Mayo Clin Proc 43:191-204 (Mar.) 1968

PSILOCYBIN-INDUCED CHANGES IN PSYCHOLOGIC FUNCTION, ELECTROENCEPHALOGRAM, AND LIGHT-EVOKED POTENTIALS IN HUMAN SUBJECTS*

Robert R. Rynearson, M.D.,† Resident in Psychiatry
M. Robert Wilson, Jr., M.D., Section of Psychiatry
Reginald G. Bickford, M.B., Section of Physiology

Psychedelic agents, their illicit use, mode of action, effect, and potential heuristic and clinical value have in recent months been the object of extensive public interest and concern, and for many years have been the object of scientific investigation. The paucity of concrete data regarding the psychologic and neurophysiologic changes induced in man by these chemicals has in part contributed to the anxiety and conflicting attitudes concerning their use, as well as to the consonant legal and moral implications. D-lysergic acid diethylamide (LSD), psilocybin (hydroxydimethyltryptamine phosphate), bufotenine, dimethyltryptamine (DMT), and mescaline (5-hydroxydimethyltryptamine) are five of the most potent of these agents.

The investigation reported in this paper was designed to assay certain anticipated parameters of physiologic, neurophysiologic, and psychologic effects in human subjects in relation to the administration of psilocybin.

Isolated by Hofman in the Sandoz laboratories in 1958, psilocybin is the active principle derived from the hallucinogenic mushroom *Psilocybe mexicana* Heim. Its structure, confirmed by total synthesis, is the phosphoric acid ester of 4-hydroxydimethyltryptamine. As a psychotropic agent, this drug has significance in the study of mental processes.[1-5]

Neurophysiologic changes related to psychotropic action might be reflected in electroencephalographic (EEG) records obtained from subjects who are under the influence of such a drug. Since previous studies of psilocybin[6,7] have emphasized the predominant visual effects experienced by the subjects, significant EEG changes would be logically sought in the parieto-occipital region of the human scalp. In designing a program for recording of these potentials, we believed that changes in the signal input to the cortex (evoked potentials)

*This investigation was supported in part by Research Grants NB-07066 and NB-02056 from the National Institutes of Health, Public Health Service.

†Mayo Graduate School of Medicine (University of Minnesota), Rochester.

as well as spontaneous activity represented by the electroencephalogram should be quantitated by the available computer techniques of averaging and frequency analysis. Unfortunately, only limited information has been available on the form and nature of the normal components of the evoked potentials in man and such that exists indicates the occurrence of considerable individual variability.[8] Thus control runs in which a placebo was used were included in order to assess the intrusion on the experimental situation of such factors as boredom, lack of attention, and drowsiness, all known to have a significant effect on evoked potentials. In addition to observation of the evoked potentials with the use of psilocybin, the nature of the systemic and psychologic effects of psilocybin were studied inasmuch as there is disagreement in current literature regarding these effects.[9-11]

METHOD

Twenty-two persons volunteered to take psilocybin. This group was drawn from the medical and nursing staffs of the Mayo Clinic and consisted of 19 men and 3 women. None displayed any overt signs of psychiatric illness.

In a semidarkened, quiet room the subject in a fasting state reclined on a bed after tin-disk electrodes had been attached to the scalp by collodion in the frontal, temporal, parietal, and occipital positions of the Mayo system.[12] Care was taken to have the neck muscles relaxed during visual-response testing to minimize the possibility of contamination by myogenic potentials.[13] Averaged electroretinograms (ERG) were obtained for eight subjects. These were recorded from an electrode placed close to the left lower lid margin of the eye in line with the pupil in conjunction with a reference electrode attached to the ear.

Scalp potentials from a 16-channel Grass model IV ink-writer were subjected to continuous frequency analysis by an Ediswan-Walter frequency analyzer. To obtain an overall estimate of change in alpha output, the amplitudes of individual alpha frequencies displayed by the analyzer were summated and their measure expressed as a percentage change from the control module. A similar procedure was used to estimate changes in the theta frequencies, frequencies 4, 5, 6, and 7 being summated.

