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## The Effect of N,N-Dimethyltryptamine in Human Subjects Tolerant to Lysergic Acid Diethylamide

By

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With 2 Figures in the Text

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### Introduction

In recent studies cross tolerance to lysergic acid diethylamide (LSD) in man has been demonstrated with psilocybin (ISBELL et al. 1961) and mescaline (WOLBACH et al. 1962), both of which provoke a response similar to LSD in nontolerant subjects. From these results ISBELL (1962) has suggested that "these three drugs constitute a physiologically related group of psychotomimetics" and "may indicate that the different compounds act through the same physiological or biochemical mechanisms or on some final common pathway." Consonant with this hypothesis have been demonstrations that drugs with central effects dissimilar to LSD do not exhibit cross tolerance with LSD, i.e., cholinergic blocking drugs (ISBELL et al. 1962) and d-amphetamine (ROSENBERG et al. 1963).

In an effort to examine further the similarities or dissimilarities between psychotomimetic agents by studies of cross tolerance, the present experiment was designed to test the effects of N,N-dimethyltryptamine (DMT) in human subjects following the chronic administration of and development of tolerance to LSD. Since the effects of DMT, except for a shorter onset and duration of action, resemble those of LSD (SZARA, 1957; ROSENBERG et al. 1963), it was anticipated that cross tolerance between DMT and LSD would be readily demonstrated.

The purpose of this paper is to report that subjects rendered highly tolerant to LSD exhibit only a small degree of cross tolerance to DMT.

### Methods

The experimental design was similar to the previous cross tolerance studies in man and is summarized in Table 1. In essence, control responses to DMT and LSD were compared to responses obtained following chronic LSD administration. However, in contrast to previous experiments, DMT was not administered chronically due to the lack of data on the chronic toxicity of DMT in animals.

Table 1. *Summary of experimental design*

Period	Day of chronic administration	Drugs and doses	Remarks
1st Control	5-day interval between drugs	LSD <sup>1</sup> , 1.5 mcg/kg DMT <sup>2</sup> , 1.0 mg/kg Placebo	To obtain control data in the non-tolerant subject; order of drugs randomized
Chronic LSD administration	1—13	LSD, increasing to 1.5 mcg/kg daily	To develop direct tolerance to LSD, 1.5 mcg/kg
1st Test of direct and cross tolerance	14 15	LSD, 1.5 mcg/kg DMT, 1.0 mg/kg	Test of direct and cross tolerance
Continued chronic LSD administration	16—36	LSD, increasing to 3.0 mcg/kg twice daily	To develop direct tolerance to LSD, 3.0 mcg/kg
2nd Test of direct and cross tolerance	37 38	LSD, 3.0 mcg/kg DMT, 0.5 mg/kg	Test of direct and cross tolerance
„Washout“ period	39—59	None	To lose tolerance
2nd Control	5-day interval between drugs	LSD, 1.5 mcg/kg  DMT, 0.5 mg/kg, on 4 separate occasions	To test loss of tolerance and replicate control data  To obtain additional control data

<sup>1</sup> Doses of LSD (lysergic acid diethylamide) refers to the weight of LSD tartrate.

<sup>2</sup> Doses of DMT, (N,N-dimethyltryptamine) refers to the weight of DMT as free base.

*Drug preparations.* LSD tartrate<sup>1</sup> and DMT bioxalate<sup>2</sup> were prepared as aqueous solutions. DMT was also supplied as the free base<sup>3</sup> and prepared in a fine suspension with equimolar amounts of oxalic acid. (Although the effects of DMT solution or suspension were identical, except for a small but statistically significant difference in blood pressure, the control and test responses for any particular dose were obtained with the same type of DMT.) Doses of LSD refer to the tartrate salt and doses of DMT refer to the free base. All drugs were administered intramuscularly.

*Subjects.* Six physically healthy former opiate addicts who were serving sentences for violations of United States narcotic laws vol-

<sup>1</sup> LSD monotartrate was supplied through the courtesy of Dr. R. BIRCHER, Sandoz, Inc., Hanover, N. J.

