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Cross Tolerance Between LSD and Psilocybin

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Recently it has been shown (HOFMAN *et al.*, 1958a; DELAY *et al.*, 1958; ISBELL, 1959) that O-Phosphoryl-4-hydroxy-N-dimethyl tryptamine (hereafter referred to as psilocybin), a compound isolated (HOFMAN *et al.*, 1958b) from certain species of mushrooms that are used ceremonially by Mexican Indians (WASSON and WASSON, 1957). has psychotomimetic properties similar to those of the diethylamide of lysergic acid (LSD-25). The close resemblance of the patterns of symptoms induced by LSD and psilocybin suggested that these drugs produce mental aberrations by some common action or by affecting different mechanisms sharing a common final pathway. Since the effects of LSD diminish rapidly when the drug is given daily (ISBELL *et al.*, 1956), it was felt that if the LSD and psilocybin syndromes have a common mechanism, this hypothesis could be further tested by determining if "cross tolerance" between the two drugs existed. In other words, if the degree of the reaction induced by a given dose of psilocybin was significantly less in a person tolerant to LSD, cross tolerance would be said to exist; and, conversely, the reaction to a given dose of LSD should be reduced in a person tolerant to psilocybin. In the latter case it is implied that "direct" tolerance to psilocybin can be developed.

Methods

Experiments. Two experiments were performed at different times. Experiment II was carried out to determine if administration of a larger dose of psilocybin given over a longer period of time than in Experiment I would create a greater degree of tolerance and cross tolerance.

A "cross-over" design using each patient as his own control was employed in both experiments and is summarized in Table 1.

Both experiments consisted of seven periods: (1) *first control*, in which measurements were obtained after the test doses of psilocybin and LSD, (2) *first chronic administration*, in which patients received either psilocybin or LSD once daily in doses increasing to the test level over a period of 6—12 days, (3) *first test of tolerance and cross tolerance*, in which patients were "challenged" with the drug they had been taking

Table 1. *Summary of experimental designs for Experiments I and II*

Period	Expt.	No. of Days	Drugs and Doses		Remarks
			Subjects x [1]	Subjects y [2]	
1. First control	I	7—8	LSD[3] 1.5; PP, Ps 150.	Ps[3] 150; Pl, LSD 1.5	To obtain basal data
	II	8—9	LSD 1.5, Pl, Ps 210	Ps 210, Pl, LSD	Order of tests randomized. At least 5 days between Ps and LSD
2. First chronic administration	I	6—7	LSD increasing to 1.5	Ps increasing to 150	To develop tolerance
	II	12	LSD increasing to 1.5	Ps increasing to 210	
3. First test of tolerance and cross-tolerance	I	2	LSD 1.5, Ps 150	Ps 150, LSD 1.5	Test of tolerance and cross tolerance
	II	2	LSD 1.5, Ps 210	Ps 210, LSD 1.5	
4. Withdrawal period	I	7—10	Pl	Pl	To lose tolerance
	II	13	None	None	
5. Second control	I	7—8	Pl, Ps 150, LSD 1.5	LSD 1.5, Pl, Ps 150	To replicate control data
	II	8—9	Pl, Ps 210, LSD 1.5	LSD 1.5, Pl, Ps 210	To test loss of tolerance
6. Second chronic administration	I	6—7	Ps increasing to 150	LSD increasing to 1.5	"Cross-over" to develop tolerance
	II	12	Ps increasing to 210	LSD increasing to 1.5	
7. Second test of tolerance and cross-tolerance	I	2	Ps 150, LSD 1.5	LSD 1.5, Ps 150	Test of tolerance and cross tolerance
	II	2	Ps 210, LSD 1.5	LSD 1.5, Ps 210	

[1] Subjects "x" received LSD chronically, first.

[2] Subjects "y" received psilocybin chronically, first.

