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Observations on Direct and Cross Tolerance with LSD and D-Amphetamine in Man*

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With 3 Figures in the Text

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Introduction

Previous studies in man demonstrated that, on chronic administration, cross tolerance develops between lysergic acid diethylamide (LSD) and psilocybin (Isbell et al. 1961) and between LSD and mescaline (Wolbach et al. 1962). Thus, mescaline, although different in chemical structure, appears to be biologically related to LSD and psilocybin.

A study of cross tolerance in man between LSD and D-amphetamine seemed to be indicated as part of a continuing investigation to separate drugs which induce mental changes into groups on the basis of biological, rather than chemical, similarities.

In man, many effects of either LSD or D-amphetamine are qualitatively similar. Adequate doses of either drug can produce euphoria, anxiety, insomnia, elevation of body temperature, increased blood pressure and pupillary dilatation (Isbell et al. 1956; Leake 1958). Although D-amphetamine in single therapeutic doses does not usually cause illusions, hallucinations, or bizarre thinking, it sometimes creates a psychotic state when taken chronically.

The purpose of this paper is to report that the effects of single doses of LSD and D-amphetamine in man are dissimilar, and that although a high degree of direct tolerance develops to both LSD and D-amphetamine, subjects tolerant to D-amphetamine are not cross tolerant to LSD and *vice versa*.

The biological (cross tolerance) and structural relationships among LSD, mescaline, psilocybin, and D-amphetamine are illustrated in Fig. 1.

* A preliminary report was presented at the annual meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N.J., April 1962.

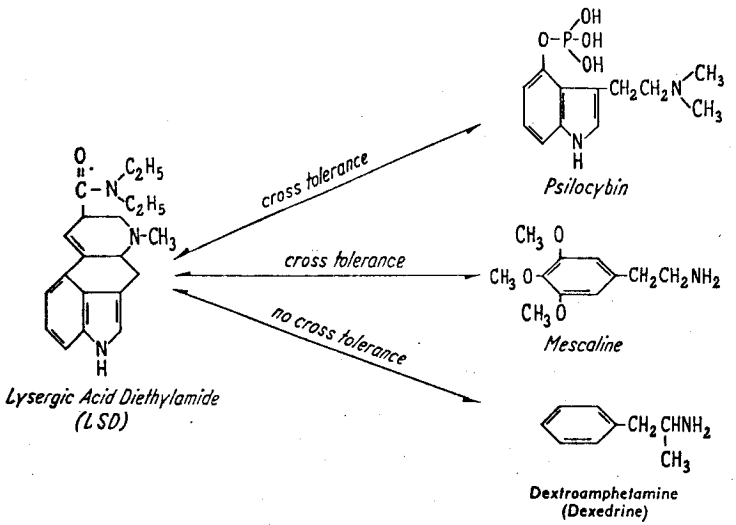

Fig. 1. Biological (cross tolerance) and structural relationships among LSD, psilocybin, mescaline, and D-amphetamine

Methods

Experimental design. A "single blind" (subjects did not know the drugs they were receiving but observers did know) cross-over design was employed in this experiment and is summarized in Table 1. The design was similar to that used in testing cross tolerance in man between LSD and psilocybin (ISBELL et al. 1961) and between LSD and mescaline (WOLBACH et al. 1962).

The experiment consisted of seven periods: (1) first control, in which measurements were obtained after test doses of placebo, LSD, and D-amphetamine at intervals of at least five days; (2) first chronic administration, in which patients received either LSD or D-amphetamine daily over a period of 13 days; (3) first test of direct and cross tolerance, in which subjects were "tested" with the drug they had been receiving chronically (test of "direct" tolerance) and on the subsequent day "challenged" with the drug they had not been receiving (test of "cross" tolerance); (4) a "washout" period, in which the subjects received no drugs for 10—14 days in order to lose tolerance; (5) second control period, in which the test doses of placebo, LSD and D-amphetamine 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 they had not taken in the first period of chronic administration ("cross over"); and (7) finally, the second test

