Effects of a Hallucinogenic Agent in Totally Blind Subjects

ALEX E. KRILL, M.D.; HUBERT J. ALPERT, A.B., and ADRIAN M. OSTFELD, M.D., Chicago

A previous study demonstrated that lysergic acid diethylamide (LSD) induced measurable changes in human retinal function while visual hallucinations and illusions were being experienced.[1] The changes were evident in both dark-adaptation and electroretinographic studies and were interpreted as mildly hypoxic or toxic retinal effects of LSD. In the dark-adaptation curve, LSD delayed the rod-cone break and elevated the entire rod threshold. In the electroretinogram (ERG), the drug increased the scotopic *b*-wave amplitudes and in some subjects also increased the scotopic *a*-wave amplitudes.

Because hallucinations and illusions were reported only when measurable ERG and dark-adaptation changes occurred, a possible retinal role in the induction of hallucinations was considered. Consequently, the present study was undertaken to clarify the role of a functioning retina in the induction of LSD-induced visual changes by studying subjects with total blindness (no light perception) and, insofar as could be determined, normal central nervous system function.

Method

Twenty-four totally blind subjects were studied. Four subjects were totally blind by the age of 2 and were designated as "congenitally blind." All of these subjects probably had some vision at birth. The other 20 subjects were not totally blind until late childhood or some time thereafter; these subjects were designated as the "non-congenital group."

Submitted for publication July 11, 1962.

Present address, Dr. Krill: Department of Surgery, Section of Ophthalmology, The University of Chicago, 950 East 59th St., Chicago 37.

From the Departments of Ophthalmology and Preventive Medicine, University of Illinois College of Medicine.

Supported by United States Public Health Service Grant MY 2302.

The approximate age of complete visual loss (no light perception in either eye) in all subjects is shown in the second column of Table 1. The age range was 16 to 76 with a mean age of 44. Fifteen were women, 7 Negro. The average education level was 1 to 2 years of high school; 6 had some college training.

All subjects were hospitalized for a minimum of 2½ days. A general medical history and physical examination (including a complete neurological evaluation) were carried out on each subject. Routine laboratory studies were also done. Subjects with moderately severe hypertension or diabetes

TABLE 1.

Subj. *	Age (Yrs.)	Race	Sex	Age No LP
1	16	W	M	4 mo.
2	71	W	F	2?
3	52	W	F	8 mo.
4	41	N	M	1
5	74	W	F	74
6	42	W	F	25
7	56	W	M	55
8	27	W	F	25
9	55	N	M	47
10	29	N	M	15
11	44	W	M	23
12	67	W	F	8.5
13	48	W	F	17
14	76	W	F	43
15	58	W	F	30
16	44	W	F	16
17	70	W	F	8
18	38	N	M	36
19	33	N	M	30
20	39	W	M	37
21	50	W	F	27
22	72	W	F	12
23	70	W	M	41?
24	51	N	F	29

* "Congenital subjects" 1-4; "Noncongenital subjects" 5-24.
† Key for hallucinations: V, Visual; T, Tactile; G, Gustatory; SP, Spontaneous Visual Experiences; O, Olfactory; A, Auditory.

mellitus, coronary artery disease, evident psychotic or serious neurotic disturbances, or with any evidence of a neurological disorder outside the visual system were excluded from this study.

The various causes of blindness in all subjects and the principal ocular findings are shown in Table 1. In 2 subjects with intact normal-sized eyeballs, electroretinograms were obtained.

All data pertinent to this study were obtained in a small semi-soundproof room 7×10½ ft. The subjects were questioned by the same interviewer, a second-year medical student, and the full content of each interview was tape-recorded.

The tape-recorded data obtained prior to the actual experiment fell into 2 categories: (1) The visual history up to the time of total blindness (*a*, the age at which vision was impaired; *b*, the rate of visual loss; *c*, the age of total blindness); (2) The visual experiences after blindness (*a*, the subject's visual memory; *b*, the presence and complexity of visual dreams; *c*, the presence of spontaneous visual experiences; *d*, the nature of present environmental perceptions).

