THE BLACK VAULT

205

Psychopharmacologia 3, 1—14 (1962)

From the National Institute of Mental Health Addiction Research Center
U.S. Public Health Service Hospital Lexington, Kentucky, U.S.A.

Cross Tolerance between Mescaline and LSD-25
With a Comparison of the Mescaline and LSD Reactions

By
A. B. Wolbach, Jr., Harris Isbell and E. J. Miner

With 2 Figures in the Text

(Received November 8, 1961)

Although some differences have been reported, the reactions produced in man by the diethylamide of lysergic acid (LSD-25) and mescaline seem very similar. Both drugs cause autonomic stimulation manifested by increased pupillary size, increase in pulse rate and blood pressure, and elevation of body temperature (Balestrieri and Fontanari; Buchanan; Hoch *et al.*; Isbell *et al.*, 1956; Stockings; Stoll). Both create anxiety, difficulty in concentration and thinking, flight of ideas, fluctuations in mood, perceptual distortion in all sensory modalities, true- and pseudo-hallucinations usually of visual nature, and depersonalization (Abramson *et al.*; Beringer; Buchanan; Guttman and Maclay; Hoch *et al.*; Isbell *et al.*, 1956; Mayer-Gross; Rinkel *et al.*; Stockings; Stoll). Some authors have referred to the mental state induced by either agents as "experimental schizophrenia" (Rinkel *et al.*; Stockings).

The clinical resemblance of the syndromes caused by mescaline and LSD-25 suggest that these drugs, despite differences in chemical structure, either share a common mechanism of action or act on final common pathway. This hypothesis is strengthened by reports of cross tolerance between the two drugs (Balestrieri, 1957, 1960; Balestrieri and Fontanari).

The purposes of this paper are: (1) to present a quantitative comparison of the effects of LSD-25 and mescaline in the same subjects; and (2) to show, in confirmation of Balestrieri (1957 und 1960) and Balestrieri and Fontanari, that direct tolerance develops to mescaline, and that subjects tolerant to mescaline are cross tolerant to LSD and *vice versa*.

Methods

Experiments. Two experiments were performed. Experiment I was a comparison of the effects and a determination of the equivalent dosages of LSD, mescaline, and psilocin in 10 subjects. The data on psilocin will

B-374

not be presented in this paper but will be reported separately. Experiment II was a study of cross tolerance between LSD and mescaline in 10 subjects.

Experiment I

Experimental design. A "single-blind" cross-over design was employed in this experiment (patients did not know the drugs they were receiving, but observers did known). Each subject received, in randomized order at weekly intervals, two doses of LSD and mescaline. Placebos were not included since experience (ISBELL *et al.*, 1956, 1961) has shown that former morphine addicts do not react markedly to placebos. For comparison, placebo data from another experiment (ISBELL *et al.*, 1959) are presented.

Subjects. The subjects who volunteered for this experiment were former opiate addicts who were serving sentences for violation of United States narcotic laws. Their ages varied between 25 to 35 years, all were physically healthy males, and none presented any evidence of the major psychoses. All had psychiatric diagnoses of character or personality disorders and all had received LSD in previous experiments.

General conditions. The subjects entered a special ward devoted to clinical research the night before the day on which test drug was administered and remained until the following morning. Observations were performed by specially trained aides with long experience in detecting behavioral changes due to drugs. The patients were told nothing about the nature of the drugs they were to receive or the purposes of the experiments.

Drugs and doses. LSD tartrate and mescaline hydrochloride were administered intramuscularly in doses of 0.75 mcg/kg and 1.5 mcg/kg (LSD), and 2.5 mg/kg and 5.0 mg/kg (mescaline). The drug concentrations employed for LSD and mescaline were 30 mcg/ml and 1000 mg/ml respectively, in distilled water. Prior to administration each dose was diluted to a constant 5 ml volume with sterile pyrogen-free physiological saline solution. The following detailed observations were made at hourly intervals after 10 minutes rest in bed, twice before, and eight times after administration of drugs: rectal temperature, pulse rate, systolic blood pressure, pupillary size, and threshold for elicitation of the kneejerk. The methods used were those previously described by ISBELL *et al.* (1956, 1961). In addition the subjects (with the help of an aide) completed a special questionnaire at hourly intervals from 7.30 a.m. to 3.30 p.m. At these same times general notes on behavior were written. Clinical grades of the intensity of the reaction were assigned according to the system of ISBELL *et al.* (1956).