Table 1. *Summary of experimental design*

Period	Number of days	Drugs and doses		Remarks
		Subjects X[1]	Subjects Y[2]	
1. 1st control	19—28	LSD[3], 0.5 LSD[3], 1.5 Dex.[3], 0.6 Placebo	LSD[3], 0.5 LSD[3], 1.5 Dex.[3], 0.6 Placebo	To obtain control data in the nontolerant subject. Order of tests randomized. Minimum of 5 days between each drug
2. 1st chronic administration	13	LSD, increasing to 1.5	Dex., increasing to 0.6	To develop tolerance
3. 1st test of direct and cross tolerance	2	LSD, 1.5 Dex., 0.6	Dex., 0.6 LSD, 0.5	Test of direct and cross tolerance
4. „Washout" period	10—14	None	None	To lose tolerance
5. 2nd control	19—28	LSD, 0.5 LSD, 1.5 Dex., 0.6 Placebo	LSD, 0.5 LSD, 1.5 Dex., 0.6 Placebo	To replicate control data and test loss of tolerance
6. 2nd chronic	13	Dex., increasing to 0.6	LSD, increasing to 1.5	"Cross-over" to develop tolerance
7. 2nd test of direct and cross tolerance	2	Dex., 0.6 LSD, 0.5	LSD, 1.5 Dex., 0.6	Test of direct and cross tolerance

[1] Subjects "X" received LSD chronically, first.
[2] Subjects "Y" received D-amphetamine chronically, first.
[3] LSD = lysergic acid diethylamide; Dex. = D-amphetamine. Except for controls, which were randomized, 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 D-amphetamine.

and challenge for "direct" and "cross" tolerance, with test doses of LSD or D-amphetamine, as in Period 3.

Drugs and doses. LSD tartrate, D-amphetamine sulfate[1], and placebo (physiological saline) were administered intramuscularly as aqueous solutions at 8 a.m. with the subjects fasting. All doses refer to the salts.

During the first and second control periods the subjects received in randomized order: 0.5 mcg/kg and 1.5 mcg/kg of LSD, placebo, and 0.6 mg/kg of D-amphetamine. Detailed observations were made on these test days. These control experiments were conducted at intervals of at least five days in order to minimize the development of tolerance during these periods.

During the first period of chronic drug administration each subject received in randomized order either 0.3 mcg/kg of LSD or 0.075 mg/kg

[1] We are indebted to Dr. R. BIRCHER, Sandoz Pharmaceuticals, Hanover, N.J., and to Smith Kline and French Laboratories, Philadelphia, Pa., for supplies of lysergic acid diethylamide tartrate and dextroamphetamine sulfate.

of D-amphetamine on the first day. The doses of the same drugs were increased daily, until by the fifth day each subject was receiving either 1.5 mcg/kg of LSD or 0.6 mg/kg of D-amphetamine. These maximal doses were then maintained through the 13th day. During the periods of chronic drug administration detailed observations were not made.

On the first day after completing the period of chronic administration each subject was "tested" with the dose of the drug that he had been receiving chronically (test of "direct" tolerance). On the following day each subject was "challenged" with the test dose of the alternate drug (test of "cross" tolerance). On both of these days detailed measurements were made.

The subjects then received no drug for 10—14 days in order to lose any tolerance they had developed.

Following the above withdrawal period, the "second control" measurements were obtained in a manner similar to that employed in the first control period. Afterwards each subject again received a drug chronically; those subjects who had taken LSD in the first period of chronic administration being given D-amphetamine according to the schedules described above and *vice versa*. They were then "tested" and "challenged" with LSD or D-amphetamine as described above, thus completing the cross-over design.

The blood pressure elevation from D-amphetamine limited the maximal dose of this drug to 0.6 mg/kg and, with respect to the pattern of all responses from either drug, equivalent dosages of LSD and D-amphetamine could not be established. For these reasons, following the chronic administration of D-amphetamine, the subjects were challenged for cross tolerance with a relatively low dose of LSD (0.5 mcg/kg), a procedure which should enhance the demonstration of a low degree of cross tolerance.

Subjects. The 10 subjects who volunteered and served in this experiment were former opiate addicts who were serving sentences for violation of the United States narcotic laws. Each subject was male, their ages varied from 25 to 36 years, 7 were Negro and 3 were Puerto Rican. None exhibited signs of physical illness or psychosis. All subjects had received no narcotic drugs for at least six months, but some had received psychotomimetic drugs in other tests no less than one week prior to beginning this experiment.