[3] LSD = diethylamide of lysergic acid; Pl = placebo; Ps = psilocybin. The order of administration of the drug in each period is indicated by the order in which they appear in the section of the table for that period. Figures after the symbols for the drugs indicate the dose in mcg/kg.

(test of "direct tolerance") and on the subsequent day with the drug they had not been taking (test of "cross" tolerance), (4) *a withdrawal or "washout" period*, in which the patients received placebos (Experiment I) or no drug (Experiment II) in order to lose tolerance, (5) *a second control period*, in which the test doses of LSD and psilocybin were repeated, in order to replicate the control data obtained in the first control period and to determine if tolerance had been completely lost, (6) *second chronic administration*, in which the patients received daily doses of the alternate drug that they had not taken in the first period of chronic administration ("cross-over"), and (7) finally, the *second challenge*, with test doses of LSD and psilocybin as in period 3.

Drugs and Doses. LSD and psilocybin[1] were given in 30 cc of cherry syrup at 8 a.m. with the patients fasting. The syrup, which was used to mask the bitter taste of the psilocybin, served as the placebo. In the first and second control periods the patients received in randomized order 1.5 mcg/kg of LSD, placebo, and 150 mcg/kg (Experiment I) or 210 mcg/kg of psilocybin (Experiment II) 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 that any tolerance conferred by the first drug would be lost.

During the first and second periods of chronic administration the patients in Experiment I received 0.25 mcg/kg of LSD or 25 mcg/kg of psilocybin on the first day. These doses were increased 0.25 mcg/kg (LSD) or 25 mcg/kg (psilocybin) daily until the patients were receiving 1.5 mcg/kg of LSD or 150 mcg/kg of psilocybin on the sixth day. These doses were maintained until the tests of tolerance and cross tolerance were performed. In Experiment II the patients received 0.15 mcg/kg of LSD or 21 mcg/kg of psilocybin on the first day of chronic administration, increasing by 0.15 mcg/kg of LSD or 21 mcg/kg of psilocybin daily until the patients were receiving 1.5 mcg/kg of LSD or 210 mcg/kg of psilocybin on the tenth day. These doses were maintained through the twelfth day. The order in which the patients received the drugs in the first and second periods of chronic administration was randomized in both Experiments I and II. During these periods of chronic administration, detailed observations were not made.

On the first day after completion of the period of chronic administration the patients were "challenged" with the dose of drug they had been receiving (test of direct tolerance). On the second day, they were

[1] We are indebted to Drs. R. Brecher and C. Henze of Sandoz Pharmaceuticals, Hanover, New Jersey, for supplies of psilocybin and diethylamide of lysergic acid tartrate (LSD-25).

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 placebos for 7—10 days (Experiment I) or no drug for 13 days (Experiment II). It was presumed that the patients would lose any tolerance they had developed, since in previous experiments (ISBELL *et al.*, 1956) tolerance was largely dissipated within three days after discontinuation of LSD.

Following this withdrawal period, second control measurements were obtained after the patients had received in randomized order placebo (Experiments I and II), 1.5 mcg/kg of LSD (Experiments I and II) and 150 mcg/kg (Experiment I) or 210 mcg/kg of psilocybin (Experiment II), with at least five days intervening between administration of LSD and psilocybin.

The patients then again received the drugs chronically, those patients who had taken LSD in the first period of chronic administration were given psilocybin according to the schedules described above and vice versa. They were then "challenged" with LSD and psilocybin in the manner described above.

Preliminary Assay. *Experiment II.* Since the test dose of psilocybin (150 mcg/kg) had a lesser degree of effect than the test dose of LSD (1.5 mcg/kg), a preliminary assay was carried out prior to Experiment II. The dose-response curves obtained by ISBELL (1959) were extended and 210 mcg/kg of psilocybin were estimated to be equal to 1.5 mcg/kg of LSD. Accordingly, the above doses of LSD and psilocybin were administered on two occasions at intervals of seven days in random order to 10 subjects. Statistical analyses (see below for method) revealed no significant differences in any of the comparisons made (Table 5, Assay Study).