Analysis of data. The changes in rectal temperature, pulse rate, pupillary size, blood pressure and threshold for elicitation of the knee

jerk were calculated by subtracting the average of the two pre-drug observations from the values obtained at the various hours after the drug. The areas under the time-action curves for each of the above measurements composed of these figures were calculated by the method of WINTER and FLATAKER, thus converting all the data on a particular drug, a particular measurement, and a particular day to one figure termed "degree-hours" (temperature), "rate hours" (pulse rate), etc. "Positive" answers on the questionnaire were scored by counting all positive responses that were not scored positively before the drugs were given. Means and standard errors of the means were calculated according to standard statistical techniques (EDWARDS). Calculations of the relative potency of LSD and mescaline were performed on each of these parameters, using a method (GADDUM) for four-point assays.

In order to obtain time-action curves, changes in temperature, pulse rate, systolic blood pressure, pupillary size, and threshold for the kneejerk were tabulated and averaged for each observation time after the drugs. The number of positive responses on the questionnaire were also averaged at each observation time. In addition to providing data on the time-action course, these tabulations identified the time at which the greatest (peak) responses occurred. Additional calculations of relative potency (GADDUM) were made using these peak values.

In order to compare the patterns of subjective response the 57 questions were classified into nine categories[1]. The questionnaires were then scored by counting the number of patients responding positively to a given question, after which the scores for all the questions constituting the particular category were summed.

Experiment II

Experimental design. A "cross-over" design using each patient as his own control was employed in this experiment and is summarized in Table 1. The design was similar to that used in testing cross-tolerance between LSD and psilocybin (ISBELL *et al.*, 1961).

Subjects. The same 10 subjects were employed who were used in Experiment I.

General conditions. Subjects were housed in the same special research ward mentioned in Experiment I. Temperature, respiratory rate, and blood pressure were measured three times daily after the patients had rested quietly in bed during days on which special measurements were

[1] The nine categories are shown in Table 5 and are the same that were used in comparing LSD and psilocybin (ISBELL 1959). As previously explained, a large number of other categories could be devised and many questions could be classified in various categories. The classification therefore is completely arbitrary.

Table 1. *Summary of experimental design. Experiment II*

Period	Number of days	Drugs and doses		Remarks
		Subjects X[1]	Subjects Y[2]	
1. 1st control	7—21	LSD[3] 1.5, Mesc.[3] 5.0	Mesc. 5.0, LSD 1.5	To obtain basal data. Order of tests randomized. Minimum of 5 days between LSD and mescaline
2. 1st chronic administration	14	LSD increasing to 1.5	Mesc. increasing to 5.0	To develop tolerance
3. 1st test of tolerance and cross-tolerance	2	LSD 1.5, Mesc. 5.0	Mesc. 5.0, LSD 1.5	Test of tolerance and cross tolerance
4. Withdrawal period	14	none	none	To lose tolerance
5. 2nd control	10—24	Mesc. 5.0, LSD 1.5	LSD 1.5, Mesc. 5.0	To replicate control data and test loss of tolerance
6. 2nd chronic administration	14	Mesc. increasing to 5.0	LSD increasing to 1.5	"Cross-over" to develop tolerance
7. 2nd test of tolerance and cross-tolerance	2	Mesc. 5.0, LSD 1.5	LSD 1.5, Mesc. 5.0	Test of tolerance and cross-tolerance

[1] Subjects "X" received LSD chronically, first.
[2] Subjects "Y" received mescaline chronically, first.
[3] LSD = diethylamide of lysergic acid; Mesc. = mescaline. The order of administration of the drug in each period is indicated by the order in which they appear in the section of table for that period. Figures after symbols for drugs indicate the dose in mcg/kg for LSD and mg/kg for mescaline.

not being made. All measurements were made by the same aides as in Experiment I.

Drugs and doses. LSD and mescaline were administered intramuscularly at 8 a.m. (during the control period and on test days) or at 6 a.m. (during the periods of chronic intoxication). No placebos were employed in this study because of the negligible subjective response of our subjects, because placebos have no real value in assessing tolerance and cross tolerance, and because the addition of placebo trials would have prolonged the experiment unnecessarily. In the first and second control periods the patients received LSD 1.5 mcg/kg, and mescaline 5.0 mg/kg in randomized order before chronic administration of the drugs was begun. Detailed observations were made on these test days. These control experiments were conducted at intervals of at least five days in order to prevent development of tolerance during the control period.