General conditions. The subjects were housed 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 recorded daily.

Experimental observations. During each test day of the control periods and on the two days after chronic drug administration when the subjects were tested for direct and cross tolerance, the following observations were made according to the methods previously described (ISBELL et al. 1961), at hourly intervals after 10 minutes rest in bed, twice before and eight times after the drug was administered: rectal temperature, pulse rate and blood pressure were determined in the usual manner; pupillary diameter under constant lighting conditions was estimated by comparison with circles of varying size on a card; and threshold for elicitation of the kneejerk was determined by the minimal degree of arc through which a mounted reflex hammer must fall in order to elicit the patellar reflex.

The subjective drug effects were quantitatively evaluated by two methods, a questionnaire and a clinical grade. A 49-item questionnaire was administered by an aide at hourly intervals from 7:30 a.m. to 3:30 p.m.; each question was scored as either present or absent for that particular hour. Seventeen of the questions which were selected from the Addiction Research Center Inventory were relatively specific[1] for LSD, 15 were relatively specific for amphetamine, and 17 were common to both drugs (HILL and HAERTZEN, to be published). A "clinical grade" 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) as previously described by ISBELL et al. (1956). In addition, at hourly intervals general notes on behavior were recorded by the aides, but these were not quantified.

Analysis of data. Data recording and statistical analyses were similar to the methods employed in previous tests of direct and cross tolerance (ISBELL et al. 1961; WOLBACH et al. 1962).

The changes in each physiological measurement were calculated by subtracting each individual's pre-drug response (average of the two pre-drug observations) from his post-drug response at each hourly interval. From these data areas under the time action curves were calculated by the method of WINTER and FLATAKER (1950). With regard to the questionnaire, the total number of positive responses were counted over the entire period, eliminating those questions scored positively before the drug had been given. Means and standard errors of the means

[1] The specificity for each question is relative, not absolute, as determined in single dose studies (HAERTZEN et al. 1961) where a greater percentage of subjects responded affirmatively after one drug as compared to other drugs. Typical specific questions concerning LSD are: "Do you have a weird feeling?" "Do you feel an increasing awareness of bodily sensations?" Typical specific questions re amphetamine are: "Do you feel like catching up on all your work?" "Does your memory seem sharper to you than usual?" Questions relatively specific for both LSD and amphetamine are: "Do you seem to be a changed person?" "Do you feel more excited than dreamy?"

for both the total and peak (maximum intensity during the experimental period) responses were calculated according to standard statistical techniques.

All statistical comparisons were made by both the *t*-test for paired observations (EDWARDS 1946) and the non-parametric rank order test for paired observations (WILCOXON 1949). Since the statistical significances by this latter method usually agreed well with the former, only the results with the *t*-test are presented except where a discrepancy exists.

Upon comparing the responses to identical drugs and doses for the two control periods, the increase in pulse rate with LSD (1.5 mcg/kg) and pupillary diameter with LSD (0.5 mcg/kg) were statistically less in the second control period. Therefore, when testing for tolerance, the control data from the first or second control period were employed for comparison according to the respective period of chronic drug administration. For example, if a subject received D-amphetamine throughout the second period of chronic drug administration, his response to D-amphetamine during the second control period would be used in comparing for direct tolerance to D-amphetamine.

The determination of direct and cross tolerance with D-amphetamine and LSD involved four different comparisons for both peak responses areas under the time action curves: (1) control response to LSD vs response to LSD after chronic administration of LSD ("direct" tolerance to LSD), (2) control response to D-amphetamine vs response to D-amphetamine after chronic administration of LSD ("cross" tolerance to D-amphetamine), (3) control response to D-amphetamine vs response to D-amphetamine following the chronic administration of D-amphetamine ("direct" tolerance to D-amphetamine), and (4) control response to LSD vs response to LSD following the chronic administration of D-amphetamine ("cross" tolerance to LSD). Tolerance was considered to be present if either the peak or total (area) test responses were statistically less than their respective control values.

