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COMPARISON OF THE REACTIONS INDUCED BY PSILOCYBIN AND LSD-25 IN MAN

By

Harris Isbell

From the

National Institute of Mental Health,

Addiction Research Center,

U. S. Public Health Service,

Lexington, Kentucky.

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The use of certain intoxicating mushrooms by Indians in Mexico has been reviewed by Hofmann et al. (1958). V. P. and R. G. Wasson (1957) have reported the way in which the mushrooms are taken by the Mexican Indians and the hallucinatory experiences occurring following their ingestion. Hofmann et al. (1958a) have described the identification of the mushrooms and their successful culture by Heim, and by Heim and Cailleux. Hofmann et al. (1958) isolated a pure compound from the mushrooms which had the characteristics of an indoleamine and which contained phosphorus. Later the compound was identified as O-Phosphoryl-4-hydroxy-N-dimethyl tryptamine, was synthesized (Hofmann, 1958; Hofmann et al., 1958 a and b) and named psilocybin. Preliminary studies in man (Hofmann et al, 1958a) showed that the compound, in doses of 4 to 8 mg, induced an abnormal mental state resembling that seen after LSD or mescaline. In animals (Cerletti, 1958), psilocybin caused neurovegetative symptoms although it had no high degree of activity on peripheral

autonomic structures. The autonomic effects of psilocybin seemed to be due to central sympathetic stimulation. It facilitated spinal reflexes and caused an "arousal" pattern in the EEG, although motor behavior was depressed.

Because of the chemical relationship of psilocybin to serotonin and to bufotenine, and because of the possible role of serotonin (5-hydroxy tryptamine) in the function of the central nervous system, a detailed comparison of the effects of psilocybin with those of the diethylamide of d-lysergic acid (LSD-25) in man was thought to be of interest.

METHODS

Preliminary Experiments. In order to confirm the dose range reported by Hofmann et al. (1958a), several preliminary experiments were done in which 7 volunteers ingested psilocybin orally in doses ranging from 0.5 to 8.0 mg/70 kg of body weight. These experiments indicated that psilocybin caused definite mental effects in doses of 2 to 8 mg/70 kg which were accompanied by pupillary dilatation, increased tendon reflexes, and increased blood pressure. The mental effects of psilocybin seemed to resemble those of LSD. A more detailed experiment was then carried out utilizing 9 patients.

Subjects. The subjects used in these experiments were all negro males who were former drug addicts and who were serving sentences for violation of the United States narcotic laws. Their ages ranged between 22 and 40 years. All were in good physical health, and none presented evidence of any of the major psychoses. All had experienced the effects of LSD-25 in previous experiments.

General Conditions. The experiments were all conducted in a special ward devoted to clinical research. Observations were made by specially trained attendants with many years of experience in observing patients who have received various drugs. The patients entered this special ward on the night before the experiments were conducted. They were awakened at 6:30 a.m. Each patient was free to mix and mingle with other patients in a common dayroom, or to remain in his own room, as he preferred.

Drugs. LSD-25 and psilocybin[1] were administered in solution in raspberry syrup. The syrup was used in order to mask the slightly bitter taste of psilocybin. Drugs were administered at 8 a.m. with the patients fasting. All patients received, in a randomized balanced order, a placebo, 1.0 and 1.5 mcg/kg of LSD, 57, 86, and 114 mcg/kg of psilocybin (4.0, 6.0 and 8.0 mg/70 kg). The "single-blind" procedure was followed throughout. The patients were not aware of the identity of the drugs given on a specific day but one of the attendants, for reasons of safety, did know what medication had been given.

Observations. The following observations were made at hourly intervals from 7 a.m. to 4 p.m. after the patients had rested quietly for ten minutes in bed: rectal temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure, diameter of pupils, and thresholds for eliciting the kneejerk. Methods for making these measurements were those previously described (Isbell et al, 1956; Isbell et al, 1958). At hourly intervals from 7:30 a.m. to 3:30 p.m. patients completed a questionnaire[2] modified from that of Abramson et al (1955), with the help of an aide. A short mental status examination was made one and one-half to two hours after the drug and a grade[3] (scale 0-4) of the intensity of the reaction was assigned according to the system used in rating the intensity of the LSD reaction (Isbell et al, 1956).