During the first and second periods of chronic administration, the patients received intramuscularly 0.30 mcg/kg of LSD or 1 mg/kg of

mescaline on the first day. These doses were increased by 0.30 mcg/kg (LSD) or 1 mg/kg (mescaline) daily until the patients were receiving 1.5 mcg/kg of LSD or 5.0 mg/kg of mescaline on the fifth day. These doses were maintained through the 14th day after beginning chronic intoxication. On the 15th day the patients were "challenged" with the dose of drug they had been receiving (test of "direct" tolerance). On the 16th day they were "challenged" with the test dose of the alternate drug (test of "cross" tolerance). On both of these days detailed measurements were made.

The patients then received no medication for 14 days in order to lose tolerance.

Following this withdrawal period, "second control" measurements were obtained after the patients had received in randomized order mescaline 5.0 mg/kg, and LSD 1.5 mcg/kg, with at least five days intervening between administration of either drug.

The patients then again received the drugs chronically; those patients who had received LSD in the first period of chronic administration were given mescaline according to the schedules described above and *vice versa*. They were then "challenged" with LSD and mescaline in the same manner as previously described.

Observations. On test days all observations were performed in identical fashion to those described in Experiment I.

Analysis of data. The areas under the time-action curves were obtained for each subject and each test condition (including first and second controls and all "challenging" tests) in the manner described in Experiment I. In addition, mean peak response values were obtained (as in Experiment I) for each parameter except "clinical grade," since the latter consisted of only a single figure.

The difference in the various area measurements after 1.5 mcg/kg of LSD on the first and second controls were evaluated by a t-test for paired observations (EDWARDS). Data on the two sets of controls after 5.0 mg/kg of mescaline were treated similarly. Increase in blood pressure was significantly greater after LSD. There were no significant differences on other parameters (Table 2). In addition, the differences between the two controls were evaluated by a non-parametric rank order test for paired observations (WILCOXON). Since the significances of the differences by this latter statistical technique agreed well with those obtained by the t-test on the time-action (area) figures, only the latter are herein presented.

In order to test for equivalence of the doses of LSD and mescaline in Experiment II, the average peak values obtained on the two controls with 1.5 mcg/kg of LSD were compared with the average values obtained

Table 2. *Reproducibility of responses to LSD and mescaline in first and second controls* ($N = 10$)

Measure	LSD-25	Mescaline
Temperature	+ 0.282 ± 0.372	− 0.516 ± 0.480
Pulse rate	+14.95 ± 13.68	+18.65 ± 14.12
Blood pressure	+33.35 ± 14.03[1]	−10.30 ± 9.71
Pupillary change	+ 0.325 ± 1.75	− 0.263 ± 1.27
Kneejerk	− 6.24 ± 12.95	+ 2.75 ± 21.83
Responses to questionnaire	+10.35 ± 9.68	− 4.60 ± 8.56
Clinical grade	+ 0.150 ± 0.211	+ 0.100 ± 0.221

Figures represent the mean differences ± the standard errors of the differences between responses to LSD-25 (1.5 mcg/kg) and mescaline (5.0 mg/kg) in the first and second controls.

\+ Indicates an increased response on the second control.

— Indicates a decreased response in the second control.

[1] Indicates significance ($P < 0.05$).

on the two controls with 5.0 mg/kg of mescaline (Table 3), using the t-test for paired data. Similar calculations were made using the area measurements.

The differences in the response after chronic administration of both LSD and mescaline were evaluated by comparing the responses after first and second chronic administrations of LSD and/or mescaline with their respective first and second controls using the t-test for replicated data (EDWARDS). Four different comparisons were made: (1) response to LSD after chronic administration of LSD ("direct" tolerance to LSD), (2) response to mescaline after chronic administration of LSD ("cross" tolerance to mescaline), (3) response to mescaline after chronic administration of mescaline ("direct" tolerance to mescaline), and (4) response to LSD after chronic administration of mescaline ("crosss" tolerance to LSD). The signs of the differences were so arranged that a minus (—) sign indicated a decrease in the measurements after chronic administration as compared with control, and a plus (+) sign indicated an increase.