<sup>2</sup> Dimethyltryptamine bioxalate was supplied through the courtesy of Dr. R. BIRCHER, Sandoz, Inc., Hanover, N. J., and additional supplies were obtained from the California Corporation for Biochemical Research, Los Angeles, Calif.

<sup>3</sup> Dimethyltryptamine base was furnished through the courtesy of Dr. JOSEPH P. WEBB, Upjohn Company, Kalamazoo, Mich.

untested for this experiment. Each subject was male, ages varied from 23—37 years, and all exhibited no evidence of psychosis. None of these subjects had received narcotic drugs for at least six months, but some had received psychotomimetic drugs in other tests one week or more before beginning this experiment.

*General conditions.* The subjects lived in a special ward devoted to clinical research and were observed by specially trained aides with long experience in detecting drug-induced behavioral changes. Temperature, respiratory rate, pulse rate and blood pressure were measured three times daily on days when special measurements were not being determined. Body weight, caloric intake, and routine notes on behavior were also recorded daily.

*Chronic LSD administration.* LSD was administered intramuscularly daily at 6 a.m. on an increasing dosage schedule so that a maximum dose of 1.5 mcg/kg was attained by the 6th day and remained constant through the 14th day. After testing for direct tolerance to LSD, 1.5 mcg/kg (14th day), and cross tolerance with DMT, 1.0 mg/kg (15th day), the dose of LSD was gradually increased to 3 mcg/kg twice daily and maintained at that level until the 37th day when the subjects were tested for direct tolerance to LSD, 3.0 mcg/kg (37th day) and cross tolerance with DMT, 0.5 mg/kg (38th day). These latter dosages were selected because the control data and earlier reports with LSD (ISBELL et al. 1956) indicated that the effects produced by single doses of LSD (3.0 mcg/kg) in nontolerant subjects would be greater than those of DMT (0.5 mg/kg).

*Experimental observations.* During each test day of the control periods and on the two days following chronic LSD administration, when the subjects were tested for direct (LSD) and cross (DMT) tolerance, detailed observations were made at selected intervals throughout the day. On test days all drugs were administered intramuscularly at 8 a.m. Physiological measurements consisted of pulse rate, blood pressure, pupillary size (recorded photographically under constant lighting conditions) and threshold for elicitation of the kneejerk (determined by the minimal degree of arc through which a mounted reflex hammer must fall in order to elicit the patellar reflex). When LSD was administered these observations were recorded at hourly intervals twice before and seven times after administering the drug. Due to the rapid onset and short duration of action of DMT the post-drug observations were made at 15—30, 60, 120 and 180 minutes.

The subjective (psychological) drug effects were evaluated by a questionnaire (ISBELL et al. 1961; ROSENBERG et al. 1963). The 63-item questionnaire, composed of questions from the Addiction Research Center Inventory (HILL et al. 1963) was administered by trained aides

at hourly intervals from 7:30 a.m. to 2:30 p.m. (LSD) or 7:30 a.m. to 11:30 p.m. (DMT). In addition a clinical grade (ISBELL et al. 1961) from 0—4 was assigned by a physician according to the peak intensity of the reaction (0 representing no change and 4 representing hallucinations with loss of insight). In addition detailed notes on behavior were recorded at hourly intervals, but these were not quantified.

*Analysis of data.* For each test period changes for the various measurements were calculated by subtracting each subject's average pre-drug response from each of his subsequent post-drug measurements. From these values the area under the time-action curves (a value employed to represent the total response) was calculated by the method of WINTER and FLATAKER (1950) for each subject on each test day, and also the average time and magnitude of the maximal (peak) response was determined.

For the 6 subjects, means and standard errors of the means for each parameter were calculated by standard statistical techniques. Significance of the various comparisons were evaluated by the *t*-test for paired observations (EDWARDS, 1946); a difference was considered statistically significant if  $P < 0.05$ .

Since the effects of DMT were of short duration (Fig. 1) only the peak responses with this drug were utilized. On the other hand, both the peak and total responses with LSD were suitable for evaluation; however only the peak responses are presented here since these results agreed well with those obtained employing the total responses.