Subjects. The subjects who volunteered for both experiments were former opiate addicts who were serving sentences for violation of the 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. Ten subjects served in Experiment I. and 9 in Experiment II.

General Conditions. Subjects were housed in a special ward devoted to clinical research. 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 not being made. The patients were observed by specially trained aides with long experience in detecting drug-induced changes in behavior.

Observations. During each day of the control periods and the periods of chronic drug administration during which the patients were "chal-

lenged" with placebo, LSD or psilocybin, the following 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 knee jerk. The methods used were those previously described (ISBELL *et al.*, 1956; ISBELL *et al.*, 1959; ISBELL, 1959). In addition, the patients (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 on the basis of the system of ISBELL *et al.* (1956).

Analysis of Data. The changes in rectal temperature, pulse and respiratory rates, pupillary size, blood pressure, and threshold for elicitation of the knee jerk after administration of placebo and drugs were calculated by subtracting the average of the two pre-drug observations from the values obtained at various hours. The areas under the time-action curves for each particular measurement composed of these figures were calculated by the method of WINTER and FLATAKER (1956), thus converting all the data on a particular subject, a particular drug, a particular measurement, and a particular day to one figure termed "degree-hours" (temperature), "rate-hours" (pulse rate), etc. The total number of positive responses on the questionnaire were counted over the entire period, eliminating answers which were also scored positively before the drug had been given. Means and standard errors of the means were calculated according to standard statistical techniques.

The difference in the various measurements after placebo, 1.5 mcg/kg of LSD, and 150 or 210 mcg/kg of psilocybin (each individual drug against itself) in the first and second controls were evaluated by a *t*-test for paired observations (EDWARDS, 1946). In Experiment I the only statistically significant difference found between the two sets of controls was a decrease in the pyretogenic effect of psilocybin (Table 2). In Experiment II, significant decreases in the number of positive responses on the questionnaire occurred in the second control (Table 3) after both LSD and psilocybin. Because of these differences in the two controls, the changes in response to the test doses of psilocybin and LSD after chronic administration of either drug were evaluated by comparing the effects of LSD and psilocybin after the first and second periods of chronic drug administration with the corresponding first or second control. In addition, calculations were made using the averages of the two controls. The latter procedure did not alter the significance of the differences greatly, so only the tables showing the differences calculated with the individual first and second controls are presented herein.

Table 2. *Differences in responses to placebo, LSD-25, and psilocybin on first and second controls in Experiment I*

Measure	Placebo	LSD-25	Psilocybin
Temperature	+ 0.08 ± 0.63	+ 0.42 ± 0.64	− 1.24 ± 0.53*
Pulse rate	− 11.53 ± 13.30	− 12.62 ± 18.40	− 19.60 ± 9.30
Blood pressure	− 1.10 ± 15.70	− 1.35 ± 12.70	− 25.40 ± 11.60
Pupillary size	− 0.29 ± 1.65	+ 0.52 ± 1.18	+ 0.10 ± 0.83
Knee jerk	− 12.50 ± 11.90	− 14.33 ± 21.75	+ 17.38 ± 18.70
Responses on questionnaire	+ 0.00 ± 1.31	− 0.50 ± 6.10	+ 4.00 ± 9.65
Clinical grade	+ 0.10 ± 0.10	− 0.30 ± 0.20	+ 0.20 ± 0.41

Figures represent the mean differences ± standard errors of the differences between responses to the same dose of the same drug (placebo, 1.5 mcg/kg of LSD-25 and 150 mcg/kg of psilocybin) on the first and second controls on 10 subjects. None of the differences *except* that for temperature change after psilocybin were significant.

+ Indicates that the average measurement was increased on the second control.
− Indicates that it was decreased.
* = $P < .05$.