Analysis of Data. The change after drugs in rectal temperature, pulse and respiratory rates, systolic and diastolic blood pressures, pupillary size, and threshold for elicitation of the kneejerk were calculated by subtracting the figures obtained at various hours after the drugs from the average of the two pre-drug observations. The areas under the time-action curves for each subject, and for each dose of each medication for the various measurements, were then calculated by the

method of Winter and Flataker (1950). This procedure converts all the data on a particular measurement for an individual receiving a given dose of a drug to one figure. The number of positive responses on the questionnaires after the drugs were counted over the entire observation period, eliminating answers which were also scored positively before the drugs. Means and standard errors of means were calculated according to standard statistical techniques. The t-test for paired observations was used in evaluating the significance of differences in the "objective" (temperature, pupils, etc.) signs (Edwards, 1946). Nonparametric tests (Wilcoxon, 1949) were used in evaluating the significance of differences in the number of positive responses on the questionnaire and on the clinical grade.

Measurements of pupillary diameter (an "objective" measure) and number of positive responses on the questionnaire (a "subjective" measure) were tabulated and averaged at each observation time before and after the drugs, in order to obtain time-action curves.

Regression lines for dose-effect curves, calculations of relative potency and confidence limits were calculated by the methods described by Bliss (1952).

In order to compare the pattern of subjective response, the 57 questions constituting the questionnaire were classified into nine categories.[4] The questionnaires were then scored by counting the number of patients responding positively to a given question two or more times after administration of the drug, after which the number of patients responding positively to a given category of questions was determined by adding the totals for all the questions constituting the particular category.

RESULTS

General Clinical Description of the Psilocybin Reaction. This description of the reaction occurring after psilocybin is based primarily on the data obtained with the 114 mcgm/kg dose. Following administration of psilocybin orally the patients usually spontaneously reported the first subjective effects within 10 to 15 minutes. These effects consisted of vague sensations that things looked, felt, or seemed peculiar, and were accompanied by mild anxiety. After 30 minutes, anxiety became quite definite and was expressed as consisting of fear that something evil was going to happen, fear of insanity, or of death. At this time, changes in mood, usually in the direction of elation (despite the anxiety) and sometimes in the direction of depression, occurred. The patients reported

increased keenness of hearing, paresthesia, and blurring of vision. One hour after the drug the reaction was well developed. Anxiety became more marked and, in some cases was intense. Elation, when present, was great and in some patients was expressed by almost continuous gales of laughter. Alterations in practically all sensory modalities were mentioned, particularly in touch, hearing and vision. As is the case with LSD, distortion of visual perception was outstanding, and involved distance, depth, size, shape and color. Visual distortion usually varied rapidly from moment-to-moment. Perception of elementary visual hallucinations were commonly reported. These entoptic phenomena consisted of colored lights which flickered and coalesced to form patterns varying in a kaleidoscopic fashion, or of shadows that seemed to dance on the wall. In sensitive patients, the lights or shadows were perceived as a definite person, object, or animal which the individual could name. The patients reported increased difficulty in thinking, difficulty in concentration, and in carrying out simple arithmetical calculations or reading. They reported a "rush of thoughts," with one thought replacing another before the first was completed. A feeling of alteration in the individual's own body occurred consistently and varied

from simple feeling of being light or heavy to marked alterations in size, shape or color. Some patients felt they had become very large, or had shrunk to the size of children. Their hands or feet did not seem to be their own, and sometimes took on the appearance of animal paws. At times, patients had the sensation that they could see the blood and bones in their own body or in that of another person. They reported many fantasies or dream-like states in which they seemed to be elsewhere. Fantastic experiences, such as trips to the moon or living in gorgeous castles, were occasionally reported. Despite these striking subjective experiences, the patients remained oriented in time, place and person. In most instances the patients did not lose their insight, but realized that the effects were due to the drug. Two of the 9 patients, however, did lose insight and felt that their experiences were caused by the experimenters controlling their minds. Reaction usually reached its peak one and one-half hours after the drug was given and remained intense for two to three hours. It subsided almost completely five to six hours after the drug was given. The subjects most frequently compared the subjective experiences after psilocybin to those occurring after LSD or marihuana.

Objective Measurements. The data on the objective measurements are shown in table 1. Significant changes as compared with the placebo were observed after both doses of LSD and after one or more of the doses of psilocybin in the cases of rectal temperature, pulse and respiratory rates, systolic blood pressure, pupillary size, and threshold for elicitation of the kneejerk. Thus, psilocybin induced a pattern of autonomic and central nervous system excitation similar to that caused by LSD, but was, of course, less potent than the latter drug.