After the initial interview, the subject was given either a placebo or 1μg. per kilogram of LSD according to double-blind procedures. The order of administration was decided by coin flips; each experiment was done on a separate day. Both solutions were identically flavored with cherry syrup. Tape-recorded interviews * were obtained immediately after LSD or the placebo and at subsequent 30-minute intervals for 3½ hours. If subjects reported unusual experiences, the interviews were continued until these experiences were over. A list of questions asked is shown in Table 2.

The tape recordings were evaluated separately by 2 of us. Six categories of data were abstracted from the recordings for correlation with drug and placebo effects. These categories were: (1) visual history (estimated duration of normal vision and of total blindness); (2) presence or absence of visual elements in dreams; (3) presence or absence of current spontaneous visual phenomena (such as

* Some of these questions were selected from a questionnaire devised by Abramson for assessing LSD effect.[2]

Tabulation of Data

Diagnosis	Main Recent Ocular Finding	SP	Hallucinations, LSD †				
			V	A	T	G	O
Congenital cataracts	Phthisis bulbae O.U.	−	−	+	+	−	+
Trauma	Phthisis bulbae O.U.	−	−	+	+	−	−
Trauma	Enucleation O.U.	−	−	+	+	−	+
?	Enucleation O.U.	−	−	+	+	+	+
Wide-angle glaucoma	Enucleation O.U.	+	+	+	−	−	−
Juvenile glaucoma	Phthisis bulbae O.U.	+	+	−	+	−	+
Metastatic panopthalmitis	Phthisis bulbae O.U.	+	+	−	+	−	−
Congenital glaucoma	Enucleation O.D. Absolute glaucoma O.S.	+	+	+	−	−	−
Glaucoma O.U. Retinal detachment O.D.	Retinal detachment O.D. Absolute glaucoma O.S.	+	+	+	+	−	−
Uveitis	Phthisis bulbae O.U.	+	+	+	+	−	−
Trauma O.D. Symp. ophthalmia O.S.	Phthisis bulbae O.U.	+	+	−	+	−	−
Ophthalmia neonatorum	Phthisis bulbae O.U.	+	+	+	+	+	+
Uveitis Secondary glaucoma	Absolute glaucoma O.U.	+	+	+	+	−	−
Tumor O.D. Absolute glaucoma O.S.	Enucleation O.U.	+	+	+	+	−	+
Congenital cataracts	Phthisis bulbae O.U.	+	+	+	+	−	−
?	Enucleation O.U.	+	+	+	+	+	+
Ophthalmia neonaterum	Enucleation O.D. Phthisis bulbae O.S.	+	+	+	+	−	−
Trauma O.U.	Phthisis bulbae O.S. Optic atrophy O.D.	+	−	−	+	−	−
Uveitis	Phthisis bulbae O.U.	+	−	−	+	−	+
Toxic amblyopia	Optic atrophy O.U.	+	−	−	+	−	−
Uveitis	Enucleation O.U.	−	−	+	+	+	−
Metastatic panophthalmitis	Phthisis bulbae O.U.	−	−	−	−	−	−
Trauma?	Phthisis bulbae O.D. Enucleation O.S.	−	−	−	+	+	−
Trauma	Phthisis bulbae O.D. Enucleation O.S.	−	−	−	+	−	−

TABLE 2.—*Postdrug Questionnaire*

1. How do you feel ? (details)
2. How does your body feel? (details)
3. Is there any change in what you hear? What have you heard?
   Have you heard any confusing things?
4. Do things seem completely dark in this room? If not, what are you aware of? (Then be specific—lights, spots, faces, landscapes, relation of these to events of past life.)
5. Does the room seem different in any way?
6. Does anything feel different (bedsheet, face, ear)?
7. Can you smell anything? (details)
8. Can you taste anything? (details)
9. Do you think anything is happening to any part of you?
10. Is it hard to concentrate?
11. Are you having a lot of thoughts? About what?
12. Are you having trouble telling me about anything?
13. Do you feel silly?

lights, spots, faces, etc.); (4) estimated intelligence of the subject; (5) acuity of visual memory; (6) the use of visual imagery in answers to specific questions. Four-point rating scales (Table 3) were devised for classifying 4 of the 6 categories of information.