Table 3. *Equivalence of dosage of LSD and mescaline, Experiment II* ($N = 10$

Measure	Mean Difference in response (R_{LSD}-R_{Mesc})
Temperature	−0.0055 ± 0.05
Pulse rate	+2.80 ± 1.85
Blood pressure	+4.15 ± 1.44[1]
Pupillary change	−0.212 ± 0.171
Kneejerk	+1.94 ± 2.10
Responses to questionnaire	+1.45 ± 1.92
Clinical grade	−0.35 ± 0.24

Figures respresent mean differences ± S.E. of differences between mean peak control responses to LSD-25 (1.5 mcg/kg) and mescaline (5.0 mg/kg).

\+ Indicates LSD-25 stronger in effect than mescaline.

— Indicates mescaline stronger in effect than LSD-25.

[1] Indicates significance ($P < 0.02$).

Since mescaline has a longer duration of action than LSD the differences (except for "clinical grade") were also evaluated, using values obtained at the peak of both LSD and mescaline reactions rather than using the areas (integrated time action curves) as described above. In addition, the differences were evaluated by WILCOXON's non-parametric rank order test for paired observations. The significance of the differences by these statistical techniques agreed well with those obtained by the t-test on the time-action (area) figures, so only the differences obtained by the area method are shown in this paper.

Results

Experiment I. The objective and subjective changes induced by LSD and mescaline were very similar. As can be seen in Table 4, both drugs

Table 4. *Comparison of the total course of the LSD and mescaline reactions*

Measure	Placebo[1]	Treatment			
		LSD-25		mescaline	
		0.75[2]	1.5[2]	2.5[3]	3.0[3]
Temperature[4]	+ 2.7 ± 0.3	+ 3.5 ± 0.4	4.3 ± 0.5	+ 3.4 ± 0.4	+ 4.6 ± 0.4
Pulse rate[4]	+37.8 ± 14.5	+50.2 ± 10.2	56.6 ± 7.7	+38.4 ± 9.3	+71.1 ± 17.7
Blood pressure[4]	+15.6 ± 13.5	+45.5 ± 12.5	65.2 ± 10.1	+45.4 ± 13.5	+76.6 ± 12.4
Pupillary change[4]	+ 0.2 ± 1.4	+ 8.0 ± 0.9	12.9 ± 1.6	+10.4 ± 1.6	+17.3 ± 2.0
Kneejerk[4]	−20.7 ± 11.1	−54.2 ± 11.0	−54.0 ± 9.6	−65.5 ± 15.1	−70.1 ± 16.9
Positive answers[5]	0.1 ± 0.3	37.1 ± 4.7	72.8 ± 11.1	35.8 ± 5.9	67.2 ± 12.1
Clinical grade[6]	0 ± 0	1.85 ± 0.2	2.45 ± 0.2	1.65 ± 0.2	2.1 ± 0.2

[1] Data from 9 other subjects in another experiment (ISBELL 1959).
[2] Dose in mcg/kg.
[3] Dose in mg/kg.
[4] Figures are means (9 subjects on placebo; 10 on LSD and mescaline) ± standard errors of areas under time-action curves ("degree-hours," "beat-hours," etc.). The signs indicate increases (+) or decreases (—) in the measurement from pre-drug controls.
[5] Means ± standard errors of number of questions scored positively in the $7^1/_2$ hours after the drug which were not scored positively before the drug.
[6] Means ± standard errors of intensity of mental reaction based on a scale of 0—4.

caused increases over pre-drug measurements in body temperature, pulse rate, systolic blood pressure, and pupillary size, and both decreased the threshold for elicitation of the kneejerk. The table also shows that

Table 5. *Comparison of pattern of subjective response on questionnaire after mescaline and LSD-25*

Category[1]	Number of questions[2]	Total responses possible	Number of responses in category				
			placebo[3]	LSD		mescaline	
				0.75	1.5	2.5	5.0
General	7	70	0	18	30	19	26
Difficulty in thinking	4	40	0	0	14	3	4
Alteration in mood	3	30	0	14	15	6	9
Alteration in touch	4	40	0	13	20	15	26
Alteration in hearing	4	36	0	16	20	11	18
Visual distortion	10	40	0	10	39	12	23
"Elementary" hallucinations	5	45	0	8	20	8	20
"True" hallucinations	4	40	0	2	6	1	5
Depersonalization	13	130	0	26	44	23	34

[1] Refers to type of question, 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 category.