Table 3. *Differences in responses to placebo, LSD-25, and psilocybin in first and second controls in Experiment II*

Measure	Placebo	LSD-25	Psilocybin
Temperature	0.07 ± 0.74	− 1.31 ± 0.58	− 1.36 ± 0.68
Pulse rate	− 9.72 ± 9.81	− 37.61 ± 17.09	+ 1.50 ± 19.50
Blood pressure	+ 21.44 ± 16.43	− 15.56 ± 18.13	6.33 ± 18.98
Pupillary change	− 0.10 ± 1.66	+ 2.00 ± 1.82	+ 0.43 ± 1.59
Knee jerk	+ 14.44 ± 6.65	+ 3.75 ± 29.24	− 20.16 ± 19.91
Responses to questionnaire	0	− 32.00 ± 12.35*	− 29.00 ± 9.20**
Clinical grade	0	− 0.55 ± 0.28	− 0.38 ± 0.30

Figures represent the mean differences ± the standard errors of the differences between responses to the same doses of the same drug (placebo, 1.5 mcg/kg of LSD, and 210 mcg/kg of psilocybin) in the first and second controls on 9 subjects.

+ Indicates an increased response on second control.
− Indicates a decreased response on second control.
* Indicates significance < 0.05.
** Indicates significance < 0.02.

The differences in the effects of the two individual drugs (LSD vs psilocybin) were also calculated for both control periods using the same statistical technique for paired observations (Tables 4 and 5).

As explained above, the differences in the response after chronic administration of both LSD and psilocybin were calculated by comparing the responses after first and second chronic administrations of LSD and/or psilocybin with their respective first and second controls. Four different comparisons were made: (1) response to LSD after chronic administration of LSD ("direct" tolerance to LSD), (2) response to psilocybin after chronic administration of LSD ("cross" tolerance to psilocybin), (3) response to psilocybin after chronic administration of

Table 4. *Equivalence of dosage of LSD and psilocybin in Experiment I*

Measure	First Control	Second Control
Temperature	−1.14 ± 0.73	+0.52 ± 0.66
Pulse rate	+24.05 ± 13.26	+31.00 ± 18.11
Blood pressure	+22.75 ± 20.39	+46.80 ± 15.43**
Pupillary size	+4.33 ± 1.24***	+4.74 ± 1.24***
Knee jerk	−6.88 ± 29.80	+25.82 ± 17.81
Responses on questionnaire	+41.40 ± 8.85***	+37.10 ± 16.45*
Clinical grade	+0.60 ± 0.16***	+0.10 ± 0.46

Figures represent mean differences ± standard errors of the differences between responses to LSD-25 (1.5 mcg/kg) and responsesto psilocybin (150 mcg/kg) in 10 subjects, on two separate occasions (1st and 2nd controls).

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$.

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

— Indicates psilocybin stronger in effect than LSD-25.

Table 5. *Equivalence of dosage of LSD and psilocybin in Experiment II*

Measure	Assay Study (N = 10)	First Control (N = 9)	Second Control (N = 9)
Temperature	−0.66 ± 0.40	−0.34 ± 0.53	−0.29 ± 0.66
Pulse rate	+25.35 ± 11.98	+65.66 ± 11.84**	+28.56 ± 13.47
Blood pressure	+35.50 ± 22.81	+44.44 ± 22.24	+22.44 ± 16.00
Pupillary change	−2.22 ± 1.20	+1.85 ± 1.60	−3.42 ± 1.37*
Knee jerk	+24.62 ± 29.86	−4.72 ± 23.53	+33.19 ± 21.04
Responses to questionnaire	+9.70 ± 10.74	+16.78 ± 10.98	+13.78 ± 8.98
Clinical grade	−0.05 ± 0.22	−0.11 ± 0.20	−0.28 ± 0.18

Figures represent the mean differences ± the standard errors of the differences between responses to single doses of LSD-25 (1.5 mcg/kg) and responses to psilocybin (210 mcg/kg) on three separate occasions.

\+ Indicates LSD-25 produced a greater response.

— Indicates psilocybin produced a greater response.

* Indicates significance < 0.05.