When disagreement existed between the 2 raters, the evaluations were repeated. A subsequent evaluation was made of the per cent agreement between the 2 observers in the rating of the 6 variables.

The postplacebo and postdrug recordings were reviewed without the reviewer's knowing the preparation given. Counts were made of the number of subjects reporting visual hallucinations, and the number reporting tactile, olfactory, gustatory, and auditory hallucinations. The visual hallucinations were divided into simple and complex, chromatic and achromatic. The definitions of the various subjective phenomena used here are those of English and English.[3] A comparison was made of the number of each kind of hallucination after placebo and LSD.

TABLE 3.—*Four-Point Rating Scales*

Visual History

1. Lost sight in infancy—"congenitally blind."
2. Lost object perception as a child.
3. Had good vision while an adult.
4. Lost all vision within the last 3 years.

General Intelligence

1. Slow of speech, limited vocabulary, less than 8 grades of education.
2. Slightly greater communicative ability, some high school education.
3. Communicates well, completed high school.
4. Verbal fluency, wealth of vocabulary, some college education.

Visual Memory

1. Recalls no objects, faces, or colors.
2. Some recollection of either objects, faces, or colors.
3. Rather clear recollection of objects, faces, and colors.
4. Vivid recollection of all past images.

Visual Imagery

1. All questions answered in terms of touch, hearing, smell without visual reference.
2. One indirect visual reference such as mentioning one color, or speaking of a tall person.
3. Frequent but somewhat vague visual references as in 2.
4. Vivid and frequent visual references.

The occurrences of visual hallucinations were related to the 6 categories of data evaluated. The ratings and number of visual hallucinations were initially placed in 4×4 contingency tables and contingency coefficients determined. Then the 4×4 tables were collapsed into 2×2 tables and the Fisher exact probabilities test carried out.[4]

Because of the small size of the "congenital group," a quantitative evaluation of their data was not made. It was considered justifiable to separate these 4 subjects because of the minimal amount of preblindness experience in this group.

TABLE 4.—*Hallucinations with LSD*

	Noncongenitals (20) Total	Congenitals (4) Total
Visual	14	0
Simple	12	
Complex	2	
Colored	7	
Noncolored	7	
Auditory	11	4
Tactile	17	4
Olfactory	5	3
Gustatory	4	1

Results

Thirteen of the 24 subjects reported visual alterations after LSD (Table 4). Eleven subjects reported simple hallucinations, and 2 subjects reported complex hallucinations (faces, persons, furniture, etc.). Five of the subjects reporting simple, and the 2 subjects reporting complex hallucinations described color (Subjects 10 and 14). The frequency of LSD-induced nonvisual hallucinations is shown in Table 4.

No subjects reported subjective visual phenomena when the placebo trial preceded LSD. However, when the placebo trial followed LSD, 3 subjects reported visual hallucinations. Two of these 3 subjects reported more vivid visual hallucinations in the prior LSD trial. Four subjects reported nonvisual

hallucinations when the placebo trial was first and 10 when the placebo trial was second.

There was complete agreement between the 2 observers in evaluation of 3 of the 6 categories of data. The maximum disagreement was in the evaluation of estimated intelligence (4 subjects). However, in no category was the disagreement in ratings more than 1 scale unit.

The reporting of visual hallucinations was related to only 1 of the 6 categories of data. Only subjects who reported visual phenomena in normal life experience reported visual hallucinations after LSD ($P<0.002$).† Subjects who normally perceived only a constant homogenous gray or black field did not experience hallucinations after the drug (bottom of Table 1). Those who perceived spots, flickers of light, or colors during ordinary life experiences were the only ones who reported such occurrences after LSD. It appeared that LSD increased the frequency and intensity with which such events took place.