Results

The effects of single doses in nontolerant subjects. The total responses obtained with placebo, LSD (0.5 mcg/kg), LSD (1.5 mcg/kg), and D-amphetamine (0.6 mg/kg) in the first control period are listed in Table 2.

LSD (1.5 mcg/kg) produced statistically significant increases in body temperature, pulse rate, blood pressure, pupillary size, responses to the questionnaire, and clinical grade, and a significant decrease in threshold for the kneejerk as compared to placebo. The lower dose of LSD

Table 2. *The effects of placebo, LSD, and* D-*amphetamine in single doses to 10 nontolerant subjects during the first control period*

Measure	Treatment			
	Placebo	LSD		D-amphetamine
		0.5 mcg/kg	1.5 mcg/kg	0.6 mg/kg
Temperature[1]	+ 3.31± 0.58	+ 4.07± 0.47	+ 4.63± 0.51[5]	+ 4.32± 0.64
Pulse rate[1]	+31.05±14.94	+55.65±15.57	+89.10±10.51[4]	+ 16.65±13.96
Blood pressure[1]	+ 9.45±11.95	+75.60±13.65[4]	+92.30±10.31[4]	+264.10±19.90[4]
Pupil[1]	+ 1.79± 1.30	+ 9.66± 1.18[4]	+14.75± 1.67[4]	+ 3.58± 0.72
Kneejerk[1]	− 4.70± 2.02	−18.95± 7.69	−45.68± 8.03[4]	− 15.62± 7.60
Responses to questionnaire[2]	+ 2.10± 0.62	+21.60± 4.72[4]	+66.90± 7.32[4]	+ 34.20± 7.56
Clinical grade[3]	0.0	+ 0.95± 0.19[4]	+ 2.35± 0.24[4]	+ 0.85± 0.18[4]

[1] Each figure represents the mean ± standard error of the mean for the area under the time-action curve during the 8-hour experimental period. The signs indicate an increase (+) or decrease (—) from pre-drug control values.

[2] Represents the mean for the total number of questions scored positively during the experimental period.

[3] Represents the mean for the maximum mental reaction during the experimental period.

[4] Indicates significance ($P<0.01$) compared with placebo.

[5] Indicates significance ($P<0.05$) compared with placebo.

(0.5 mcg/kg) produced fewer significant effects (increase in blood pressure, pupillary size, responses to the questionnaire, and clinical grade). With D-amphetamine, questions and clinical grade increased significantly but the only significant autonomic alteration was a rise in systolic blood pressure of much greater magnitude than that evoked with LSD.

A statistical analysis of the above data employing only the peak effects yielded similar results, and are not presented here.

The subjective response (questionnaire and clinical grade) to D-amphetamine was of the same order of magnitude as LSD, 0.5 mcg/kg; but qualitatively, a different pattern of response was observed. D-Amphetamine initially produced anxiety and euphoria lasting about four to six hours without depersonalization, confusion, or sensory distortion; this was followed by dyphoria with complaints of anorexia and insomnia lasting throughout the night. In contrast, LSD produced euphoria and anxiety with perceptual distortions and visual hallucinations which was not followed by dysphoria. The subjects usually regarded the LSD effects as a pleasant experience. This different pattern of subjective response is also illustrated quantitatively in Table 3 where

Table 3. *The response to question of different specificities with placebo, LSD, and* D-*amphetamine in single doses to 10 nontolerant subjects*

Questions relatively specific for	Treatment			
	Placebo	LSD		Amphetamine
		0.5 mcg/kg	1.5 mcg/kg	0.6 mg/kg
LSD	0.5 ± 0.22	6.4 ± 1.42	25.9 ± 1.80	8.3 ± 2.46
Amphetamine	0.4 ± 0.27	8.0 ± 2.51	16.3 ± 3.42	14.2 ± 3.38
LSD and Amphetamine	1.2 ± 0.49	7.8 ± 1.73	26.5 ± 3.68	12.6 ± 2.70

Each figure represents the mean total number of questions ± standard error of the mean answered positively in each designated category during the 8-hour experimental period.

the questions are categorized according to their reported specificity (HILL and HAERTZEN, to be published). The figures in the first column reveal a very small response to placebo under the conditions of our experiment. The second column illustrates responses of nearly equal magnitude in all three categories of questions with LSD (0.5 mcg/kg). The third column illustrates a greater response with LSD (1.5 mcg/kg) to questions relatively specific for LSD as compared to questions of the "amphetamine category". Conversely, the last column illustrates a greater response with amphetamine to questions reported to be relatively specific for amphetamine as compared to questions relatively specific for LSD.