A parallel amplifier system (Grass P5) with frequency response of 0.3 to 1,000 cycles in conjunction with a Mnemotron CAT computer and XY plotter system was used to quantitate the evoked potentials. The Grass stroboscope (flash

intensity setting = 8) was located 12 inches from the subject's eyes and his responses to the flash of light were recorded by a hand-operated signal with the timing from flash to movement measured and recorded automatically by a Hewlett-Packard interval analyzer and digital printer. When the subject failed to respond to the light flash, which occasionally happened at the peak of the drug effect, his total responses were averaged exclusive of such omissions. Personnel in the room were limited to the psychiatrist-observer, an EEG technician, and an electronic technician.

After all the instruments were calibrated, a module preliminary to the administration of psilocybin or of placebo was run as a control. This was followed by a minimum of five subsequent modules encompassing the duration of drug effect and recovery. Each module lasted approximately 30 minutes and consisted of the following five parts.

1. The EEG from the left parieto-occipital part of the scalp was subjected to frequency analysis during two 10-second intervals with subject's eyes open and four 10-second intervals with subject's eyes closed.

2. The EEG from the same region was then summated by the computer while 50 light flashes (2/sec) triggered a 0.5-second sweep display with subject's eyes open and with subject's eyes closed.

3. Procedure 2 was repeated with subject's eyes open and with a light shield attached to the stroboscope to serve as both a control for any sound associated with the flash and to provide a "no flash" observation.

4. The reaction time of the subject was measured by using 50 randomly generated stroboscopic flashes with subject's eyes open. The subject operated a hand switch. The accompanying light responses were also summated by the computer.

5. An ERG was obtained on eight subjects; 50 responses were summated by the computer.

Pupil size was estimated by comparing the subject's pupil diameter to a series of disks representing diameter scales from 3 mm to 8 mm in increments of 0.5 mm. Pupil size and pulse were not measured in six subjects. Subjects were encouraged to discuss symptoms and experiences at any time (but preferably between modules) during the experiment. Each individual experiment consisted of at least six modules which lasted an average of 4½ hours.

Ten milligrams of psilocybin or of placebo were given

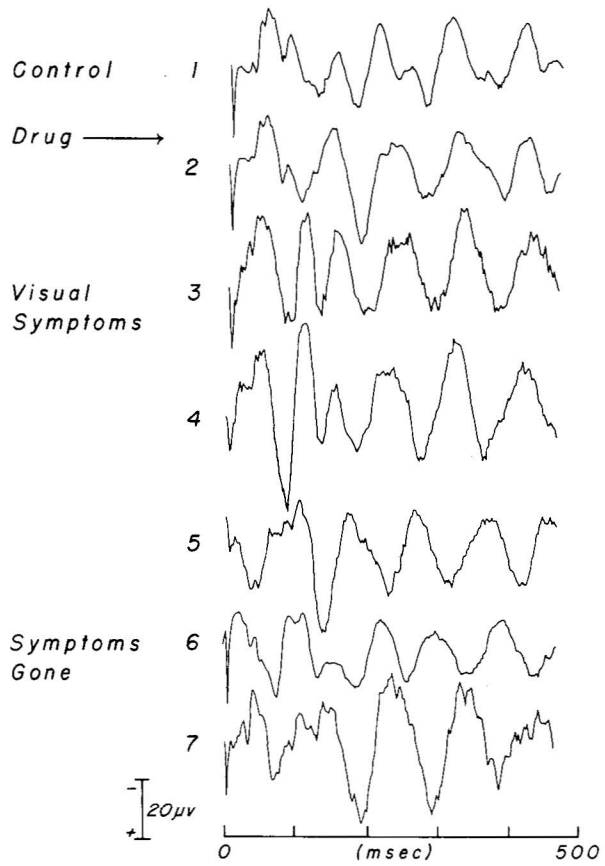

Fig. 1. Summated responses to photic stimulation at 2/sec (left parieto-occipital montage—eyes closed). Modules 1 to 7 taken at 30-minute intervals. Note appearance of new component in module 4 with negative peak at 100 msec. (Downward deflection indicates negativity of occipital region in relation to parietal.)

after the preliminary module. The subject was not given any clue as to whether the capsule given was drug or placebo.