Subjective Measurements. Significant changes, as compared with placebo, occurred after all doses of both drugs, with respect to number of positive responses on the questionnaire and to the clinical grade. Data on the "pattern of response" is shown in table 2. When the patterns after the two drugs are compared at the most nearly equivalent doses (1.0 mcgm/kg of LSD, and 114 mcgm/kg of psilocybin) it is evident that the patterns after the two drugs are very similar, except in incidence of "true hallucinations."

The time-course after placebo and the various doses of the two drugs is shown in tables 3 and 4. The time of onset is very similar after both drugs. This result may be, to some extent, an artefact of the fixed observation times, since patients consistently began to report subjective changes sooner after psilocybin than after LSD. Definite pupillary dilatation occurred one hour after both drugs, with the peak effect occurring at one hour after psilocybin and two hours after LSD. As judged by number of responses on the questionnaire, the reaction was beginning to subside by the third to the fourth hour after both drugs, reaching insignificant levels five and one-half hours after psilocybin and six and one-half hours after LSD. The length of action of psilocybin seems definitely shorter than that of LSD.

Comparative Potency of LSD and Psilocybin. From the data, a number of dose-effect curves comparing the potency of LSD and psilocybin can be constructed. Those based on the total course (pupillary diameter, number of positive responses and clinical grade) yielded estimates that LSD is approximately 100-150 times as potent as psilocybin. Since the total course of the psilocybin reaction was shorter than that of the LSD reaction these estimates of potency could be misleading. For this reason, change in pupillary diameter at two hours and the

number of positive responses at one and one-half hours were calculated and used in constructing the dose-effect curves shown in figure 1. Analysis of these data at approximately peak effect for both drugs gave potency estimates with 5 per cent confidence limits of 1 mcgm/kg of LSD being equivalent to 121 (103-156) mcgm/kg of psilocybin in the case of pupillary change, and to 110 (60-218) mcgm/kg in the case of responses on the questionnaire. These two dose-effect curves met the usual tests for parallelism and slope. Unfortunately, the preliminary experiments gave a somewhat high impression of the potency of psilocybin, so that the highest dose of psilocybin used (114 mcgm/kg) corresponded approximately to the lowest dose of LSD (1 mcgm/kg). A dose of psilocybin higher than 114 mcgm/kg and a dose of LSD lower than 1 mcgm/kg would have yielded a more elegant estimate of comparative potency.

DISCUSSION

The reactions observed after oral administration of LSD-25 and psilocybin are remarkably similar. After both drugs, there is evidence of autonomic excitation (elevated temperature, dilated pupils, increased blood pressure and increased respiratory rate) and of increased hyper-irritability in the central

nervous system (decreased threshold for elicitation of the kneejerk). After both drugs, anxiety, difficulty in concentration and thinking, sense of strangeness, marked sensory perceptual distortion (especially visual), alterations in body image (depersonalization), and elementary and true hallucinations occurred. It is, of course, possible that the methods of measurement and the situation in which the experiments were conducted contribute in some degree to this similarity. The subjects had already experienced the effects of LSD, and very likely would expect similar symptoms from any drug given in this particular testing situation. The use of a questionnaire may also suggest certain symptoms. On the other hand, patterns of effects similar to those seen after LSD have not been observed after administration of amphetamine, scopolamine, barbiturates, opiates, chlorpromazine and many other drugs with marked effects on the central nervous system. Thus it seems likely that the similarity between the reactions induced by LSD and psilocybin is a real phenomenon, and suggests that some common biochemical or physiological mechanism is responsible for the effects of the two drugs. Experiments in which subjects tolerant to LSD are challenged with psilocybin and vice versa ("cross tolerance") might help settle the question of the biological identity of the reactions caused by the two drugs.

The similarity in chemical structure of psilocybin and 5-hydroxytryptamine naturally leads one to speculate that psilocybin may cause an abnormal mental state by interfering with the actions, synthesis, disposition or metabolic degradation of 5-hydroxytryptamine. Others have hypothesized that LSD-25, bufotenine and other psychosomimetic drugs might act through such mechanisms. Since psilocybin is a much simpler compound than LSD, it may prove to be an important tool for biochemical studies bearing on the role of serotonin in brain function. Investigations in animals will be necessary to shed light on these possibilities.