Reproducibility of effects with single doses in nontolerant subjects. The differences in response to the same doses of the same drugs in the first and second control periods are listed in Table 4. In the second control period the increase in pulse rate with LSD (1.5 mcg/kg) and the pupillary dilatation with LSD (0.5 mcg/kg) were significantly less than that obtained during the first control period. Such differences might suggest that some residual tolerance was still present following the 10 to 14 day "washout" period. However, this explanation seems unlikely because the subjects who accounted for the decrease in these effects were not necessarily those who had received LSD chronically during the first period of chronic administration.

Direct and cross tolerance. Table 5 lists the mean differences in total responses to LSD or D-amphetamine between control and test, or challenge following the chronic administration of either drug.

The first column lists the mean differences in response to LSD (1.5 mcg/kg) after the chronic administration of LSD as compared with the respective control values for LSD (1.5 mcg/kg). In other words, this column summarizes the test for direct tolerance to LSD. The differences

Table 4. *Reproducibility of the effects with placebo, LSD, and* D-*amphetamine in 10 nontolerant subjects*

Measure	Treatment			
	Placebo	LSD		D-amphetamine
		0.5 mcg/kg	1.5 mcg/kg	0.6 mg/kg
Temperature[1]	− 0.57± 0.63	− 0.32± 0.39	− 0.77± 0.42	+ 0.70± 0.61
Pulse rate[1]	−14.10±18.19	−33.35±17.17	−67.60±11.88[4]	−23.65±17.08
Blood pressure[1]	+33.70±15.93	−13.60±15.88	−12.55±15.98	+ 4.10±15.86
Pupil[1]	− 1.31± 1.76	− 3.39± 1.06[5]	− 1.35± 0.80	− 0.02± 1.45
Kneejerk[1]	− 8.65± 5.73	−10.64± 7.67	−15.82±13.94	+ 3.18±12.17
Responses to questionnaire[2]	− 1.50± 1.01	− 7.40± 4.00	− 1.40± 6.83	−10.40± 6.51
Clinical grade[3]	0.00	− 0.20± 0.20	+ 0.20± 0.21	− 0.30± 0.17

[1] Each figure represents the mean difference ± standard error of the difference for the area under the time-action curve between the first and second control periods with respect to each drug and dose. The signs indicate an increased (+) or decreased (—) response in the second control period.

[2] Represents the mean difference for the total number of questions scored positively during the experimental period.

[3] Represents the mean difference for the maximum mental reaction.

[4] Indicates significance ($P<0.01$) between the first and second controls.

[5] Indicates significance ($P<0.02$) between the first and second controls.

are significantly less with regard to pupillary size, response to the questionnaire and clinical grade, thus signifying that direct tolerance to LSD has developed for these parameters. In addition, decrease in response for pulse rate and threshold for the kneejerk approached a level of statistical significance ($P = 0.05$) by the non-parametric rank order test for paired observations.

The second column lists the mean differences in responses to D-amphetamine (0.6 mg/kg) after the chronic administration of LSD as compared with the respective control values for D-amphetamine (0.6 mg/kg). In other words, this column summarizes the test for cross tolerance to D-amphetamine following the chronic administration of LSD. Since significant differences are not demonstrated, cross tolerance did not develop under these conditions between D-amphetamine and LSD.