RESULTS

Evoked Potentials.—Technically satisfactory, averaged evoked-potential records were obtained from all 22 subjects in the placebo and drug runs. As other authors have found, there was great individual variability in the form of the evoked potential to light. However, there was good consistency in results between control modules of the placebo and the drug studies on the same subject even though these were recorded on different days. In addition to the early evoked responses,

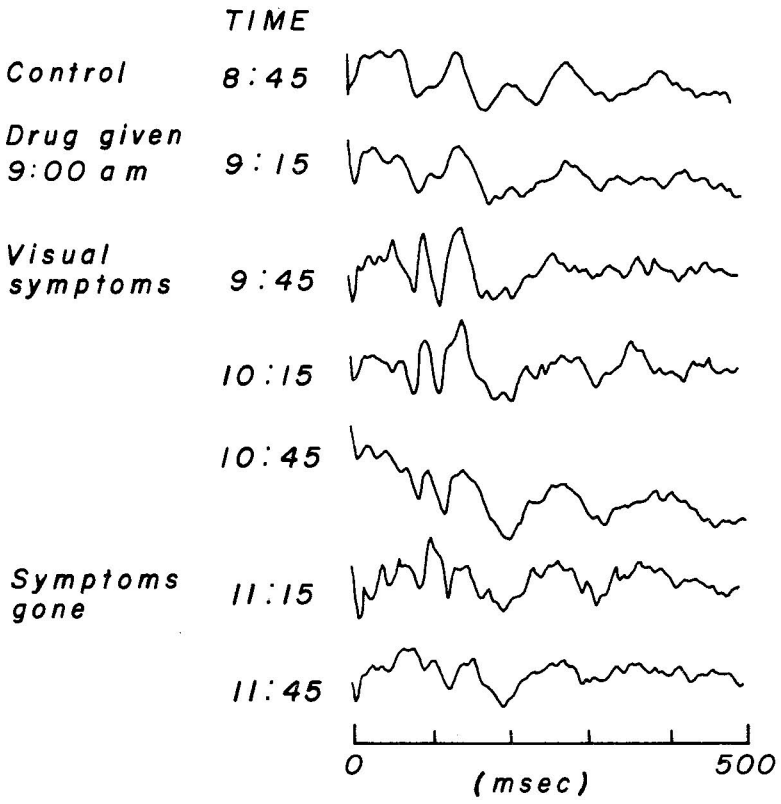

Fig. 2. Summation of 50 responses to flash stimulation with Shipton instrument (left parieto-occipital montage—eyes closed). Note appearance of new components in modules at 9:45 and 10:15, which disappear gradually and are gone at 11:45.

a number of subjects showed a marked rhythmic time-locked after-discharge such as that seen in Figure 1. These appeared characteristically in the eyes-closed module.

Although all 22 subjects reported visual changes related to ingestion of the drug as compared with the placebo, only 4 subjects seemed to show significant differences in their evoked potentials (Fig. 1, 2, 3, and 4). In Figure 1 the subject appears to develop a new negative component (downward deflection indicating relative negativity of occipital electrode) at 100 msec. Furthermore, in modules 5 and 6 the rhythmic after-discharge is shifted in phase by 180° compared with the earlier modules and module 7. In modules 5, 6, and 7, as visual symptoms disappeared the negative component of module 4 is no longer seen. Thus in this example, it appears