[3] Based on responses of 10 different subjects in another experiment.

the changes in the various measures were far greater than those that occurred in a different group of subjects after placebo. The magnitude of these changes was about the same after 0.75 mcg/kg of LSD and 2.5 mg/kg of mescaline, or after 1.5 mcg/kg of LSD and 5.0 mg/kg of mescaline. Both drugs induced anxiety, alterations in mood (generally "euphoric"), difficulty in thinking and concentration, sensory perceptual distortion particularly visual, and both caused true- and pseudo-hallucinations. The subjective symptoms reported after mescaline were very similar to those described in the literature. Table 5 illustrates the similarity of the patterns of the subjective response after LSD and mescaline.

Table 6. *Relative potencies of mescaline and LSD calculated from various measurements*

Measure	Relative potency[1]	95% confidence limits
Areas		
Temperature	3270	2666—3731
Blood pressure	3084	2275—4000
Pupils[2]	2392	1779—3274
Total answers	3355	2487—5065
Peak values		
Temperature	3280	3165— 3401
Blood pressure	3344	1698— 7518
Pupils	2970	2008— 4201
Answers	4878	2832—10000
Clinical grade	3460	2194— 5450

[1] $\frac{\text{Mcg mescaline hcl}}{\text{Mcg LSD-25 tartrate}}$ at equal effect

[2] Did not meet criterion for equivalence of dosage.

LSD and mescaline differed in time-action course. In general the action of mescaline persisted longer than that of LSD with peak effect being reached later and/or being longer sustained (Fig. 1 and 2). These

curves show that pupillary dilatation after both mescaline and LSD lasts much longer than do the subjective effects. They also show that the peak subjective effects of mescaline, as measured by the responses on the questionnaire, were less than those after LSD. The subjective effects of mescaline subsided more slowly than did those of LSD.

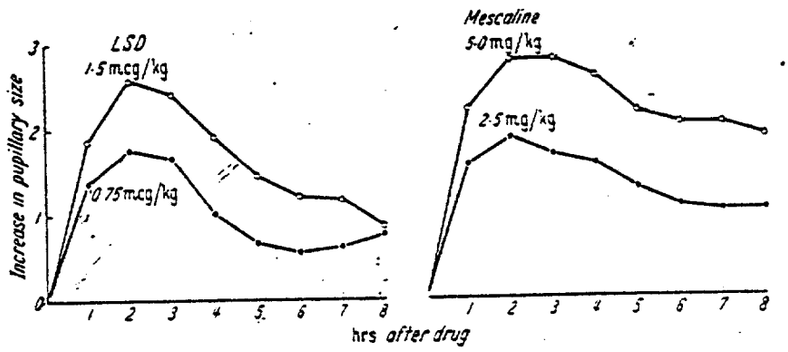

Fig. 1. Time course of pupillary dilatation after LSD and mescaline

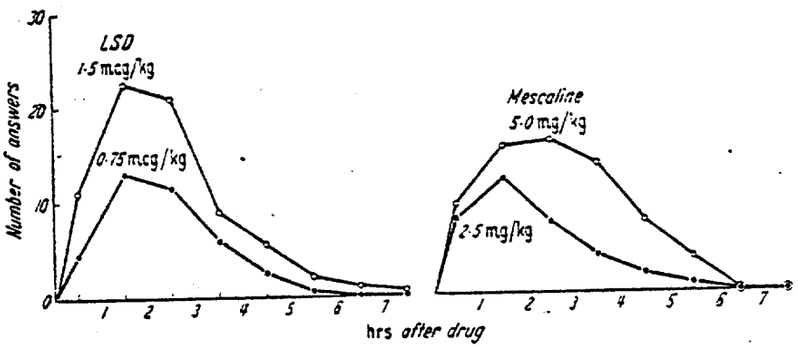

Fig. 2. Time course of subjective response after LSD and mescaline

Calculations of relative potency are summarized in Table 6. Significant dose-effect slopes were not obtained for pulse rate and threshold for the kneejerk for either area or peak data, so these measures are omitted from the table. Significant slopes were obtained on all other measures and, with the exception of area measurement for pupillary change which did not meet the criterion for equivalence of effects at the doses used, the regression lines for all these measures met the requirements for equivalence of dosage and parallelism. These calculations show that LSD tartrate is about 2400 to 4900 times as potent as mescaline hydrochloride, depending on the measurement chosen. On a molecular basis, LSD is 4500 to 9275 times as potent as mescaline. It should

be noted that mescaline is more potent in dilating pupils relative to its potency in inducing subjective responses than is LSD.