SUMMARY

1. The reaction induced by oral administration of 57 to 114 mcgm/kg of O-Phosphoryl-4-hydroxy-N-dimethyltryptamine (psilocybin) has been compared with that induced by a placebo and LSD-25 (1.0 to 1.5 mcgm/kg) in 9 subjects.

2. Both LSD and psilocybin caused elevations in body temperature, pulse and respiratory rates, and systolic blood pressure. Threshold for elicitation of the kneejerk was decreased by both drugs.

3. After both drugs, abnormal mental states characterized by feelings of strangeness, difficulty in thinking, anxiety, altered sensory perception (particularly visual), elementary and true visual hallucinations, and alterations of body image were reported by the subjects.

4. The effects of psilocybin did not persist as long as those of LSD.

5. LSD is 100 to 150 times as potent as psilocybin.

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FOOTNOTE 1.

Footnote 1. We are indebted to Drs. R. Bircher and C. Henze of the Medical Department, Sandoz Pharmaceuticals, Hanover, New Jersey, for generous supplies of LSD-25 and psilocybin.

FOOTNOTE 3.

Footnote 3. The clinical grade was based on the mental status examination and grades assigned according to the following scheme:

Grade 0: No reaction,

Grade 1: Anxiety and nervousness without perceptual distortion or hallucinations,

Grade 2: Anxiety, nervousness and visual perceptual distortion without "true" hallucinations,

Grade 3: Anxiety, nervousness, perceptual distortion and "true" hallucinations but with insight maintained (patients report that effects are due to drugs), and

Grade 4: Same as grade 3, except that insight (realization that the effects are due to the drug) is lost.

The grading system has the disadvantage that the various grades may not form a continuous scale. It gives no information concerning the quantitative aspects of the symptoms which go into determining the grades. Like the questionnaire, however, it yields reproducible data on repeated administration of the same dose of LSD, and good dose-effect responses are obtained.

FOOTNOTE 4.

Footnote 4. The nine categories are shown in table 2. It is of course evident that a large number of other categories could be devised and that there might be many ways of classifying a particular question. There appears to be no easy way out of this difficulty, so the classification must be regarded as completely arbitrary.

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Table 1

Comparison of total course of psilocybin and LSD reactions.

Measure	Placebo	LSD-25		Psilocybin		
		TREATMENT				
		1.0 mcg/kg	1.5 mcg/kg	57 mcg/kg	86 mcg/kg	114 mcg/kg
Temperature[1]	+ 2.7 ± 0.32	+ 4.8[x] ± 0.44	+ 4.9[x] ± 0.48	+ 3.5[x] ± 0.26	+ 5.7[x] ± 1.35	+ 4.6[x] ± 0.26
Pulse Rate[1]	+37.8 ± 14.5	+67.3[x] ±17.8	+82.8[x] ±10.9	+31.9 ± 8.9	+41.6 ± 10.4	+79.1[x] ± 12.6
Respiratory Rate[1]	+13.1 ± 3.1	+32.9[x] ± 3.9	+36.7[x] ± 7.1	+24.5 ± 8.1	+26.4 ± 8.2	+37.5[x] ± 7.1
Systolic Blood Pressure[1]	+15.6 ± 13.5	+64.8[x] ± 10.9	+94.6[x] ± 17.5	+31.4 ± 12.6	+61.7[x] ± 11	+47.8 ± 16.9
Diastolic Blood Pressure[1]	-17.5 ± 11.9	+ 9.1 ± 19.1	+35.2[x] ± 10.7	+ 8.2 ± 9.7	+15.7 ± 11	+ 6.6 ± 13.6
Pupillary Diameter[1]	0.2 ± 1.4	+10.2[x] ± 1.18	+15.0[x] ± 2.1	+ 3.9[x] ± 0.9	+ 6.0[x] ± 1.4	+ 5.4[x] ± 1.9
Patellar Reflex[1]	+20.7 ± 11.1	-50.9 ± 31[x]	-72.9 ± 21.7[x]	+ 7.1 ± 19.2	-47.6[x] ± 10.4	-65.5[x] ± 23.8
No positive answers[2]	0.1 ± 0.3	57[xx] ± 23.2	98[xx] ± 26.6	24[xx] ± 5.9	38[xx] ± 16.3	38[xx] ± 11
Clinical grade[3]	0 ± 0	2.2[xx] ± 0.38	2.8[xx] ± 0.17	1.2[xx] ± 0.2	1.83[xx] ± 0.4	2.0[xx] ± 0.36

1 - Figures are means ± standard errors (9 subjects) of areas under time-action curves ("degree-hours," "beat-hours," etc.). The signs indicate increases (+) or decreases (-) in the measurement.