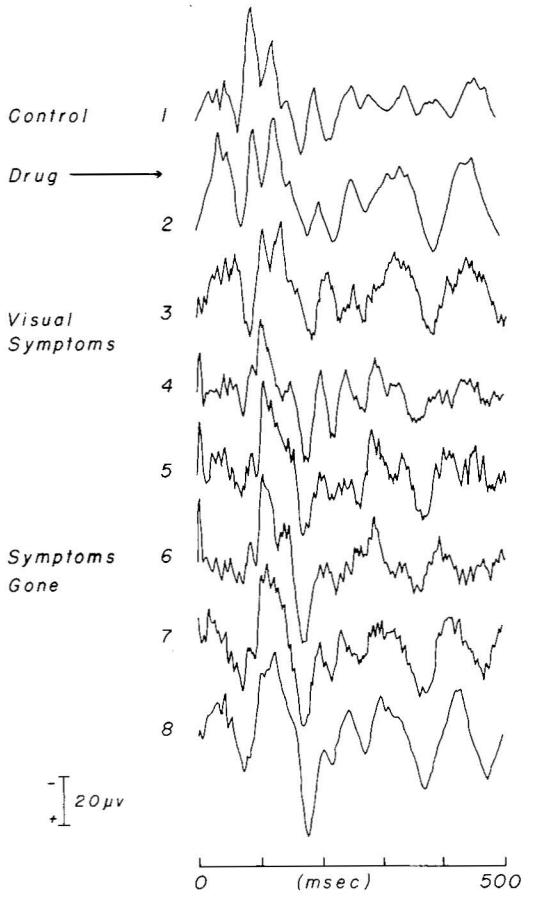

Fig. 3. Summation of 50 responses to light flash with diminution of early component of evoked potential in modules 4, 5, and 6 and progressive appearance of a negative component at 180 msec (left parieto-occipital montage—eyes closed).

that a change in components of the evoked potential itself was correlated with the occurrence of visual symptoms.

A subject with less tendency to rhythmic after-discharge is represented in Figure 2. These observations were made on a Shipton averager. After the drug was given at 9 a.m., the module at 9:45, when visual symptoms commenced, shows the appearance of three new waves with occipital positive peaks (upward in this montage) at 80, 100, and 120 msec respectively. These components were also seen in the 10:15 module but thereafter gradually disappeared as symptoms

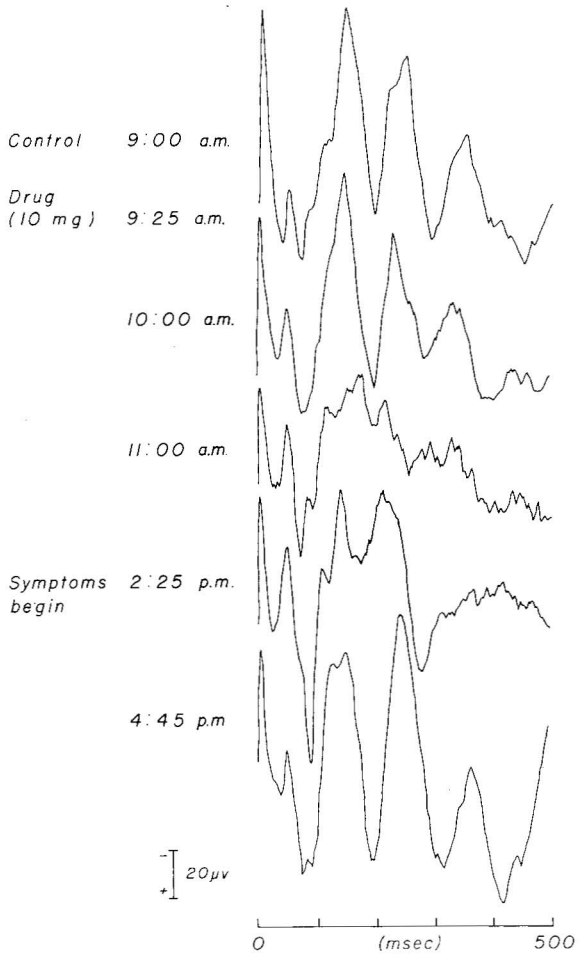

Fig. 4. Summation of 50 responses to photic stimulation (parieto-occipital montage—eyes closed). Note appearance of negative component at 100 msec in 2:25 p.m. module.

decreased and were finally absent in the 10:45 module when visual symptoms were gone. Thus, here again there is a good correlation between the appearance of new components in the evoked potential and the occurrence of drug-induced visual symptoms.

In the subject represented in Figure 3, changes occurred in relation to drug action but there was a tendency for reduction and simplification of the discharge rather than the appearance of new components at the height of drug action.

