

Pupil Dilatation in Normal and Schizophrenic Subjects Following Lysergic Acid Diethylamide Ingestion

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In view of findings that schizophrenic patients require higher doses of lysergic acid diethylamide to produce psychologic disturbances than do normal subjects,¹⁻⁷ this study was made to determine whether the absorption of LSD-25 into the central nervous system of such patients, as measured by pupillary dilatation, differed from that of normal subjects.

The recent study of the metabolism of LSD-25 by Axelrod, Brody, Witkop, and Evarts⁸ demonstrated the presence of considerable amounts of the drug in the brain and cerebrospinal fluid of a cat after intravenous injection of 1.0 mg/kg., indicating that the substance could pass the blood-brain barrier. This was true also in the monkey injected intravenously in a dose of 0.2 mg/kg., where the biologic half-life (the time required for the plasma level to fall to half its value) was found to be about 100 minutes.

A constantly noted phenomenon after the ingestion of LSD-25 is the dilatation of the pupils. The effect of LSD-25 on the pupils is, according to Rothlin,⁹ brought about by stimulation of the mesencephalon and the medullary center. Cerletti,¹⁰ too, feels that the vegetative symptoms are of central origin. We have, therefore, studied pupillary dilatation after a standard dose of LSD-25 (75 μ g) to determine whether there would be any parallelism between the psychic and the autonomic effects of the drug.

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Despite the fact that pupillary dilatation is commonly observed, there has been little effort to measure it accurately. The size of the pupil has been measured directly by means of a millimeter ruler, or estimated by comparison with black circles of known diameter on a card held alongside the patient's eyes.¹¹ In only one study have actual photographs been taken, that of Greiner, Burch, and Edelberg,¹² in which in two normal subjects given a dose of 40 μ g the pupil dilated to 33% over the initial level in approximately two and one-half hours and remained at that level for at least a period of six hours.

Present Study

The subjects were photographed in a room with standard illumination, with external light excluded, under nonfasting conditions in the morning. After being in the room for 15 minutes to accustom his eyes to the illumination, the subject sat in a chair with an adjustable head rest. A set of empty metal eyeglass frames was then slipped on. On the lower arc of each frame had been soldered a piece of steel on which was pasted a 2 cm. portion of a celluloid ruler, which was included in the picture of the pupil. By means of a 35 mm. camera with special lenses, a color photograph was taken of one pupil (usually the left) with an electronic flash. The subject was then given 75 μ g of lysergic acid diethylamide in solution, and the same eye was rephotographed at intervals of 15, 30, 50, 70, 90, and 120 minutes. The study was limited to two hours, because by that time both the degree of pupillary dilatation and the psychologic reaction had reached their peak. Since the duration of the effect was not of interest, the subject was then given chlorpromazine by mouth to diminish the intensity of the effect. In only one subject (a schizophrenic patient) was there an untoward physiologic effect of temporary weakness, and he was not included in the study.

The normal subjects for the study included 10 men from the staff of Worcester State Hospital

and the Worcester Foundation for Experimental Biology, including mostly scientific professional men and maintenance personnel. They ranged in age from 22-35 years, with an average of 31.4 years. On the whole, they were a scientifically sophisticated group. The patients were all schizophrenic men, ranging in age from 24 to 60, with a mean of 39.5 years. They had been hospitalized from 2 to 20 years, with a mean of 7.7 years. They included the various subtypes of schizophrenia, four being classified as catatonic, three as paranoid, one as hebephrenic, one as chronic undifferentiated type, and one under "other types." Practically all had been unresponsive to the various forms of therapy. None had received tranquilizing drugs for at least three months before the test procedure.

Measurements of the pupil were made by projecting the 35 mm. colored slide on a screen so that the pupil was enlarged to at least 10 times its normal size. Since the ruler lay in essentially the same focal plane as the pupil, it was included in the photograph. The circumference of the pupil and the length of 1 cm. on the projection were traced on transparent paper, and the diameter of the pupil was easily measured from the accompanying length of the millimeter ruler. Only the horizontal diameter of the pupil was measured, since a drooping of the upper lid occasionally obscured the measurement of the circumference. Duplicate tracings were made of 100 photographs to determine the accuracy of measurement. It was found that on duplicate tracings, the median difference between the measurements of the diameter was 0.10 mm., and the mean difference 0.14 mm.

In order to evaluate psychic factors inherent in the situation, photographs were taken of the pupils of the first four normal subjects to whom water alone and lysergic acid diethylamide solution (75 μ g) were given in random order three to seven days apart. There was initially some degree of tension on the part of the subjects as to whether they were receiving the lysergic acid or water, but it remained at a mild level on the day on which they received the water, whereas on the lysergic acid day they noted definite psychologic changes within themselves within an hour after taking the drug.

The average values for the pupillary diameters on each of the two days for the four subjects is shown in Figure 1. On

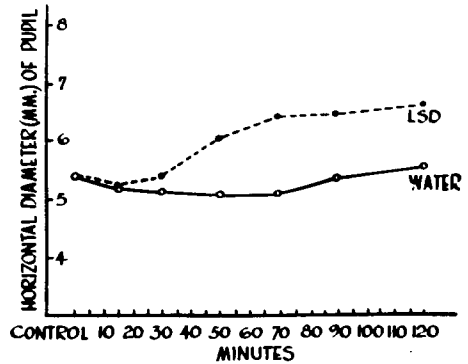


Fig. 1.—Averages of horizontal diameters of pupils of four normal subjects over a period of two hours after the ingestion of (a) water, and (b) 75 μ g of lysergic acid diethylamide.

the day in which they received water there was essentially no change. The ingestion of lysergic acid resulted in a dilatation of the pupils, which was apparent by the 50-minute reading. Two hours after the ingestion of water the pupillary diameter had increased an average of 0.16 mm., as compared with 1.20 mm. after the ingestion of lysergic acid. It is certain that a mild degree of tension did not affect the pupillary diameter in a sophisticated group. As for the patients, they were in general indifferent to the procedure.