The effects of the three control doses of DMT suspension (0.5 mg/kg) did not differ significantly; hence calculations presented herein were performed using the average of these three controls. Likewise the response to LSD (1.5 mcg/kg) in the two controls were not statistically different, so their average was utilized for the calculations.

The statistical tests of tolerance involved two general categories of comparisons: 1. direct tolerance to LSD: control response to LSD vs response to LSD after the chronic administration of LSD; 2. cross tolerance to DMT in subjects tolerant to LSD: control response to DMT vs response to DMT following the chronic administration of LSD. In all instances tolerance was considered to be present if the test response was statistically less ( $P < 0.05$ ) than the respective control value.

## Results

*The effects of single doses of LSD, DMT and placebo in nontolerant subjects.* Except for onset and duration of action a similar pattern of subjective and autonomic effects were obtained with single doses of LSD and DMT in the nontolerant subjects. Either drug provoked a

subjective response consisting of euphoria, anxiety, visual hallucinations and perceptual distortions, accompanied by autonomic changes consisting of pupillary dilatation, systolic hypertension and a decrease in the threshold of the kneejerk. The effects of DMT were maximal by 15–30 minutes and had largely subsided after one hour, while effects of LSD were maximal between 2–3 hours and still detectable after 4–5 hours. The time action courses of the subjective response (questionnaire) obtained with single control doses of LSD (1.5 mcg/kg), DMT (0.5 and 1.0 mg/kg) and placebo are illustrated in Fig. 1. Regarding peak effects, it is apparent that LSD (1.5 mcg/kg) is approximately equivalent to DMT (0.5 mg/kg), while a much greater response is obtained with DMT (1.0 mg/kg). A similar pattern was observed when time action curves were constructed for the autonomic changes produced by these drugs.

The peak response obtained for each parameter with LSD (1.5 mcg/kg), DMT (1.0 and 0.5 mg/kg) and placebo are listed in Table 2. Although the most obvious effects with either drug were the subjective response and pupillary dilatation, a rise in systolic blood pressure and decrease in the threshold for the kneejerk were also statistically different from those responses obtained with placebo.

Table 3 lists the mean differences and statistical significance between the peak responses for the following control conditions:

1. DMT, 1 mg/kg vs DMT, 0.5 mg/kg,
2. DMT, 1 mg/kg vs LSD, 1.5 mcg/kg, and
3. DMT, 0.5 mg/kg vs LSD, 1.5 mcg/kg.

The first two columns illustrate that for most parameters DMT (1 mg/kg) provoked a greater response than DMT (0.5 mg/kg) or LSD (1.5 mcg/kg). However, as illustrated in the third column, the peak responses for all parameters with DMT (0.5 mg/kg) were quantitatively similar to those obtained with LSD (1.5 mcg/kg).

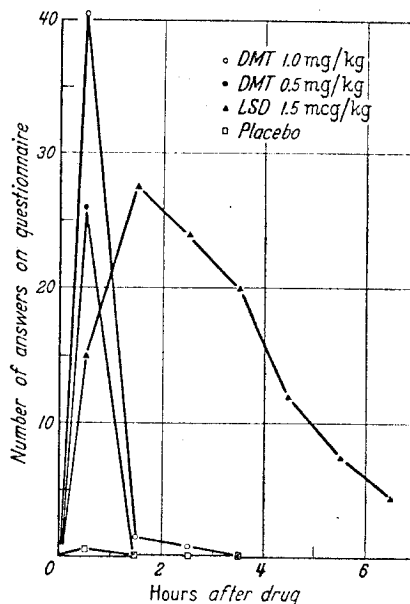


Fig. 1. Time course of the subjective response with single doses of DMT (0.5 and 1.0 mg/kg), LSD (1.5 mcg/kg), and placebo in nontolerant human subjects. Each point represents the mean number of positive responses on the questionnaire obtained from 6 subjects

Table 2. Comparison of a placebo with single doses of LSD and DMT in nontolerant human subjects