Experiment II. *Cross tolerance between LSD and mescaline. Controls.* The differences in responses to the same drug in first and second controls after LSD and mescaline are shown in Table 2. The only change that was statistically significant ($p < 0.05$) was an increased elevation of blood pressure after the second control dose of LSD. This could indicate simple variability of response to LSD on this particular parameter. The table shows that no significant degree of residual tolerance was present at the time the second controls were done.

Equivalence of dosage. The differences in the mean peak responses to the two different active drugs (LSD and mescaline) are presented in Table 3. It will be noted that although four of the six comparisons indicate that LSD may have produced a somewhat stronger response than mescaline, the only statistically significant difference between the two drugs is in elevation of blood pressure. The magnitude of the difference is small and probably reflects the variability of response on blood pressure after LSD when administered on separate occasions to the same subjects (see above). Since the majority of differences are positive, there is some indication that, on the average, the peak effects of LSD may have been somewhat stronger than those of mescaline. Similar calculations using area measurements instead of peak values gave identical results with one exception. Total pupillary dilatation after mescaline was significantly greater than that after LSD. This difference from the results with the peak data reflects the more sustained action of mescaline on the pupil.

Tolerance and cross tolerance. The differences in responses to LSD and mescaline after chronic administration of either drug and their respective first and second controls are shown in Table 7. In this table the first column of figures shows the difference in response to LSD as compared with the corresponding first or second control after chronic administration of LSD, and reflects "direct" tolerance to LSD. The second column of figures shows the difference in response to mescaline as compared with the appropriate control after chronic administration of LSD, and reflects "cross" tolerance to mescaline. Similarly, the third column of figures presents measures of "direct" tolerance to mescaline, and the fourth column of figures, "cross" tolerance to LSD.

Inspection of Table 7 shows that all the signs are negative, indicating an average decrease in response on all measures. In the case of "direct" tolerance to LSD (first column of figures), the differences were statistically significant in six of the seven measures. In the case of "direct" tolerance to mescaline (third column of figures), statistically significant change occurred in three measures, and in the case of "cross" tolerance

to LSD (fourth column of figures), significant degrees of change occurred in four parameters. The measures which reflected "direct" tolerance and "cross" tolerance most clearly were pupillary diameter, responses on questionnaire, and the clinical grades.

Table 7. *Tolerance and cross tolerance*

Measure	After LSD chronically (14 days)		After mescaline chronically (14 days)	
	test with LSD "direct" tolerance to LSD	challenge with mescaline "cross" tolerance to mescaline	test with mescaline "direct" tolerance to mescaline	challenge with LSD "cross" tolerance to LSD
Temperature	− 0.275 ± 0.139	− 0.503 ± 0.564	− 1.14 ± 0.59	− 0.231 ± 0.493
Pulse rate	− 26.90 ± 12.35	− 48.10 ± 13.03[3]	− 33.00 ± 16.15	− 24.20 ± 12.95
Blood pressure	− 46.25 ± 14.10[3]	− 42.05 ± 16.50[1]	− 32.60 ± 14.98	− 62.90 ± 11.30[3]
Pupillary change	− 12.20 ± 1.29[3]	− 9.11 ± 1.22[3]	− 3.40 ± 1.28[3]	− 6.88 ± 0.76[3]
Kneejerk	− 40.25 ± 16.25[1]	− 53.85 ± 18.79[2]	− 8.78 ± 11.71	− 19.58 ± 13.57
Responses to questionnaire	− 40.85 ± 3.90[3]	− 69.30 ± 15.63[3]	− 47.35 ± 7.61[3]	− 56.40 ± 9.70[3]
Clinical grade	− 1.20 ± 0.20[3]	− 1.40 ± 0.32[3]	− 1.45 ± 0.24[3]	− 1.30 ± 0.30[3]

Figures represent the mean differences ± the standard errors of the differences between responses to first control doses of LSD-25 (1.5 mcg/kg) or mescaline (5.0 mg/kg) and identical "test" and "challenging" doses of these drugs after a first period of chronic intoxication with either drug; and, second control doses of LSD-25 (1.5 mcg/kg) or mescaline (5.0 mg/kg) and identical "test" and "challenging" doses of these drugs after a second period of chronic intoxication with the other drug.

\+ Indicates increase in response after chronic intoxication.

— Indicates a decrease in response after chronic intoxication.

[1] Indicates significance ($P < 0.05$).

[2] Indicates significance ($P < 0.02$).

