseconds after the flash are written out (Fig 4). The changes in the evoked response proper were, however, not very marked. The most consistent finding was a slight decrease in amplitude of the major positive component. The fact that these changes were indeed quite slight can be observed by a comparison of the summed curves, as shown in Fig 5. There is no marked change at flash rate of one per second while there is some reduction in amplitude of the major positive component at three flashes per second.

Individual inspection of the records showed that there were no consistent changes in amplitude or latency of the components prior to the major positive peak, at flash rate of one per second. A slight decrease in amplitude of the major positive peak occurred in six of the subjects, it remained unchanged in two. Individual inspections of the latencies of this component showed a slight decrease in four subjects; they remained the same in two and increased in two others. The apparent increase in latency as shown on "LSD I" in Fig 5 is actually due to one subject only who had originally two positive peaks, one at 110 milliseconds and the other at 160 milliseconds. Immediately after LSD administration the 110 millisecond peak decreased markedly but the second positive peak remained unaffected and is, therefore, represented on the summed curve.

At three flashes per second the 30 millisecond negative peak appeared in four of the eight subjects and the amplitude of the major positive peak was decreased somewhat in seven subjects. It showed a slight increase in one.

3. Electroretinogram: The summed retinal responses for six subjects are shown in Fig 6. It can be noted that in the control condition the small negative α wave, with its peak at 15 milliseconds, is of similar amplitude at one flash and three flashes per second. However, the large positive β-wave with its peak at 50 milliseconds is higher at one flash than at three flashes per second. LSD did not influence the α-wave in a consistent manner at either flash rate but the β-wave increased somewhat in amplitude at both flash rates. Study of the individual subject's curves showed that this increase in the β-wave occurred in four of the six subjects. The β-wave decreased slightly in one and remained unchanged in another. There was no consistent change in the latencies of this wave. The amplitude of the α wave showed no change in three subjects, a decrease in two, and an increase in one other. There was no consistent change in late components of the electroretinogram.

Comment

After completion of the investigation and during the time this report was prepared, a study appeared in the literature by Chapman[22] dealing with changes in the occipital evoked potential as a result of LSD administration. Although the techniques differed somewhat, especially in regard to dosage and route of drug administration, the main findings were quite consistent in the two studies. Chapman noted, likewise, a disappearance of the rhythmic after discharge and a decrease in amplitude of the major positive component of the occipital potential. The disappearance of the rhythmic after discharge is undoubtedly related to the changes that are taking place in the background EEG because rhythms in the α-frequency range are usually replaced by low-voltage desynchronized activity after drug administration. It is important to

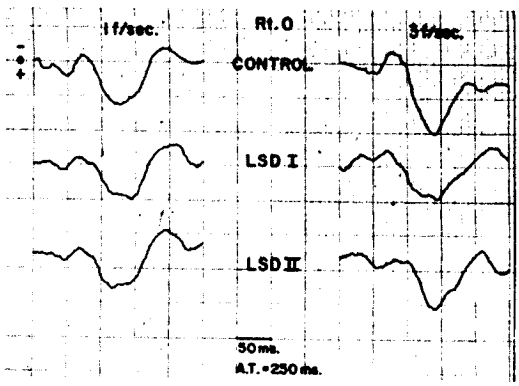

Fig 5.—Summed occipital responses of eight subjects before and after LSD administration. There are no pronounced changes at 1 flash/second. Some decrease in amplitude occurs when 3 flashes/second are used.

point out that LSD does not produce, for the most part, an actual increase in fast activity, as for instance, barbiturates or chlordiazepoxide hydrochloride (Librium), but it decreases the amount of slower components in the resting EEG thereby giving an impression of having produced a faster recording. Frequency analysis demonstrates this phenomenon quite clearly. The changes in those components of the evoked potential which occur within 250 milliseconds after the flash are quite minor and more pronounced at somewhat more rapid flash repetition than at slower flash rates. They consisted mainly of a slight decrease in amplitude of the major positive component and this as well as the inconsistent latency changes agreed with Chapman's observations. Inasmuch as the major positive component is also reduced in amplitude when