2 - Means ± standard errors of number of questions scored positively in the 7½ hours after the drug which were not scored positively before the drug.

3 - Means ± standard errors of intensity of mental reaction based on a scale of 0-4.

[x] - Significantly different from placebo ($P < 0.05$).

[xx] - Significantly different from placebo ($P < 0.05$, non-parametric test).

Table 2

Comparison of pattern of "mental" response after psilocybin and LSD in 9 subjects.

Category[1]	Number of Questions	Total Responses Possible[2]	Number of Responses in Category					
			Placebo	LSD		Psilocybin		
				1.0	1.5	57	86	11
General	7	63	0	25	36	16	23	2
Difficulty in thinking	4	36	0	10	19	2	8	
Alteration in mood	3	27	0	9	15	3	8	
Alteration in touch	4	36	0	11	17	3	4	1
Alteration in hearing	4	36	0	14	16	6	8	
Visual distortion	10	40	0	19	31	13	16	1
"Elementary" hallucinations	5	45	0	11	18	5	9	
"True" hallucinations	4	36	0	5	9	3	2	
Depersonalization	13	117	0	19	33	15	14	1

1 - Refers to type of questions, e.g., "feeling strange" (general); "feet look old" (depersonalization); "am happy" (mood); "things look small" (visual distortion); "is difficult to concentrate" (thinking), etc.

2 - Number of subjects times number of questions in the category.

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Table 3

Time course of effects of LSD-25 and psilocybin on pupillary size.

Treatment	Hours Before or After Drug									
	-1	0	+1	+2	+3	+4	+5	+6	+7	+8
Placebo	3.8	3.7	3.9	3.8	3.9	3.8	3.7	3.9	3.9	3.9
LSD, 1.0 mcg/kg	3.8	3.8	4.9	5.4	5.4	5.2	5.2	4.9	4.9	4.8
LSD, 1.5 mcg/kg	3.7	3.7	5.6	6.1	6.1	5.3	5.9	5.6	5.4	5.3
Psilocybin 57 mcg/kg	4.1	4.1	4.8	4.4	4.4	4.3	4.3	4.4	4.4	4.6
Psilocybin 86 mcg/kg	3.8	3.9	5.1	4.9	4.7	4.7	4.4	4.6	4.4	4.5
Psilocybin 114 mcg/kg	4.3	4.4	5.8	5.9	5.4	5.1	4.9	4.7	4.6	4.5

Figures are means of pupillary diameter in millimeter on 9 subjects.

Table 4

Time course of effects of LSD-25 and psilocybin on questionnaire.

	Hours Before or After Drug								
Treatment	- 1/2	+ 1/2	+ 1½	+2½	+3½	+4½	+5½	+6½	+
Placebo	0	0.1	0	0	0	0	0	0	
LSD, 1.0 mcg/kg	0	3.9	12.3	14.3	13.2	7.4	4.1	1.2	0
LSD, 1.5 mcg/kg	0	5.1	18.5	19.8	17.7	15.8	10.9	6.8	1
Psilocybin, 57 mcg/kg	0	2.4	5.1	6.3	6.6	2.9	0.6	0.22	
Psilocybin, 86 mcg/kg	0	2.0	10.8	10.9	7.9	4.9	0.6	0	
Psilocybin, 114 mcg/kg	0	6.4	12.6	10.6	6.1	1.9	0.33	0	

LEGEND FOR FIGURE 1.

Figure 1. Relationship of dose of LSD-25 and psilocybin to change in size of pupils and to number of positive responses on the questionnaire.