The average values of pupillary diameters for the two groups of subjects are shown in the accompanying Table. The normal subjects show a definite degree of dilatation at 50 minutes from 5.5 to 6.0 mm., which increases to 6.5 mm. by the two-hour reading. The patients' initial level is slightly smaller, 4.9 mm., and again at 50 minutes this level is increased to 5.5 mm. and, finally, to 6.1 mm. The average pupillary dilatation in the two-hour period is 1.0 mm. for the normal subjects and 1.2 mm. for the patients. Thus, except for the lower

Mean Horizontal Diameters of Pupils of Ten Normal and Ten Schizophrenic Men After Ingesting 75 μ g Lysergic Acid Diethylamide

Subjects	No.	Before LSD	Interval After LSD, Min.					
			15	30	50	70	90	120
Normal	10	5.5	5.2	5.5	6.0	6.2	6.3	6.5
Schizophrenic	10	4.9	5.2	5.2	5.5	5.6	5.7	6.1

PUPIL DILATATION AFTER LSD-25 INGESTION

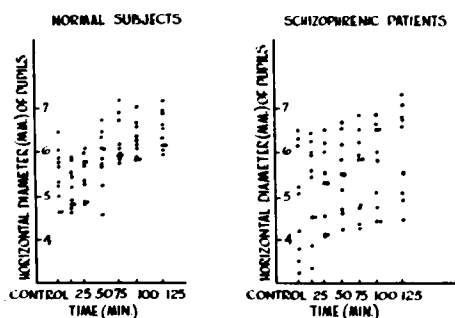


Fig. 2.—Individual values for horizontal diameter of pupils of 10 normal and 10 schizophrenic subjects over a period of two hours after the ingestion of 75 μ g of lysergic acid diethylamide.

initial value for the patients, the trends in the two groups are quite similar.

A scatter diagram of the individual measurements in each subject (Fig. 2), however, reveals much more variability in the patients, both in the initial levels and throughout the period of observation, a frequent characteristic phenomenon noted in physiologic studies of schizophrenic patients.

On the whole, the pupillary dilatation is not very marked in either group when measured by this technique. In only one subject, a patient who was thrown into a panic, either by the procedure or by the lysergic acid or by both, was there a clinically obvious dilatation, from an initial level of 3.3 mm. to a final level of 6.7 mm. Incidentally, for the group as a whole, the initial size of the pupil had no particular influence on the degree of increase, so that the initially smaller pupils of the psychotic group were not appreciably influenced to any greater degree by the mydriatic effect of the drug.

All of the normal subjects showed some overt psychologic disturbance after the administration of lysergic acid diethylamide, which was marked in five, moderate in three, and mild in two. The reactions included feelings of tension, difficulty in concentration and expression, some degree of depersonalization, spatial distortions, visual illusions, outbursts of laughter, feelings of bodily distortions, and, in one subject,

erotic sensations. These feelings began 30 to 60 minutes after taking the drug and seemed to come and go in waves. In the schizophrenic patients, the psychologic disturbances seemed very much less. One patient became acutely disturbed in a panic-like state and another exhibited paranoid trends, but the other eight seemed essentially unaffected by the drug. This finding of a lessened reactivity to this dosage level is consistent with the results of the studies previously cited.^{1,7}

No relationship was noted between the degree of overt psychologic disturbance in the subjects and the change in the pupillary diameters except in the one acutely disturbed patient. Nor was any relationship noted in the patients between the change in pupillary diameter and the chronological age, duration of hospitalization, or subtype classification.

Comment

It is evident, then, that the pupillary reactions of schizophrenic patients to a 75 μ g dose of lysergic acid diethylamide are essentially the same as those of normal subjects. It is evident from this reaction that the lysergic acid is not metabolized to any greater degree in the patients than in the normal subjects. If the mydriatic activity of the drug is dependent on a central locus of action, as Rothlin⁹ and Cerletti¹⁰ have stated, it is obvious that absorption of the drug into the central nervous system is equally good in the two groups of subjects.

Consequently, the greater resistiveness of schizophrenic patients to exhibiting psychologic disturbances after the ingestion of lysergic acid is not to be explained on either of the above-mentioned factors. It must be due to some metabolic disturbance in higher centers. It is quite true, as many observers have noted, that there is no high correlation between the autonomic and the psychic effects of the drug. Consequently, any explanation of the psychologic resistiveness of schizophrenic patients to the

drug must await a physiologic explanation of its psychotomimetic properties.

Summary

A photographic study was made of the pupillary reactions to the ingestion of 75 μ g of lysergic acid diethylamide (LSD-25) in 10 normal men and 10 male patients with chronic schizophrenia. Although the normal subjects exhibited far greater psychologic disturbances than the patients, the amount of pupillary dilatation was the same in the two groups. It is evident that the two groups cannot be differentiated on the basis of this autonomic (pupillary) reaction to the drug. This finding may indicate that the lower psychologic responsivity of the schizophrenic patient to the drug is not due to inadequate absorption of the material into the central nervous system.

Kenneth Morey gave expert photographic assistance.

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