[3] Indicates significance ($P < 0.01$).

Discussion

As expected from the descriptions in the literature, the reactions induced by LSD and mescaline proved remarkably similar, differing chiefly in rate of onset and duration of action. Both drugs caused similar changes in autonomic functions which were nearly identical in degree at doses inducing equivalent grades of mental aberration. The subjective symptoms reported after the two drugs were very similar in kind and incidence. It is, of course, possible that the similarity in the subjective response was partly caused by the methods of measurement and the experimental situation. All of our subjects had received LSD on other occasions and might have expected similar symptoms from any drug given in this particular testing situation. In addition, the use of the questionnaire may suggest certain symptoms. However there are cogent

reasons against the similarity being due to the experimental situation or to suggestion. The patterns of effect after many other drugs (amphetamine, scopolamine, marihuana, etc.) in the same kind of subjects and under the same conditions differ markedly from the pattern induced by mescaline and LSD. In addition, the similarity between the LSD and mescaline reactions is readily apparent in the descriptions in the literature, even though the subjects were tested under widely varying conditions with different methods, and in subjects who received only mescaline or LSD. Thus it seems likely that the similarity between the reactions caused by LSD and mescaline is a real phenomenon and not an artifact due to the methods of testing.

The similarity of the effects of LSD and mescaline suggests that the two drugs act by common mechanisms or through some final common pathway. This hypothesis is strongly reinforced by the finding (in agreement with BALESTRIERI, 1957) that definite cross tolerance developed between both drugs on chronic administration. Direct tolerance to mescaline and cross tolerance to LSD could not be demonstrated on as many measures in patients receiving mescaline chronically as could direct tolerance to LSD and cross tolerance to mescaline in patients receiving LSD chronically. However a high degree of direct and cross tolerance occurred in both instances on the most reliable and least variable of the measures (pupillary change, responses on the questionnaire, and clinical grade).

Since persons directly tolerant to LSD are cross tolerant to psilocybin (ISBELL, 1961) it seems likely, although not proved by direct experiments, that persons directly tolerant to psilocybin would be cross tolerant to mescaline. LSD, mescaline, and psilocybin appear to constitute a definite group of drugs with identical or closely related biological effects, just as morphine, methadone and meperidine constitute a biologically related group of analgesic drugs exhibiting high degrees of cross tolerance.

Since psilocybin is an indole and since LSD can be regarded as an indole, one might hypothesize that the similarities in biological effect and the development of tolerance and cross tolerance are related to similarities in chemical configuration. Mescaline is, however, not an indole, and although it has been postulated that mescaline is converted to an indole in the body, no direct evidence of such a biotransformation exists at present. In fact, investigators who have studied the biotransformation of mescaline have reported that mescaline is excreeted largely unchanged (WOODS *et al.*), or partly unchanged and partly as 3.4.5-trimethoxyphenylacetic acid (SPECTOR). For the moment, it seems best to attribute the similarities of action of LSD, mescaline and psilocybin to some common biological mechanism rather than to similarities in chemical structure.

Summary

1. The reactions caused by intramuscular administration of 0.75 mcg/kg and 1.5 mcg/kg of LSD-25 have been compared in the same 10 subjects with those induced by 2.5 mg/kg and 5.0 mg/kg of mescaline.

2. Both LSD and mescaline caused dilatation of the pupils, increase in body temperature, elevation of pulse rate and increase in systolic blood pressure. Both drugs decreased the threshold for elicitation of the kneejerk.

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

4. The effects of mescaline appeared more slowly and persisted somewhat longer than did the effects of LSD.

5. LSD tartrate is 2400—4900 times as potent as mescaline hydrochloride. On a molecular basis, LSD is 4500 to 9275 times as potent as mescaline.

6. Patients receiving LSD daily developed direct tolerance to LSD; such patients were also cross tolerant to mescaline. Likewise patients receiving mescaline daily became tolerant to mescaline and cross tolerant to LSD.

7. It was inferred that LSD, psilocybin and mescaline probably share common mechanisms of action or some common final pathway.

Acknowledgments. We are indebted to Drs. R. Bircher and C. Henze of Sandoz Pharmaceuticals, Hanover, N.J., for supplies of diethylamide of lysergic acid tartrate (LSD-25), and to Dr. L. A. Pirk, Hoffmann-La Roche, Inc., Nutley Park, N.J., for supplies of mescaline hydrochloride.