Three subjects with spontaneous visual activity did not experience visual hallucinations after LSD (Subjects 18, 19, and 20). Two of these 3 subjects (both with total optic atrophy) had at least 1 eye with a functioning retina, on which electroretinograms were obtained (Subjects 18 and 20). The post-LSD ERG of these 2 subjects tested showed *b*-wave amplitude increases (Table 5) similar to those noted in recordings from normal-sighted subjects reporting hallucinations,[1] despite the fact that neither blind subject reported visual phenomena. The postplacebo ERG showed *b*-wave amplitude decreases (Table 5). The postplacebo ERG from normal subjects also showed a decrease in *b*-wave amplitude or in a few subjects did not change in size.[1]

† Through the use of the Fisher exact probabilities test for 2×2 tables.[4]

TABLE 5.—*B-Wave Amplitude Changes, Microvolts*

	Postplacebo				
	I1	I2	I4	I8	I16
Subject 18	−40.0		−82.5		−65.0
Subject 20	−100.0	−4.0	−32.0	−18.0	−60.0
	Post-LSD				
	I1	I2	I4	I8	I16
Subject 18	+12.5		+3.0		+152.5
Subject 20	+44.0	+86.0	+94.0	+76.0	+28.0

Comment

It is evident that a normal retina is not needed for the occurrence of LSD-induced visual experiences. These visual experiences do not seem to differ from the hallucinations reported by normal subjects after LSD.

Such phenomena occurred only in blind subjects who reported prior visual activity. The drug increased the frequency of visual events such as spots, lights, dots, and flickers. However, the complex visual experiences reported by 3 subjects after LSD did not occur after placebo or in ordinary experience.

It is interesting to note that duration of blindness was not related to the occurrence of visual hallucinations; nor was intelligence, acuity of visual memory, or use of visual imagery in speech.

Three other reports deal with the effects of hallucinogenic drugs on blind subjects. Alema[5] reported that 50μg. of orally administered LSD induced elaborate visual hallucinations in a subject with bilateral enucleations of the eyeball. However, the effects of 50μg. of LSD are stated to have persisted for the incredibly long period of 5 days (they usually last 6 hours). This subject was noted to have spontaneous visual activity. Zador[6] administered mescaline orally in doses of 0.05 to 0.4 gm. to 10 blind subjects. Elaborate visual hallucinations usually followed. Most of the subjects had prior spontaneous visual activity, but it is difficult to evaluate this activity because they also had central nervous system diseases. The presence or absence of light perception was not specified for this group, and no control studies were carried out. Forrer and Goldner[7] gave LSD, 1μg. per kilogram, to 2 blind volunteers, both of whom had suffered destruction of the optic nerves. Neither reported visual hallucinations, no mention was made of prior spontaneous

hallucinations, and no mention was made of prior spontaneous visual activity.

Clearly, LSD does not affect the visual system exclusively. In the blind subjects as in the normal ones, nonvisual hallucinations occurred. However, auditory, tactile, olfactory, and gustatory hallucinations occurred more frequently than is usually reported by normal subjects (Table 4). In 4 studies of normal volunteers,[1,8-10] 27%, 12%, 7%, and 37% of the subjects reported auditory hallucinations, and 0%, 7%, 13%, and 4% reported gustatory hallucinations. In this study 55% of the subjects reported auditory hallucinations, and 20% reported gustatory hallucinations.

There are at least 2 probable reasons for the increased frequency of nonvisual hallucinations in the blind group. Blind subjects tend to note and report nonvisual phenomena more carefully. Furthermore, their dependence on nonvisual senses may physiologically alter other perceptual functioning in such a way as to make this group more susceptible to the nonvisual effects of LSD.

The ERG findings in 2 subjects (Subjects 18 and 20), both with total optic atrophy, establish an independent retinal effect of LSD, since centrifugal control from higher visual centers was unlikely. In normal subjects the simultaneous occurrence of retinal and higher visual center changes (interpreted as hallucinations) may reflect a similar LSD sensitivity of various segments of the visual pathways.

The absence of visual hallucinations in these 2 subjects indicates that not all totally blind subjects with spontaneous visual activity experience visual hallucinations after LSD (3 in this study).