It can be seen, for instance, that the negative component (downward deflection) appearing in modules 1 and 2 at 90 msec tends to disappear at the height of the drug action and reappear later in modules 7 and 8 after symptoms had disappeared. In addition, after-discharge seems to become less prominent at the height of drug action, to reappear as late waves in module 8. A progressive change seen from module 4 onward is the appearance of a prominent negative component at 180 msec (module 8). This component did not correlate with the changes in visual symptoms but appeared to become progressively more prominent as the experiment continued. In this instance, diminution in the evoked potential is associated with increasing alertness related to the action of the drug in this subject and indicated by increase of muscle noise in modules 3 to 7. It is known that shifts of consciousness toward the alert state tend to produce diminution in evoked potentials.[14]

Figure 4 shows much rhythmic activity following the early evoked potential component at 80 msec in the control and early morning responses. When symptoms became evident at 2:25 p.m. there was considerable increase in the negative component at 100 msec which was seen to a lesser extent at 4:45 p.m. as visual symptoms began to abate. This may represent a change related to the hallucinogenic effect of the drug but the evidence is not compelling.

The placebo runs in these four subjects showed no significant change related to administration of the placebo. The remaining 18 subjects who received the drug showed no significant changes in evoked potentials related to the period of hallucinosis.

Studies of Alpha Rhythm With Frequency Analyzer.—In 17 subjects, the alpha rhythm was well developed and provided good material for the observation of the drug effects on this system. A typical example is shown in Figure 5. In the control tracing, the existence of alpha components with peaks at 8 and 10 cycles and with subsidiary peaks at 9 and 11 cycles can be noted. At the time of module 3, 35 minutes after administration of the drug and when visual symptoms were present, there was a marked change in the alpha rhythm, with reduction in all frequency components of some 50%. Peaks still remained at 8 and 11 cycles. In module 5, the tracing returned approximately to the control level seen in module 1. This subject showed no change in the evoked potential pattern. This degree of alpha reduction was not an unexpected finding since these subjects were preoccupied with

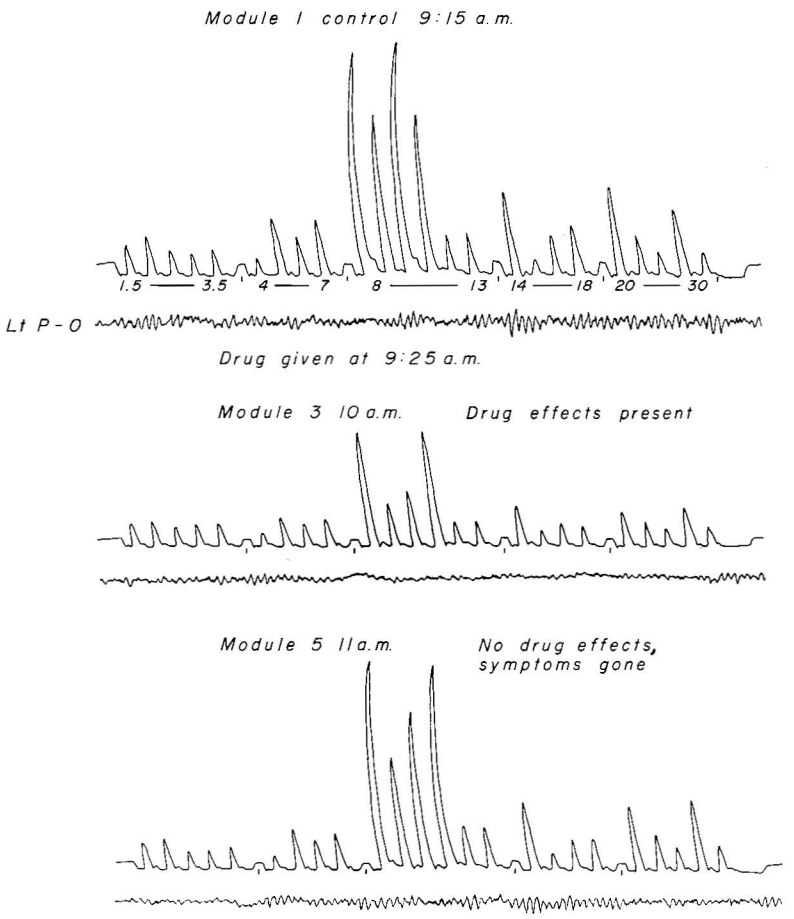

Fig. 5. Left parieto-occipitally derived alpha rhythm (eyes closed) analyzed by Grey Walter analyzer. Note diminution in alpha amplitude and persistence without significant change in frequency in module 3 and virtual recovery in module 5 after drug effect had disappeared.

their visual hallucinations, and the effects that were seen could well be explained as resulting from the well-known mechanisms of attention inhibition of the alpha process. The diminution of alpha rhythm was not associated with any tendency to slowing or to acceleration in frequency. The latter effect has sometimes been noted in conditions of attention.[15] Alerting effects with diminution of spontaneous rhythms have also been reported in rabbits by Brodey and colleagues[6] with administration of psilocybin.