The third column lists the mean differences in responses to D-amphetamine (0.6 mg/kg) after the chronic administration of D-amphetamine as compared with the respective control values for D-amphetamine (0.6 mg/kg). In other words, this column summarizes the test for direct tolerance to D-amphetamine following the chronic administration of D-amphetamine. The differences are significantly less with regard to rectal temperature, systolic blood pressure, responses to the question-

Table 5. *Tolerance and cross tolerance*

Measure	After LSD chronically (13 days)		After D-amphetamine chronically (13 days)	
	Test with LSD, 1.5 mcg/kg, "direct" tolerance to LSD	Challenge with D-amphetamine, 0.6 mg/kg, "cross" tolerance to D-amphetamine	Test with D-amphetamine, 0.6 mg/kg, "direct" tolerance to D-amphetamine	Challenge with LSD, 0..5 mcg/kg, "cross" tolerance to LSD
Temperature[1]	− 0.92± 0.56	+ 0.67± 0.67	− 1.79± 0.45[4]	− 0.14± 0.54
Pulse rate[1]	−41.45±18.50	+ 7.50±11.71	+ 25.05±13.52	− 6.40±18.22
Blood pressure[1]	− 5.70±12.99	+23.10±21.91	−147.50±17.70[4]	+ 4.55±21.25
Pupillary changes[1]	− 9.17± 1.94[4]	− 0.70± 1.42	+ 0.06± 1.15	− 0.94± 1.03
Kneejerk[1]	−30.67±15.13	− 5.25± 9.54	− 4.19±10.25	+11.92± 8.56
Responses to questionnaire [2]	−67.30± 7.27[4]	− 1.60± 4.52	− 23.10± 7.92[5]	− 2.50± 8.52
Clinical grade[3]	− 2.25± 0.26[4]	− 0.05± 0.24	− 0.55± 0.14[4]	− 0.20± 0.21

[1] Each figure represents the mean difference ± standard error of the difference for the area under the time-action curve between the control response to LSD or D-amphetamine and the respective "test" or "challenge" response following the chronic administration of either drug. The signs indicate an increased (+) or decreased (—) response after chronic intoxication.

[2] Represents the mean difference for the total number of questions scored positively during the experimental period.

[3] Represents the mean difference for the maximum mental reaction.

[4] Indicates significance ($P < 0.01$) between the control and "test" or "challenge" response.

[5] Indicates significance ($P < 0.02$) between the control and "test" or "challenge" response.

naire and clinical grade, thus signifying that direct tolerance to D-amphetamine has developed for these parameters. However, when the peak responses were analyzed in a similar manner, a statistically significant difference was not obtained for rectal temperature.

The fourth column lists the mean differences in responses to LSD (0.5 mcg/kg) after the chronic administration of D-amphetamine, as compared with the respective control values for LSD (0.5 mcg/kg). In other words, this column summarizes the test for cross tolerance to LSD following chronic administration of D-amphetamine. Since significant differences are not demonstrated, cross tolerance did not develop under these conditions between LSD and D-amphetamine.

Fig. 2 and 3 illustrate the time action curves for subjective effects before and after the chronic administration of LSD and D-amphetamine. Fig. 2a illustrates direct tolerance to LSD with respect to subjective effects, while Fig. 2b shows the absence of cross tolerance to LSD

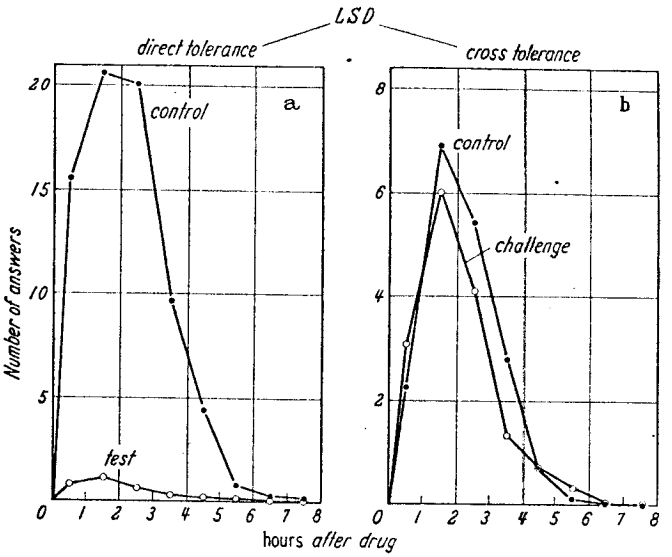

Fig. 2a and b. Time course of the subjective response with LSD before (•) and after (o) the chronic administration of LSD (Fig. 2a) and D-amphetamine (Fig. 2b). Note in Fig. 2a the marked diminution in response to LSD, 1.5 mcg/kg, following chronic LSD administration (i.e., direct tolerance present); but in Fig. 2b the normal response to LSD, 0.5 mcg/kg, following chronic D-amphetamine administration (i.e., cross tolerance absent)