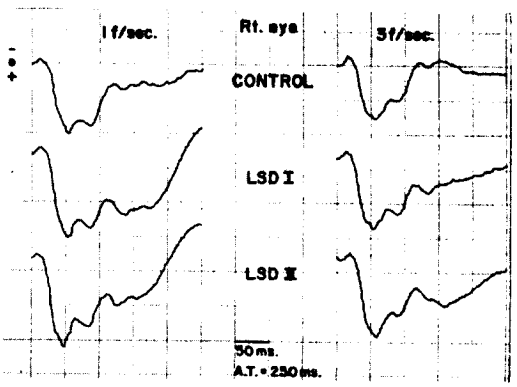

Fig 6.—Summed electroretinographic responses of six subjects before and after LSD administration. An increase in amplitude of the β-wave can be noted after drug infusion.

the subjects have the eyes open or perform arithmetic tasks mentally,[23] it is likely that this reduction is the physiological accompaniment of the diffusely heightened sensory perceptions of the subjects. This heightened awareness to internal as well as external sensations is of course a prominent feature of the LSD state.

The changes in the electroretinogram in form of an increase in the β-wave are of interest because they demonstrate that visual perceptions could be altered by drug induced changes in the periphery. This increase in the β-wave of the ERG, as a result of LSD, had also been noted by Ostfeld[24] in human volunteers. He reported, however, in addition that blind persons with no measureable ERG did show "significantly more 'hallucinations' (unusual visual experiences) after LSD than after placebo administration." These findings indicate that, although the retina participates in the toxic process, it is not the main or sole area responsible for the subjective visual changes.

There is one other observation in the material presented here that deserves further comment. The drug was given intravenously in order to obtain a rapid concentration in the brain. It was expected that the height of the psychotic-like symptomatology would be reached within a few minutes after the infusion was terminated and it was furthermore expected that the clinical and the electroencephalographic changes would begin to subside thereafter. This was not the case. Although some of the symptoms were present immediately after the infusion was terminated, they increased subsequently over the next one to two hours. The data on the frequency analysis of the EEG and the changes in the ERG showed that the most pronounced effects were actually at the time when the electrographic testing was terminated. This was approximately 30 to 40 minutes after cessation of drug infusion. Further electrographic changes may well have taken place subsequently. This finding of gradually progressive change, after the maximum amount of drug had been administered, is in contrast to what is seen with other drugs like: barbiturates, chlordiazepoxide, or convulsants which show the maximum effect at the time of maximum dosage. The psychosomimetic agent phencyclidine hydrochloride, likewise, shows its maximum clinical and electrographic effects during and immediately after drug infusion.[25] The unusual behavior of LSD in this respect, suggests that the psychosomimetic properties of this agent are probably not the result of the immediate interaction of the compound itself with nervous tissue. It appears more likely that the symptoms which are of psychiatric importance are due to secondary effects. They may occur either as a result of a breakdown product of the drug itself, or through excessive stimulation or inhibition of normal body metabolites.

Summary

LSD-25 was administered by intravenous drip to eight healthy volunteer subjects in a dose of 1μg/kg. It was observed that the EEG showed progressive desynchronization. Slower frequencies were more affected than those in the β-range. The "rhythmic after discharge" of the photic evoked potential disappeared in most instances and the major positive component of the potential tended to decrease somewhat in amplitude. The β-wave of the electroretinogram tended to increase in amplitude. Latency shifts were not pronounced either in the occipital response or in the electroretinogram. The drug effect increased progressively over a period of one to two hours after the infusion had been stopped. This suggests that the mechanism for the psychosomimetic action of LSD lies in alterations of body metabolites rather than in a direct action of the drug on the brain.

Generic and Trade Names of Drugs

Cyclopentolate—*Cyclogyl.*

Chlordiazepoxide hydrochloride—*Librium.*

REFERENCES

1. Stoll, W.A.: LSD, a Hallucinatory Agent From the Ergot Group, *Schweiz Arch Neurol Psychiat* **60**:279, 1947.

2. Annotated Bibliography, *Delysid LSD 25,* Hanover, NJ: Sandoz Pharmaceuticals.

3. Bradley, P.B.; Elkes, C.; and Elkes, J.: On Some Effects of Lysergic Acid Diethylamide (LSD 25) in Normal Volunteers, *J Physiol* **121**:50-51, 1953.

4. Gastaut, H.; Ferrer, S.; and Castells, C.: Action de la diéthylamide de l'acide d-lysergique (LSD 25) sur les fonctions psychiques et l'électroencephalogramme, *Confin Neurol* **3**:102-120, 1953.