Review of the whole group (22 subjects) showed the

following overall effects on the EEG rhythms. In the drug run, the integrated alpha frequencies decreased in amount by 14.2% and the theta frequencies decreased by 12.5%. In the placebo runs, alpha frequencies decreased by 8.2% and theta frequencies increased by 13.2%. This effect is probably related to boredom and minor degrees of drowsiness.

Electroretinographic Data.—The ERG from the eight subjects on whom these were obtained showed no significant alterations in the evoked potential as summated by the computer. This may be compared with the conclusions of Apter[10] who found demonstrable changes in the ERG of cats under the influence of LSD-25, a compound related chemically to psilocybin.

Physiologic Changes.—Data from the interval analyzer showed that the average reaction time was slowed 24.3% during psilocybin runs; this is most likely a reflection of the subjects' preoccupation with drug effects; the subjects regularly reported little interest in responding to the light. During placebo runs, however, the reaction time improved an average of 6.3% when modules taken before and after the capsule were compared.

The size of the pupil increased an average of 57.1% with psilocybin but decreased an average of 5.5% with the placebo.

The pulse rate increased an average of 14.5% with psilocybin. There was no change in the average pulse rate during the placebo runs.

During the drug runs, the systolic blood pressure increased an average of 12.1% and the diastolic pressure increased an average of 20.2%; an average of 0.3% decrease in systolic pressure and 0.7% decrease in diastolic pressure was recorded during the placebo runs.

Psychic Changes.—As with other psychotomimetic drugs, the psychic changes engendered by psilocybin can be described under three categories of mental functioning: perceptual, affective, and cognitive. From the experience of 22 volunteers in our series, the following represent some of the more outstanding examples.

1. Perceptual Changes.—Distortions involving the modalities of vision, hearing, and touch were reported by 17 subjects. No frank auditory hallucinations were reported but increased auditory acuity was a common experience. Paresthesia of the circumoral region and a feeling of lightness or heaviness of the extremities were reported by 19 subjects;

frequently these were the initial symptoms. Distortions of body-image perception were described by several; one subject said that he felt "... like an El Greco painting ... I'm long and drawn out ..."; others felt short and stubby. Many subjects complained of feeling cold and requested a blanket, which might have been a consequence of the drug's autonomic effects. Visual distortions were the most commonly noted changes in perception. These varied from multicolored, nondescript patterns with a stimulus from the light flashes while the eyes were closed to frank visual hallucinations with the eyes open. One rather poetic subject treated us to a vivid verbal tapestry of his hallucinations proceeding in a stream of consciousness fashioned from accounts of butterflies and Siamese dancers to a detailed description of crustaceans and their underwater environment. Colors, moreover, possessed a unique index to the affect accompanying these perceptive distortions so that gray was a portent of melancholy and gold was a messenger of jubilance. This dramatic unfolding of imagery continued for almost an hour for one subject and this subject like many others was loathe to brook any interruptions such as questions from the examiner and requests for cooperation in the recording of the EEG. Other subjects, although somewhat less articulate in their descriptions, recounted myriad perceptual distortions.

2. Affective Changes.—Affective changes related to drug ingestion included not only those that were clearly associated with the content of the perceptual distortions as noted above but also those that were frequently of a less explicable nature. Anxiety was an early symptom in 20 of the 22 subjects. One subject experienced repeated acute anxiety attacks. The next most prevalent affect was euphoria; 18 subjects during the early phase of drug effect experienced uncontrolled laughter and were unable to identify the reason for their mirth when questioned. One subject expressed great anger at the psychiatrist-observer on arising from a transient delusional state which was presumably drug-related. Another subject underwent an abreaction of poignant and rather potent repressed material. Almost universal in the experience of the 22 subjects was a period of depression manifested by extreme fatigue, abulia, and lassitude which followed the termination of drug effect and persisted from 3 to 36 hours.