Measure <sup>1</sup>	Placebo	LSD, 1.5 mcg/kg	DMT, 0.5 mg/kg	DMT, 1.0 mg/kg
Pulse rate . . . . .	+ 7.0 ± 1.71	+ 14.8 ± 2.61	+ 12.9 ± 2.02	+ 18.8 ± 4.57
Systolic blood pressure . . . . .	+ 4.7 ± 3.18	+ 20.5 ± 3.99 <sup>4</sup>	+ 26.1 ± 2.70 <sup>4</sup>	+ 41.7 ± 3.22 <sup>4</sup>
Kneejerk threshold . . . . .	+ 0.4 ± 1.98	- 9.9 ± 1.97 <sup>4</sup>	- 9.7 ± 1.76 <sup>2</sup>	- 16.9 ± 4.49 <sup>4</sup>
Pupil size . . . . .	- 1.3 ± 1.26	+ 10.6 ± 1.72 <sup>4</sup>	+ 10.4 ± 1.52 <sup>4</sup>	+ 18.1 ± 2.24 <sup>3</sup>
Positive answers on questionnaire . . . . .	+ 0.5 ± 0.34	+ 27.5 ± 3.89 <sup>4</sup>	+ 26.2 ± 3.64 <sup>4</sup>	+ 40.5 ± 2.55 <sup>4</sup>
Clinical grade . . . . .	0	+ 2.8 ± 0.13 <sup>4</sup>	+ 2.6 ± 0.10 <sup>4</sup>	+ 3.4 ± 0.08 <sup>4</sup>

Each value represents the mean peak response (difference between pre-drug and maximum post-drug response) ± S.E.M. following single doses of placebo, LSD (1.5 mcg/kg), and DMT (0.5 and 1.0 mg/kg) to 6 nontolerant human subjects. The signs indicate an increase (+) or decrease (—) from pre-drug control values.

<sup>1</sup> All values are calculated in conventional units except kneejerk threshold — minimal degree arc through which a mounted reflex hammer must fall in order to elicit the patellar reflex; pupil size — area in mm<sup>2</sup>; and clinical grade — 0 (no change) to 4 (hallucinations with loss of insight).

<sup>2</sup> Indicates significance ( $P < 0.05$ ) compared with placebo.

<sup>3</sup> Indicates significance ( $P < 0.02$ ) compared with placebo.

<sup>4</sup> Indicates significance ( $P < 0.01$ ) compared with placebo.

Table 3. Differences in responses to LSD (1.5 mcg/kg), DMT (0.5 mg/kg), and DMT (1.0 mg/kg) in nontolerant human subjects

Measure <sup>1</sup>	DMT, 1.0 mg/kg vs DMT, 0.5 mg/kg	DMT, 1.0 mg/kg vs LSD, 1.5 mcg/kg	DMT, 0.5 mg/kg vs LSD, 1.5 mcg/kg
Pulse rate . . . . .	+ 5.9 ± 10.22	+ 3.8 ± 4.51	+ 1.9 ± 2.98
Systolic blood pressure . . . . .	+ 15.6 ± 1.87 <sup>3</sup>	+ 21.2 ± 2.61 <sup>3</sup>	- 5.7 ± 2.77
Kneejerk threshold . . . . .	+ 7.1 ± 4.56	+ 6.9 ± 3.33	- 0.3 ± 3.18
Pupil size . . . . .	+ 7.7 ± 1.34 <sup>3</sup>	+ 7.5 ± 1.69 <sup>3</sup>	- 0.3 ± 1.00
Positive answers on questionnaire . . . . .	+ 14.3 ± 5.04 <sup>2</sup>	+ 13.0 ± 3.03 <sup>3</sup>	- 1.3 ± 4.60
Clinical grade . . . . .	+ 0.9 ± 0.10 <sup>3</sup>	+ 0.7 ± 0.08 <sup>3</sup>	- 0.2 ± 0.11

Each value represents the mean (6 subjects) difference ± S.E.M. between peak responses for the drugs and doses as categorized. The signs indicate a greater (+) or lesser (—) response for the first drug as compared to the last drug in each category.