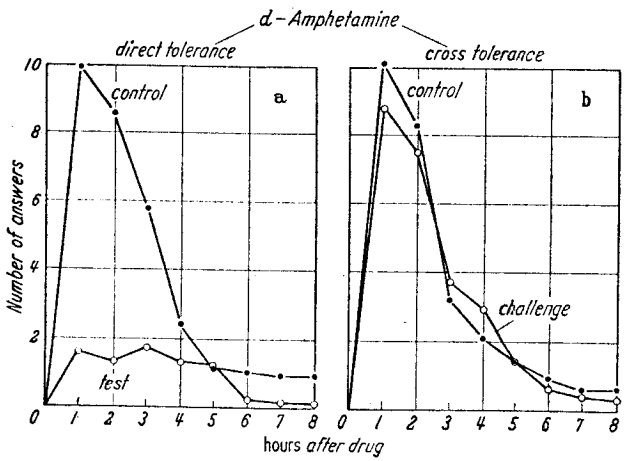

Fig. 3a and b. Time course of the subjective response with D-amphetamine before (•) and after (o) the chronic administration of D-amphetamine (Fig. 3a) and LSD (Fig. 3b). Note in Fig. 3a the marked diminution is response to D-amphetamine, 0.6 mg/kg, following chronic D-amphetamine administration (i.e., direct tolerance present); but in Fig. 3b the normal response to D-amphetamine, 0.6 mg/kg, following chronic LSD administration (i.e., cross tolerance absent)

following the chronic administration of D-amphetamine. In a similar manner, Fig. 3a illustrates direct tolerance to D-amphetamine while Fig. 3b shows the absence of cross tolerance to D-amphetamine following chronic administration of LSD.

All 10 subjects completed the experiment in good condition. Weight loss, persistent anorexia or insomnia, "amphetamine psychosis" or "amphetamine shock" were not observed during or following the experimental period.

Discussion

The effect of single doses of D-amphetamine and LSD in nontolerant subjects are similar to other reports in the literature (LEAKE 1958; ISBELL et al. 1956). Although a stimulatory response was observed with either drug, it is important to recognize that the pattern of response was different with each drug. The subjective effects with LSD consisted of anxiety and euphoria with perceptual distortions and visual hallucinations, and was regarded as a pleasant experience *in toto*; while D-amphetamine produced anxiety and euphoria without distortions or hallucinations, and was followed by dysphoria with complaints of anorexia and insomnia. It should be recalled, however, as previously emphasized and discussed by ISBELL et al. (1956) that the LSD reaction has only a "superficial resemblance to the chronic forms of any of the major psychoses".

Differences in the quality of excitation with amphetamine and LSD have also been noted in animals. Although either drug produced a behavioral excitement and alerting pattern of the EEG in cats and monkeys, BRADLEY and ELKES (1957) noted that such effects with LSD, as contrasted to amphetamine, were dependent on stimulating factors from the external environment. Similarly, HAMILTON (1960) demonstrated that rats became excitable and ran faster to escape shock after an injection with either LSD or amphetamine, but stated "... the excitability in the LSD-25 rat is not qualitatively the same as that in the rat with amphetamine." He described the amphetamine treated rat as hyperactive and alert in their living cages, whereas the rats injected with LSD appeared hypoactive until stimulated with the shock or buzzer.

The absence of psychotic episodes with D-amphetamine during either the control or chronic intoxication periods is not surprising, since the drug was given only once daily in the morning to non-psychotic subjects for 14 days. Although "amphetamine psychosis" has often been reported, the dosages required differ markedly from those in this experiment. MONROE and DRELL (1947) failed to observe psychotic reactions in any of several patients following a single dose of various amounts of amphetamine. They concluded that a dose much greater than 30 mg of amphetamine must be required to precipitate a psychosis. CONNELL (1948) reviewed several cases of amphetamine psychoses and concluded that a minimum of 50 mg, but usually a much larger dose, of amphetamine is required to induce a psychosis in single doses.