** Indicates significance < 0.01.

psilocybin ("direct" tolerance to psilocybin), and (4) response to LSD after chronic administration of psilocybin ("cross" 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.

Since psilocybin has a shorter duration of action than LSD, the differences (except clinical grade) were also evaluated, using values obtained at the peak of both LSD and psilocybin reactions rather than using the area (integrated time action curves) as described above. In addition, the differences were evaluated by a non-parametric rank order test for paired observations (WILCOXON, 1949). 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 reported in this paper.

Table 6. *Tolerance and cross tolerance, Experiment I*

Measure	After LSD chronically		After psilocybin chronically	
	LSD ("Direct" tolerance)	Psilocybin ("Cross" tolerance)	Psilocybin ("Direct" tolerance)	LSD ("Cross" tolerance)
Temperature	−2.21 ± 0.81*	−0.90 ± 0.73	−1.59 ± 0.46***	−0.22 ± 0.74
Pulse rate	−70.15 ± 11.38***	−18.05 ± 15.22	−21.20 ± 14.46	−10.65 ± 9.20
Blood pressure	−82.35 ± 18.95***	−40.50 ± 8.26***	−23.80 ± 11.97	−21.20 ± 11.85
Pupillary size	−11.04 ± 1.62***	−5.45 ± 1.68**	−3.50 ± 1.28*	−5.43 ± 1.58***
Knee jerk	−54.17 ± 24.86	−68.40 ± 17.67***	−62.12 ± 16.21***	−58.77 ± 20.81**
Responses on questionnaire	−62.20 ± 18.70***	−28.30 ± 9.20**	−10.50 ± 6.21	−57.90 ± 19.30**
Clinical grade	−1.70 ± 0.40***	−1.35 ± 0.32***	−0.85 ± 0.28**	−1.35 ± 0.31***

Figures represent the mean differences ± standard errors of the differences between respective control values and the values found upon testing with LSD-25 (1.5 mcg/kg) of psilocybin (150 mcg/kg) after chronic administration of either drug to 10 subjects.
* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$; — Indicates a decrease in response after chronic intoxication.

Table 7. *Tolerance and cross tolerance, Experiment II*

Measure	After LSD chronically (12 days)		After psilocybin chronically (12 days)	
	Test with LSD "direct" tolerance to LSD	Challenge with psilocybin "cross" tolerance to psilocybin	Test with psilocybin "direct" tolerance to psilocybin	Challenge with LSD "cross" tolerance to LSD
Temperature	−1.86 ± 0.65*	−1.65 ± 0.39***	−1.27 ± 0.81	−1.03 ± 0.56
Pulse rate	−49.16 ± 14.57***	−47.44 ± 21.39	−22.11 ± 19.70	−61.68 ± 15.69***
Blood pressure	−44.61 ± 18.37*	−5.66 ± 15.67	−29.38 ± 18.62	−57.83 ± 28.11
Pupillary change	−10.11 ± 2.29***	−9.30 ± 1.47***	−6.89 ± 1.45***	−9.41 ± 2.12***
Knee jerk	−40.97 ± 20.50	−12.69 ± 30.61	−2.41 ± 25.04	−0.97 ± 18.64
Responses to questionnaire	−55.44 ± 17.27**	−39.88 ± 14.07***	−47.11 ± 9.85***	−69.66 ± 13.38***
Clinical grade	− 1.44 ± 0.18***	− 1.38 ± 0.31***	− 2.05 ± 0.21***	−1.88 ± 0.20***

Figures represent the mean differences ± standard errors of the differences between respective control values and the values found upon testing with LSD-25 (1.5 mcg/kg) or psilocybin (210 mcg/kg) after chronic administration of either drug to 9 subjects.
+ Indicates increase in response after chronic intoxication; — Indicates a decrease in response after chronic intoxication.
* Indicates significance < 0.05; ** Indicates significance < 0.02; *** Indicates significance < 0.01.