3. Cognitive Changes.—Disturbance in the mental function of cognition was not uncommon, and ideas of reference and clear delusional mentation occurred in one subject. A feeling that time was passing rapidly was only subjective,

for most subjects were quite accurate when asked to estimate the time despite the sensation that much more time had passed. Suspiciousness and guarding were noted in two subjects and a feeling that the psychiatrist-observer was a threatening figure was reported by one. A belief in his own omniscience characterized one subject's primary effect from the drug initially but this was followed by an equally unrealistic attitude toward the psychiatrist-observer that bordered on reverence. Precise testing of the parameters of the mental status during drug effect was not undertaken.

Psychometric Data.—Valid profiles of the Minnesota Multiphasic Personality Inventory (MMPI) were obtained from 17 of the 22 subjects and the Thematic Apperception Test (TAT) was completed by 11. These tests were administered in all cases from 2 days to 2 weeks following the subject's participation in the experiment. In general, the patterns and codes on the MMPI did not stand out from what might be expected in the normal population; however, there were several instances of elevations in the scales that measure defensiveness and masculinity-feminity but the psychologist who interpreted these scores stated that such elevations were commensurate with the level of education of the subjects. Although the results of the TAT for the subjects in our series gradually had more depressive content than the average and the stories were somewhat more defensive, they were still within the range of the general population. Thus, in general, the psychometrics when applicable supported our clinical view that the subjects did not demonstrate any lasting psychopathologic changes.

DISCUSSION

One can conclude from the paucity of significant changes that the evoked potential is not a very satisfactory neurophysiologic index of higher perceptual functions related to psilocybin action; alternatively, if this information is contained in the evoked-potential envelope, we have not found an appropriate means of extracting it. In the future it may be necessary to make more subtle use of stimulus parameters in this kind of experiment. The difference in response to patterned and unpatterned light demonstrated by Spehlmann[16] suggests that we should use more physiologic stimulus parameters rather than the highly unphysiologic light flash in unraveling these problems. Thus it might be suspected that more rewarding results would come from the use of stimuli of low-intensity pattern which would be feasible with an averaging process in order to display informational changes

related to a drug which clearly acts at a highly discriminating level of cortical function. On the other hand, in cases in which changes were found in the evoked potential it could be questioned whether these were specific for psilocybin or represented more general changes in alertness level related to psilocybin hallucinosis which is known from the work of Hernández-Peón and associates[14] and others to affect the evoked potential. However, such effects related to alerting have usually been associated with simplification of the evoked potential response rather than the appearance of new components, and insofar as this is true it would not provide an adequate explanation for the changes seen in four of our subjects.

In regard to the psychic effect of psilocybin there were marked differences in the changes in cognition, affect, and perception from subject to subject such as has been noted by other investigators.[17] In the present study no specific changes were noted in psychic function which related to the rare instances in which evoked potential changes were encountered. A subsequent paper will attempt to correlate the content and quality of these psychic changes with the subject's personality as assessed by psychologic testing.

SUMMARY

The neurophysiologic, systemic, and psychologic effects of 10 mg of psilocybin on each of 22 volunteer subjects were observed. Use of currently available computer techniques to assess the electroencephalograms (EEG) monitored from the subject's visual cortex disclosed definite changes in the components of the evoked potential of four subjects. These changes correlated with the occurrence of visual symptoms. EEG data from the frequency analyzer showed that both the alpha and the theta frequencies decreased during drug effect.

No gross or significant alterations were detected in the summated electroretinographic data. During the drug runs, reaction time was slowed and pupil size, pulse rate, and blood pressure were increased. Perceptive, affective, and cognitive changes associated with the administration of psilocybin varied from one subject to another and were not specifically correlated with evoked potentials or other physiologic changes.

ACKNOWLEDGMENT

The psilocybin used was furnished through the courtesy of Dr. Rudolf Bircher, Medical Director, Sandoz Pharmaceuticals, Hanover, New Jersey. The authors are also grateful to Miss Janice Wheeler who was responsible for much of the data taking and analysis and to Mr. Don Carroll who rendered invaluable assistance in the use of the data-processing equipment.