References

Abramson, H. A., M. E. Jarvik, M. R. Kaufman, C. Kornetsky, A. Levine and M. Wagner: Lysergic acid diethylamide (LSD-25). I. Physiological and perceptual responses. J. Psychol. (Provincetown) 39, 3—60 (1955).

Balestrieri, A.: Crossed tolerance between LSD-25 and mescaline, p. 581 in Psychotropic Drugs, ed. by S. Garattini and V. Ghetti. Amsterdam-London-New York-Princeton: Elsevier Publ. Co. 1957.

— Some aspects of the sensitivity to hallucinogenic drugs, p. 44—47, Neuropsychopharmacology. Proc. of 2nd Meet., Collegium Internat. Neuropsychopharmacologicum, vol. 2, edit. by E. Rothlin. Amsterdam-London-New York-Princeton. Elsevier Publ. Co. 1960.

—, and D. Fontanari: Acquired and crossed tolerance to mescaline, LSD-25 and BOL-148. A.M.A. Arch. gen. Psychiat. 1, 279—282 (1959).

Beringer, K.: La intoxicacion por la mescalina. Arch. argent. Neurol. 2, 145—154 (1928).

Buchanan, D. N.: Meskalinrausch. Brit. J. med. Psychol. 9, 67—88 (1929).

Edwards, A. L.: Statistical analysis for students in psychology and education. New York: Rhinehart & Co. 1946.

FREEDMAN, D. X., G. K. AGHAJANIAN, E. M. ORNITZ and B. S. ROSNER: Patterns of tolerance to lysergic acid diethylamide and mescaline in rats. Science 127, 1173—1174 (1958).

GADDUM, J. H.: Bioassays and mathematics. Pharmacol. Rev. 5, 87—134 (1953).

GUTTMANN, E., and W. S. MACLAY: Mescaline and depersonalization. J. Neurol. Psychopath. 16, 193—212 (1936).

HOCH, P. H., J. P. CATTELL and H. H. PENNES: Effects of mescaline and lysergic acid (*d*-LSD-25). Amer. J. Psychiat. 108, 579—584 (1952).

ISBELL, H.: Comparison of the reactions induced by psilocybin and LSD in man. Psychopharmacologia 1, 29—38 (1959).

— R. E. BELLEVILLE, H. F. FRASER, A. WIKLER and C. R. LOGAN: Studies on lysergic acid diethylamide (LSD-25). I. Effects in former morphine addicts and development of tolerance during chronic intoxication. Arch. Neurol. Psychiat. (Chicago) 76, 468—478 (1956).

— A. B. WOLBACH, A. WIKLER and E. J. MINER: Cross tolerance between LSD and psilocybin. Psychopharmacologia 2, 147—159 (1961).

MAYER-GROSS, W.: Experimental psychoses and other mental abnormalities produced by drugs. Brit. med. J. 1951 II, 317—321.

RINKEL, M., H. J. DESHON, R. W. HYDE and H. C. SOLOMON: Experimental schizophrenia-like symptoms. Amer. J. Psychiat. 108, 572—577 (1952).

SPECTOR, E.: Identification of 3,4,5-trimethoxyphenylacetic acid as the major metabolite of mescaline in the dog. Nature (Lond.) 189, 751—752 (1961).

STOCKINGS, G. T.: A clinical study of the mescaline psychosis with special reference to the mechanism of the genesis of schizophrenic and other psychotic states. J. ment. Sci. 86, 29—47 (1940).

STOLL, W. A.: Lysergsäure-diäthylamid, ein Phantasticum aus der Mutterkorngruppe. Schweiz. Arch. Neurol. Psychiat. 60, 279—324 (1947).

WILCOXON, F.: Some rapid approximate statistical procedures. New York: American Cyanamid Comp. 1949.

WINTER, C. A., and L. FLATAKER: Studies on heptazone (6-morpholino-4,4-diphenyl-3-heptanone hydrochloride) in comparison with other analgesic drugs. J. Pharmacol. exp. Ther. 98, 305—317 (1950).

WOODS, L. A., J. COCHIN, E. J. FORNEFELD, F. G. McMAHON and M. H. SEEVERS: The estimation of amines in biological materials with critical data for cocaine and mescaline. J. Pharmacol. exp. Ther. 101, 188—199 (1951).

HARRIS ISBELL, M.D., Director N.I.M.H. Addiction Research Center
U.S. Public Health Service Hospital, Lexington, Kentucky, U.S.A.