Most reported cases of amphetamine psychosis involve chronic consumption of the drug on a schedule that would persistently interfere with

sleep. KNAPP (1952) reported several such cases and suggested that the resulting toxic state may simply be "an accumulation of normal fatigue".

The most conspicuous autonomic effect of D-amphetamine was a marked elevation in systolic blood pressure, but significant pupillary dilatation did not occur. Although mydriasis after even low doses of amphetamine has been demonstrated and studied in cats (MARLEY 1961), pupillary dilatation in man reported by other investigators (LEAKE 1958; CONNELL 1958) seems to be infrequently observed with doses comparable to those employed in the present experiment. In contrast, LSD produced a definite mydriasis which paralleled the degree of subjective effects with each of the two doses, but caused a relatively small elevation in blood pressure.

Reported information is conflicting as to whether or not direct tolerance develops to amphetamine in man (LEAKE 1958; SEEVERS 1955; VOGEL et al. 1948). That tolerance may develop is suggested by case reports of some patients who have gradually increased their daily dose of amphetamine to 200 mg or more without accentuating the effects initially obtained with a lesser amount (BLOOMBERG 1940; KNAPP 1952). The present experiment seems to be the first quantitative demonstration of the development of direct tolerance to amphetamine in man. This tolerance, with respect to blood pressure elevation and subjective effects, appears quite definite and is presented without reservation. However, it is questionable whether tolerance to the pyrexic effect would be easily reproducible since the temperature change was small, and pyrexia with amphetamine could not consistently be demonstrated with single doses to nontolerant subjects (e.g., the first control period).

It is quite apparent that direct tolerance developed to LSD with respect to subjective effects and pupillary dilatation. In addition, although not statistically significant, the other measurements tended to decrease with chronic LSD administration. This pattern of tolerance agrees well with earlier studies (ISBELL et al. 1961; WOLBACH et al. 1962) demonstrating that the subjective effects and pupillary changes are the most consistent changes induced with LSD in man, both acutely (single doses) and chronically (tolerance).

The absence of cross tolerance regarding the autonomic effects of LSD and D-amphetamine is not surprising since both single doses and the development of direct tolerance involved dissimilar parameters with respect to each drug. For example, pupillary dilatation was not observed in the control periods with the dose of D-amphetamine employed in this study; consequently, the demonstration of direct tolerance to this effect would be impossible. Therefore the absence of cross tolerance regarding pupillary dilatation must be cautiously interpreted.

The experimental condition was most favorable for the demonstration of cross tolerance to the mental effects of LSD and D-amphetamine. For

example, a greater response was obtained with the questionnaire and clinical grade with single doses (control) of LSD (1.5 mcg/kg) as compared to single doses (control) of D-amphetamine; and a high degree of direct tolerance was present to this amount of LSD when the subjects were challenged for cross tolerance with D-amphetamine. Therefore, the absence of cross tolerance to the total subjective response with LSD and D-amphetamine in man seems quite conclusive.

It is of added interest to note that mescaline and D-amphetamine are structurally related, but only the former drug induces subjective effects in man similar to LSD and exhibits cross tolerance with LSD (WOLBACH et al 1962).

These results suggest that in man LSD and D-amphetamine are not related in biological activity and probably exert their effects through dissimilar mechanisms.

Summary

1. Within the limits of this experimental design in man:

a) the spectrum of LSD effects is different from that of D-amphetamine in single doses to nontolerant subjects,

b) following the daily administration of LSD for 14 days, direct tolerance develops to LSD (1.5 mcg/kg) with respect to pupillary dilatation and mental excitation,

c) following the daily administration of D-amphetamine for 14 days, direct tolerance develops to D-amphetamine (0.6 mg/kg) with respect to temperature elevation, systolic blood pressure increase and mental excitation,

d) subjects directly tolerant to LSD (1.5 mcg/kg) are not cross tolerant to D-amphetamine (0.6 mg/kg), and subjects directly tolerant to D-amphetamine (0.6 mg/kg) are not cross tolerant to LSD (0.5 mcg/kg).

2. It is inferred that LSD and D-amphetamine probably exert their effects through dissimilar mechanisms.

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