Results

Controls. The differences in the responses to the same doses of the same drug in first and second controls after placebo, LSD and psilocybin are shown in Tables 2 (Experiment I) and 3 (Experiment II). In Experiment I, the only change that was statistically significant ($p < 0.05$) was a decline in elevation of body temperature after the second control dose of psilocybin. In Experiment II, a significant decline occurred in the number of positive responses on the questionnaire following the second control doses of both LSD and psilocybin. This might indicate that some degree of residual tolerance was still present after 13 days.

Equivalence of Dosage. The differences in the responses to the two different active drugs (LSD and psilocybin) are presented in Tables 4 (Experiment I) and 5 (Experiment II). In Experiment I the responses were generally greater, as indicated by the preponderance of positive signs in Table 4, and these differences were statistically significant on three measures in both the first and second controls. Therefore, in Experiment I, the test dose of psilocybin (150 mcg/kg) was weaker than the test dose of LSD (1.5 mcg/kg). In Experiment II, comparisons were made on three occasions — "assay study", first, and second controls. The majority of the signs in Table 5 are positive, indicating that on the average the effects of 1.5 mcg/kg of LSD were somewhat greater than those of 210 mcg/kg of psilocybin. The differences were, however, statistically significant only in the case of the pulse rate in the first control and the pupillary change in the second control. Since the failure to demonstrate statistically significant differences may have been due to the large variability in some of the measures, the effects of 210 mcg/kg of psilocybin in Experiment II may, therefore, still have been weaker than those of 1.5 mcg/kg of LSD.

Tolerance and Cross Tolerance. The differences in the responses to LSD and psilocybin after chronic administration of either drug an their respective first and second controls are shown in Tables 6 (Experiment I) and 7 (Experiment II). In both tables, the second column 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 third column shows the difference in response to psilocybin as compared with the appropriate control after chronic administration of LSD, and reflects "cross" tolerance to psilocybin. Similarly, the fourth column presents measures of "direct" tolerance to psilocybin, and the fifth column "cross" tolerance to LSD.

Inspection of the tables shows that results were very similar in the two experiments. All signs are negative in both tables, indicating an average decrease in response on all measures. In the case of "direct" tolerance to LSD (second columns), the differences reached statistical

significance on six of seven measures in both experiments. In the case of "cross" tolerance to psilocybin (third columns) the differences were statistically significant in five of seven measures (Experiment I), and four of seven measures (Experiment II). In the case of "direct" tolerance to psilocybin (fourth columns), statistically significant change occurred in four measures (Experiment I), and in three measures (Experiment II). In the case of "cross" tolerance to LSD (fifth columns): significant degrees of change occurred in four parameters in both experiments. The measures which reflected "direct" tolerance and "cross" tolerance most clearly were the pupillary diameter, responses on questionnaire and the clinical grades.

Discussion

The data show that a considerable degree of "direct" tolerance to LSD was developed in both Experiments I and II, and that patients "directly" tolerant to LSD also had a considerable degree of "cross" tolerance to psilocybin. Although statistically significant decreases did not occur on as many measures, the data indicate that definite "direct" tolerance to psilocybin was developed and that patients tolerant to psilocybin were "cross" tolerant to LSD. However, under the conditions of these experiments, the degrees of direct tolerance to psilocybin and cross tolerance to LSD were less than the degrees of direct tolerance to LSD and cross tolerance to psilocybin. In this connection, the fact that the direction of change was negative (reduction in the degree of response) may be important even though the differences did not reach statistically significant levels in all parameters. Increasing the dosage and length of time during which psilocybin was administered (Experiment II) did not result in the development of any greater degree of direct tolerance to psilocybin and cross tolerance to LSD than occurred with the lower dosage and shorter period of chronic administration in Experiment I.