5. Elkes, J.; Elkes, C.; and Bradley, P.B.: The Effect of Some Drugs on the Electrical Activity of the Brain, and on Behavior, *J Ment Sci* **100**:125-128, 1954.

6. Bente, D.; Itil, T.; and Schmid, E.E.: Elektroencephalographische Studien zutvr Wirkungsweise des LSD 25, *Psychiat Neurol* **135**:273-284, 1958.

7. Walter, W.G.: The Brain as a Machine, *Proc Roy Soc Med* **50**:799-807, 1957.

8. Goldstein, L., et al: Quantitative Electroencephalographic Analysis of Naturally Occurring (Schizophrenic) and Drug-Induced Psychotic States in Human Males, *Clin Pharmacol Ther* **4**:10-21, 1963.

9. Goldstein, L.; Murphree, H.B.; and Pfeiffer, C.C.: Quantitative Electroencephalography in Man as a Measure of CNS Stimulation, *Ann NY Acad Sci* **107**:1045-1055, 1963.

10. Schwarz, B.E.; Sem-Jacobsen, C.W.; and Petersen, M.C.: Effects of Mescaline, LSD-25, and Adrenochrome on Depth Electrograms in Man, *Arch Neurol Psychiat* **75**:579-587, 1956.

11. Sem-Jacobsen, C.W.: Depth Electrographic Studies of the Activity in the Human Brain and the Effect of Some Drugs (Including Mescaline, LSD-25 and Chlorpromazine), *Electroenceph Clin Neurophysiol* **8**:717, 1956.

12. Monroe, R.R., et al: Correlation of Rhinencephalic Electrograms With Behavior, *Electroenceph Clin Neurophysiol* **9**:623-642, 1957.

13. Monroe, R.R., and Heath, R.G.: Effects of Lysergic Acid and Various Derivatives on Depth and Cortical Electrograms, *J Neuropsychiat* **3**:76-82, 1961.

14. Brazier, M.A.B.: "Studies of Evoked Responses by Flash in Man and Cat," in *Reticular Formation of the Brain: Henry Ford Hospital International Symposium,* Boston: Little, Brown Co., 1958, p 151-168.

15. Barlow, J.S.: Rhythmic Activity Induced by Photic Stimulation in Relation to Intrinsic Alpha Activity of the Brain in Man, *Electroenceph Clin Neurophysiol* **12**:317-326, 1960.

16. Cobb, W.A., and Dawson, G.D.: The Latency and Form in Man of the Occipital Potentials Evoked by Bright Flashes, *J Physiol* **152**:108-121, 1960.

17. Ciganek, L.: *Die Elektroencephalographische Lichtreizantwort der Menschlichen Hirnrinde,* Bratislava: Verlag Der Slowakischen Akademie der Wissenschaften, 1961.

18. Ebe, M., et al: Electrical Responses Evoked by Photic Stimulation in Human Cerebral Cortex, *Tohoku J Exp Med* **77**:352-372, 1962.

19. Kooi, K.A., and Bagchi, B.K.: Observations on Early Components of the Visual Evoked Response and Occipital Rhythms, *Electroenceph Clin Neurophysiol* **17**:638-643, 1964.

20. Shagass, C., and Schwartz, M.: Psychiatric Correlates of Evoked Cerebral Cortical Potentials, *Amer J Psychiat* **119**:1055-1061, 1963.

21. Shagass, C.; Schwartz, M.; and Amadeo, M.: Some Drug Effects on Evoked Cerebral Potentials in Man, *J Neuropsychiat* **3**:49-58, 1962.

22. Chapman, L.F., and Walter, R.D.: Actions of Lysergic Acid Diethylamide on Averaged Human Cortical Evoked Responses to Light Flash, *Recent Advances in Biol Psychiat* **4**:23-35, 1965.

23. Rodin, E.A., et al: Characteristics of Visually Evoked Responses in Normal Subjects and Schizophrenic Patients, *Electroenceph Clin Neurophysiol* **17**:458, 1964.

24. Ostfeld, A.M.: Effects of LSD-25 and JB 318 on Tests of Visual and Perceptual Functions in Man, *Fed Proc* **20**:876-884, 1961.

25. Rodin, E.A.; Luby, E.D.; and Meyer, J.S.: Electroencephalographic Findings Associated With Sernyl Infusion, *Electroenceph Clin Neurophysiol* **11**:796-798, 1959.