REFERENCES

1. Adey, W. R., Bell, F. R., and Dennis, B. J.: Effects of LSD-25, Psilocybin, and Psilocin on Temporal Lobe EEG Patterns and Learned Behavior in the Cat. Neurology (Minneap) *12*:591-602 (Sept.) 1962.
2. Hollister, L. E., and Sjoberg, B. M.: Clinical Syndromes and Biochemical Alterations Following Mescaline, Lysergic Acid Diethylamide, Psilocybin and a Combination of the Three Psychotomimetic Drugs. Compr Psychiat 5:170-178 (June) 1964.
3. Leary, T., Litwin, G. H., and Metzner, R.: Reactions to Psilocybin Administered in a Supportive Environment. J Nerv Ment Dis *137*:561-573 (Dec.) 1963.
4. Marrazzi, A. S., and Hart, E. R.: Relationship of Hallucinogens to Adrenergic Cerebral Neurohumors. Science *121*:365-367 (Mar. 11) 1955.
5. Schwarz, B. E., Wakim, K. G., Bickford, R. G., and Lichtenheld, F. R.: Behavioral and Electroencephalographic Effects of Hallucinogenic Drugs: Changes in Cats on Intraventricular Injection. Arch Neurol (Chicago) *75*:83-90 (Jan.) 1956.
6. Brodey, J. F., Steiner, W. G., and Himwich, H. E.: An Electrographic Study of Psilocin and 4-Methyl-α-Methyl Tryptamine (MP-809). J Pharmacol Exp Ther *140*:8-18, 1963.
7. Hartman, A. M., and Hollister, L. E.: Effect of Mescaline, Lysergic Acid Diethylamide and Psilocybin on Color Perception. Psychopharmacologia *4*:441-451, 1963.
8. Whipple, H. E., Ed. (Katzman, R., Consult. Ed.): Sensory Evoked Response in Man. Ann NY Acad Sci *112*:1-546 (May 8) 1964.
9. Adey, W. R., and Dunlop, C. W.: The Action of Certain Cyclohexamines on Hippocampal System During Approach Performance in the Cat. J Pharmacol Exp Ther *130*:418-426, 1960.
10. Apter, Julia T.: Analeptic Action of Lysergic Acid Diethylamide (LSD-25) Against Pentobarbital. Arch Neurol (Chicago) *79*:711-715 (June) 1958.
11. Steiner, J. E., and Sulman, F. G.: Simultaneous Studies of Blood Sugar, Behavioural Changes and EEG on the Wake Rabbit After Administration of Psilocybin. Arch Int Pharmacodyn *145*:301-308, 1963.
12. Sections of Neurology and Section of Physiology, Mayo Clinic and Mayo Foundation: Clinical Examinations in Neurology. Ed. 2, Philadelphia, W. B. Saunders Company, 1963, pp. 297-310.
13. Bickford, R. G., Jacobson, J. L., and Cody, D. T. R.: Nature of Average Evoked Potentials to Sound and Other Stimuli in Man. Ann NY Acad Sci *112*:204-223 (May 8) 1964.
14. Hernández-Peón, R., Guzmán-Flores, C., Alcaraz, M., and Fernández-Guardiola, A.: Habituation in the Visual Pathway. Acta Neurol Latinoam *4*:121-129 (Oct.-Dec.) 1958.
15. Hauser, H., Schwarz, B. E., Roth, Grace, and Bickford, R. G.: Electroencephalographic Changes Related to Smoking. (Abstr.) Electroenceph Clin Neurophysiol *10*:576 (Aug.) 1958.
16. Spehlmann, R.: The Averaged Electrical Responses to Diffuse and to Patterned Light in the Human. Electroenceph Clin Neurophysiol *19*:560-569 (Dec.) 1965.
17. Delay, J., Pichot, P., Lempérière, T., Nicolas-Charles, P., and Quétin, A.-M.: Les effets psychiques de la psilocybine et les perspectives thérapeutiques. Ann Medicopsychol (Paris) *1*:899-907 (May) 1959.