The finding that "direct" tolerance to psilocybin and cross tolerance to LSD could not be shown on as many measures might be due to one, or a combination of several factors. In Experiment I, the effects of the dose of psilocybin were definitely less than the effects of the dose of LSD employed, and in Experiment II the effects of the dose of psilocybin prescribed were probably weaker than those of the LSD. Thus the stimulus for the development of tolerance during chronic administration of psilocybin may have been weaker than was the case with LSD. The length of action of psilocybin is shorter than that of LSD and, since only one dose of each drug was given daily, the stimulus for the development of tolerance was not present for as long a time during chronic administration of psilocybin, and the time during which tolerance might be declining, due to lack of sustained drug effect, was greater. Tolerance

to different effects of the two drugs might develop at different rates. Such differential rates of tolerance development occur; for example, with morphine (rapid and nearly complete tolerance to the analgesic effects, slower and only partial tolerance to the miotic and respiratory depressant effects). One might also postulate that LSD and psilocybin have somewhat different mechanisms of action or act on different receptors. It is also possible that failure to demonstrate tolerance and cross tolerance reflects nothing more than the high variability in certain of the measures used (temperature, pulse rate, blood pressure, knee jerk and, responses on the questionnaire). The data are not sufficient for a determination of the relative roles of any of these hypothetical factors.

CERLETTI (1958) did not observe direct tolerance to the pyretogenic effect of psilocybin on daily administration to rabbits, but did find that rabbits "directly" tolerant to LSD were also "cross" tolerant to the temperature-elevating action of psilocybin. Thus the results in the rabbit are similar to those observed in man, and do not help in deciding which of the possible explanations given in the preceding paragraph is the most likely.

BALESTRIERI (1960) did not observe direct tolerance to psilocybin or cross tolerance to psilocybin in patients receiving LSD chronically. The details in BALESTRIERI's paper are not sufficient for a proper evaluation, but the number of patients used was small and the doses of psilocybin employed were low.

The development of "cross" tolerance between LSD and psilocybin reinforces the idea derived from the similarity of clinical effects (ISBELL, 1959) that LSD and psilocybin induce psychic disturbances by some common mechanism, or by different mechanisms which act through a common final pathway. The data, of course, shed no light on the possible nature of such a presumed common action. Biochemical, chemical, neurophysiological or psychological mechanisms (or some combination of them) could be involved.

Summary

1. In two experiments, using a cross-over design, the development of "direct" tolerance to LSD and psilocybin was measured after 10 (Experiment I) or 9 (Experiment II) volunteers had taken LSD in doses increasing to 1.5 mcg/kg over the course of 6—7 days (Experiment I) or 13 days (Experiment II). On another occasion, the same patients received psilocybin in doses increasing to 150 mcg/kg over the course of 6—7 days (Experiment I) or 210 mcg/kg over the course of 13 days (Experiment II).

2. The development of "cross" tolerance to psilocybin in patients "directly" tolerant to LSD was measured by "challenging" the patients, after they had received LSD chronically, with 150 mcg/kg (Experiment I) or 210 mcg/kg (Experiment II) of psilocybin. "Cross" tolerance to LSD was evaluated by "challenging" the patients, after they had received psilocybin chronically, with 1.5 mcg/kg of LSD.

3. A high degree of "direct" tolerance to LSD developed in both experiments, as manifested by statistically significant reductions in six of the seven parameters of response. Patients "directly" tolerant to LSD were also "cross" tolerant to psilocybin on five (Experiment I) or four (Experiment II) parameters.

4. Definite "direct" tolerance also developed after chronic administration of psilocybin in both experiments, but statistically significant reductions occurred in fewer parameters of response (four in Experiment I and three in Experiment II) than was the case with LSD. Patients chronically treated with psilocybin were also "cross" tolerant to LSD on four (Experiment I) or three (Experiment II) measurements. The degree of "direct" tolerance to psilocybin was less than the degree of "direct" tolerance to LSD.

5. The development of "cross" tolerance between LSD and psilocybin reinforces the idea that these two drugs cause psychic disturbances by acting on some common mechanism, or on mechanisms acting through a common final pathway.

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