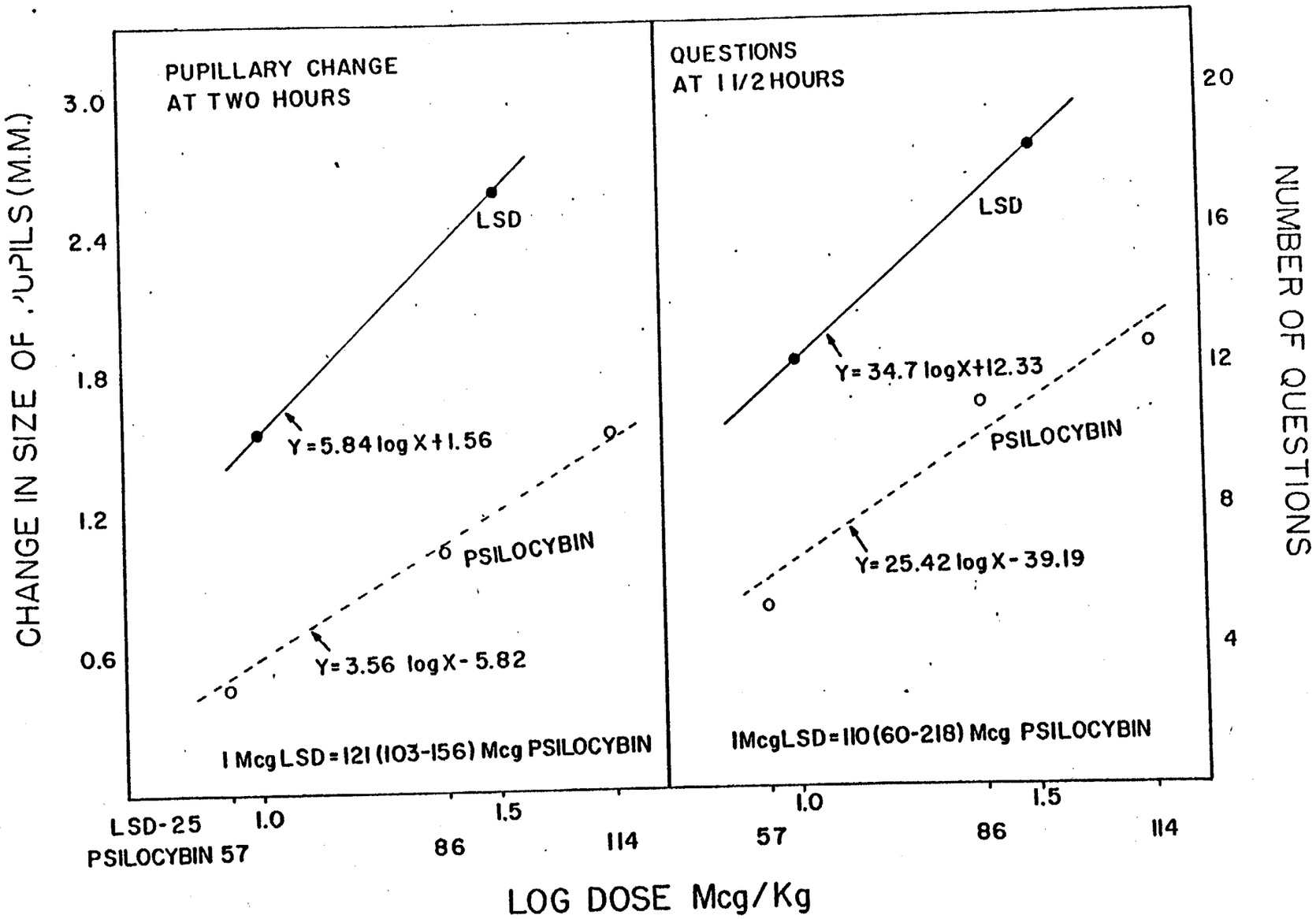
PUPILLARY CHANGE
AT TWO HOURS
QUESTIONS
AT 1 1/2 HOURS
CHANGE IN SIZE OF PUPILS (M.M.)
NUMBER OF QUESTIONS
3.0
2.4
1.8
1.2
0.6
20
16
12
8
4
LSD
Y = 5.84 log X + 1.56
PSILOCYBIN
Y = 3.56 log X - 5.82
Y = 34.7 log X + 12.33
PSILOCYBIN
Y = 25.42 log X - 39.19
1 Mcg LSD = 121 (103-156) Mcg PSILOCYBIN
1 Mcg LSD = 110 (60-218) Mcg PSILOCYBIN
LSD-25 1.0 1.5
PSILOCYBIN 57 86 114
57 1.0 86 1.5 114
LOG DOSE Mcg/Kg

FIGURE 1. Comparison of the reactions induced by psilocybin and LSD-25 in man.

By Harris Isbell, M. D.