The simple and complex hallucinations of the totally blind subjects in this study can be related in some degree to the experiments of Penfield[11] in which electrode stimulation of Area 17 produced simple noncolored forms, and stimulation of the temporal lobe produced colored and complex hallucinations. However, what results would be obtained from direct electrode stimulation of the optic radiations, optic tract, optic chiasm, or optic nerve? It has been demonstrated that stimulation of most of these areas by other means (e.g., small tumors) can induce simple or complex visual hallucinations.[12] The dilemma of the origin of LSD-induced hallucinations has not been solved.

Localization may be a meaningless concept in terms of hallucinations. Rather, the functional status of the visual network must be considered. The importance of this functional concept is implied in this study by the occurrence of drug-induced hallucinations in only those subjects experiencing spontaneous visual activity.

Summary

Twenty-four totally blind subjects were given lysergic acid diethylamide (LSD) and a placebo, in double-blind fashion and random order.

All subjects were interviewed before and after drug administration with standard questionnaires. All interviews were tape-recorded and evaluated by 2 observers. An attempt was made to correlate certain categories of data with the reporting of visual hallucinations. Electroretinograms were recorded in 2 subjects before and after LSD and placebo administration.

Thirteen subjects reported visual hallucinations after LSD which were similar to LSD-induced hallucinations reported by normal-sighted subjects. All 13 blind subjects had had prior spontaneous visual experiences. Subjects having no prior visual experience did not report drug-induced visual hallucinations.

LSD-induced nonvisual hallucinations occurred more frequently in the blind subjects than usually occur in normal-sighted subjects.

The ERG changes after LSD in 2 blind subjects with total optic atrophy were similar to those changes noted in normal subjects reporting visual hallucinations[1]; however, neither blind subject reported hallucinations.

Conclusions

LSD-induced visual hallucinations can occur without a functioning retina.

LSD produces independent retinal and higher visual pathway effects. In normal subjects the simultaneous occurrence of retinal changes and visual hallucinations suggests a similar LSD sensitivity of various segments of the visual pathways.

A visual system with some degree of function appears necessary for drug-induced hallucinations to occur. All subjects reporting visual hallucinations after LSD had a history of previous spontaneous visual activity.

Acknowledgement is made to Miss Miriam Jackson for editorial advice.

A. E. Krill, M.D., Section of Ophthalmology, University Clinics, 950 E. 59th St., Chicago 37, Ill.

REFERENCES

1. Krill, A. E., et al.: The Effect of 2 Hallucinogenic Agents on Human Retinal Function, Arch. Ophthal. 64:724, 1960.

2. Abramson, H. A., et al.: Lysergic Acid Diethylamide (LSD-25): 1. Physiological and Perceptual Responses, J. Psychol. 39:3, 1955.

3. English, H. B., and English, A. C.: A Comprehensive Dictionary of Psychological and Psychoanalytical Terms: A Guide to Usage, New York, Longmans, Green & Co., Inc., 1958.

4. Fisher, R. A., Editor: Statistical Methods for Research Workers, New York, Hafner, 1954.

5. Alema, G.: Allucinazioni da acido lisergico in cieco sen a bulbi oculari, Riv. Neurol. 22:720, 1952.

6. Zador, J.: Mesdalinwirkung bei Storungen des optischen systems, Z. Neurol. Psychiat. 127:30, 1930.

7. Forrer, G. R., and Goldner, R. D.: Experimental Physiological Studies with Lysergic Acid Diethylamide (LSD-25), Arch. Neurol. Psychiat. 65:581, 1951.

8. Bercel, N. A., et al.: Model Psychoses Induced by LSD-25 in Normals, Arch. Neurol. Psychiat. 75:588, 1956.

9. DeShon, H. J., et al.: Mental Changes Experimentally Produced by L.S.D. (d-Lysergic Acid Diethylamide Tartrate), Psychiat. Quart. 26:33, 1952.

10. Lebovits, B., et al.: LSD and JB318: A Comparison of 2 Hallucinogens: 1. An Exploratory Study, Arch. Gen. Psychiat. 2:390, 1960.

11. Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man, New York, The Macmillan Company.

12. Weinberger, L. M., and Grant, F. C.: Visual Hallucinations and Their Neuro-Optical Correlates, Arch. Ophthal. 23:166, 1940.