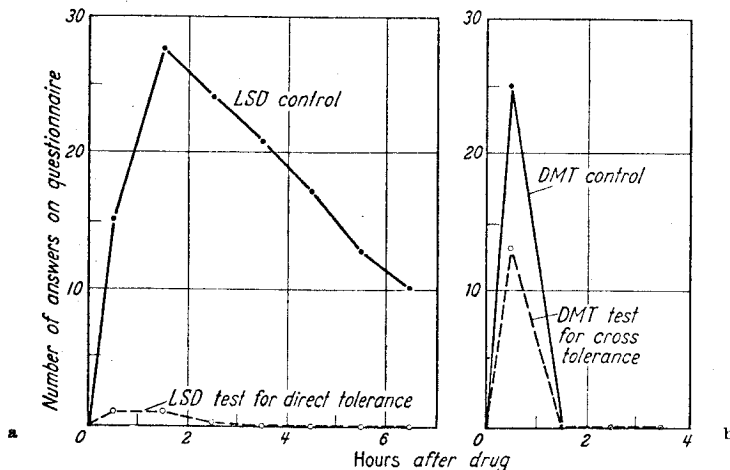
<sup>1</sup> All differences are calculated from peak values expressed in conventional units except kneejerk threshold — minimal degree arc through which a mounted reflex hammer must fall in order to elicit the patellar reflex; pupil size — area in mm<sup>2</sup>; and clinical grade — 0 (no change) to 4 (hallucinations with loss of insight).

<sup>2</sup> Indicates significance ( $P < 0.05$ ) between the two drugs in that category.

<sup>3</sup> Indicates significance ( $P < 0.01$ ) between the two drugs in that category.

*The effects of DMT in subjects rendered tolerant to LSD.* When the subjects were tested with LSD (1.5 mcg/kg) following chronic administration of LSD for 14 days a negligible response was observed, but

when these same "LSD-tolerant subjects" were challenged with DMT (1 mg/kg) on the 15th day the effects observed clinically were of about the same magnitude as those obtained with DMT (1 mg/kg) during the control period. Thus it appeared that subjects who were tolerant to LSD did not exhibit cross tolerance to DMT. However, since the control data revealed that DMT (1.0 mg/kg) exerted stronger effects



Figs. 2a and b. Subjective response to lysergic acid diethylamide (LSD) and N,N-dimethyltryptamine (DMT) before and after the chronic administration of LSD. Each point represents the mean number of positive answers on the questionnaire obtained from 6 subjects. a Illustrates the time action course of subjective effects (questionnaire) with LSD for the control (LSD, 1.5 mcg/kg) and test (LSD, 3.0 mcg/kg) following the chronic administration of LSD (3.0 mcg/kg). Only a negligible test response is obtained with LSD, thus signifying that a high degree of direct tolerance has developed. b Illustrates the control and test responses with DMT (0.5 mg/kg) following chronic administration of LSD (3.0 mcg/kg). Note that a moderate test response is still obtained with DMT, indicating that a high degree of cross tolerance has not developed

than LSD (1.5 mcg/kg), it seemed desirable to induce direct tolerance to a higher dose of LSD (3 mcg/kg) and to test for cross tolerance with a lesser dose of DMT (0.5 mg/kg). Such a design should favor the demonstration of cross tolerance, and conclusively settle the question. When this latter experiment was carried out a high degree of direct tolerance was demonstrated with LSD (3.0 mcg/kg), but upon testing for cross tolerance with DMT (0.5 mg/kg) a moderate response was still observed, thus signifying that a high degree of cross tolerance had not developed. Regarding subjective effects, Fig. 2 illustrates with time action curves the high degree of direct tolerance to LSD (Fig. 2a) but only moderate attenuation upon testing for cross tolerance with DMT (Fig. 2b).

Table 4 lists the quantitative and statistical evaluation of the tests for direct and cross tolerance.

Table 4. *Direct tolerance to LSD and cross tolerance with DMT*

Measure <sup>1</sup>	After LSD chronically <sup>2</sup> (13 days)		After LSD chronically <sup>2</sup> (36 days)	
	Test with LSD (1.5 mcg/kg) for "direct" tolerance	Test with DMT (1.0 mg/kg) for "cross" tolerance	Test <sup>4</sup> with LSD (3.0 mcg/kg) for "direct" tolerance	Test with DMT (0.5 mg/kg) for "cross" tolerance
Pulse rate . . .	— 8.5 ± 7.44	— 5.0 ± 4.25	— 11.9 ± 5.92	— 5.4 ± 4.03
Systolic blood pressure . . .	— 11.1 ± 5.17	— 10.3 ± 6.23	— 11.4 ± 5.94	— 8.7 ± 3.67
Kneejerk threshold . . .	— 4.7 ± 2.87	— 3.8 ± 4.68	— 11.8 ± 4.76 <sup>6</sup>	— 0.1 ± 3.93
Pupil size . . .	— 7.1 ± 4.06 <sup>6</sup>	— 2.9 ± 2.59	— 8.9 ± 5.69 <sup>6</sup>	— 4.1 ± 1.88
Positive answers on questionnaire . . . .	— 25.2 ± 3.37 <sup>6</sup>	— 8.2 ± 4.16	— 26.5 ± 3.56 <sup>6</sup>	— 13.5 ± 4.30 <sup>5</sup>
Clinical grade . . .	— 2.3 ± 0.42 <sup>6</sup>	— 0.8 ± 0.10 <sup>6</sup>	— 2.7 ± 0.12 <sup>6</sup>	— 1.5 ± 0.13 <sup>6</sup>

Each value represents the mean (6 subjects) difference ± S.E.M. between the control and test peak response for each of the conditions as categorized.

+ Indicates an increased response after chronic LSD.

— Indicates a decreased response after chronic LSD.

<sup>1</sup> All differences are calculated from peak values expressed in conventional units, except kneejerk threshold — minimal degree are through which a mounted reflex hammer must fall in order to elicit the patellar reflex; pupil size — area in mm<sup>2</sup>; and clinical grade — 0 (no change) to 4 (hallucinations with loss of insight).

<sup>2</sup> Maximum final dose was 1.5 mcg/kg once daily.

<sup>3</sup> Maximum final dose was 3.0 mcg/kg twice daily.

<sup>4</sup> Control LSD dose was 1.5 mcg/kg since 3.0 mcg/kg in the nontolerant subject causes reactions of excessive severity (ISBELL et al. 1956).

<sup>5</sup> Indicates significance ( $P = 0.05$ ) between control and test response.

<sup>6</sup> Indicates significance ( $P = 0.01$ ) between control and test response.

The first column lists the mean differences between control LSD (1.5 mcg/kg) peak responses and those obtained upon testing for direct tolerance to LSD (1.5 mcg/kg) following the chronic daily administration of LSD (1.5 mcg/kg). The differences are significantly less with regard to pupillary dilatation, questionnaire response and clinical grade, thus signifying that direct tolerance has developed for these parameters.

The second column lists the mean differences between control DMT (1.0 mg/kg) peak responses and those obtained upon testing for cross tolerance with DMT (1 mg/kg) in subjects exhibiting direct tolerance to LSD (1.5 mcg/kg). The clinical grade was the only measure in which a statistically significant decrease from control values was obtained, and this attenuation was relatively small when compared to the marked diminution in response when the subjects were tested for direct tolerance to LSD.

In a similar fashion the third column illustrates a high degree of direct tolerance to LSD (3 mcg/kg) with respect to threshold for the kneejerk, pupillary dilatation, questionnaire, and clinical grade. The



control values employed in these calculations were those obtained with LSD (1.5 mcg/kg) since LSD (3 mcg/kg) would most likely have produced too severe a reaction in nontolerant human subjects (ISBELL et al. 1956).

The fourth column lists the mean differences between control DMT (0.5 mg/kg) peak responses and those obtained upon testing for cross tolerance with DMT (0.5 mg/kg) in subjects exhibiting a marked degree of direct tolerance to LSD (3.0 mcg/kg). Although there was a statistically significant decrease in the questionnaire response and clinical grade (thus by definition cross tolerance was demonstrated for these two parameters), the decrease was only moderate when compared with that obtained upon testing for direct tolerance to LSD (3.0 mcg/kg). For example, regarding the mean peak response to the questionnaire, a 95 percent decrease was obtained upon testing for direct tolerance to LSD while the response to DMT diminished to only 53 percent of the control value.

### Discussion

Except for a shorter onset and duration of action, the peak effects with single doses of 0.5 mg/kg of DMT in nontolerant human subjects were equivalent to those produced by LSD (1.5 mcg/kg) with respect to all of the parameters employed in this study. This similar pattern of effects with either drug has been mentioned and discussed previously (SZARA, 1957; ROSENBERG et al. 1963). However, the present experiment seems to be the first quantitative comparison between LSD and DMT employing several parameters.

The development of a high degree of direct tolerance to LSD with respect to pupillary dilatation and mental response has been consistently demonstrated in several experiments (ISBELL et al. 1961; WOLBACH et al. 1962; ISBELL et al. 1962; ROSENBERG et al. 1963) and does not warrant further discussion in this paper.

The unanticipated result in the present experiment is that only a mild degree of cross tolerance with regard to mental response, and none to pupillary effects, could be demonstrated with DMT in subjects highly tolerant to the pupillary, kneejerk, and mental effects of LSD. It should be recalled from previous studies with LSD, mescaline, and psilocybin that direct or cross tolerance to the mental effects of these drugs was consistently accompanied by tolerance to the pupillary effects (ISBELL et al. 1961; WOLBACH et al. 1962). It also must be emphasized that in nontolerant subjects the effects produced with our final test dose of LSD (3.0 mcg/kg) would be much greater than those produced with the test dose of DMT (0.5 mg/kg). Therefore, the design of the present experiment would have favored the demonstration of a high degree of cross tolerance.

In previous studies, drugs (i.e., psilocybin and mescaline) which produced effects similar to LSD in single doses to nontolerant subjects also exhibited cross tolerance with LSD when administered chronically, while drugs dissimilar to LSD in single doses (i.e., d-amphetamine, scopolamine, and JB-318, another cholinergic blocker) did not show cross tolerance with LSD. From these results ISBELL et al. (1962) suggested that cross tolerance studies appear useful in confirming the biological similarities or dissimilarities among psychotomimetic agents, and that drugs which exhibit cross tolerance may act through the same "physiological or biochemical mechanisms or on some final common pathway." Although the basic process which is responsible for tolerance to psychotomimetic agents is unknown, it should be recognized that this adaptation could occur at either the effector sites involved in the drug's pharmacological action *per se* or at sites concerned with the distribution and biological transformation of the drug (e.g., hepatic enzymes concerned with drug metabolism). Obviously the implications derived from studies of cross tolerance would be different, depending upon which category of sites are involved.

Due to the similar spectrum of effects produced by single doses of LSD and DMT in nontolerant subjects, one should be cautious in concluding on the basis of poor cross tolerance alone that these two drugs act totally dissimilar mechanisms. However, the present demonstration of poor cross tolerance to DMT in subjects rendered tolerant to LSD does suggest that the site or mechanisms which is altered during LSD tolerance is not one which is primarily concerned with the action of DMT.

#### Summary

1. The spectrum of effects produced with single doses of N,N-dimethyltryptamine (DMT) in 6 nontolerant human subjects resembled those produced with lysergic acid diethylamide (LSD). Either drug produced an elevation in systolic blood pressure, a decrease in the threshold for the kneejerk, pupillary dilatation, and a mental response characterized by anxiety, perceptual distortions and hallucinations. The onset and duration of action was shorter with DMT (0.5 mg/kg) as compared to LSD (1.5 mcg/kg), but the maximum intensity of effects with respect to each parameter was equivalent for both drugs.

2. Following the chronic administration of LSD only a mild degree of cross tolerance to the mental response could be demonstrated with DMT (0.5 mg/kg) in subjects highly tolerant to the pupillary, kneejerk, and mental effects of LSD (3.0 mcg/kg).

3. It is inferred that the site or mechanism which is altered during LSD tolerance is not one which is primarily concerned with the action of DMT.

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