7 *Derivatives of d-Lysergic Acid and Model Psychoses*

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Abstract

Experiments on man with LSD, its congeners, and its derivatives begun 15 years ago are reviewed. In doses of 5–10 times threshold these drugs rarely produce hallucinations, but do produce other symptoms resembling a psychotic state. In most experiments reported with nonpsychotic subjects a questionnaire was employed which embodied the symptoms reported in the literature. In the design of the experiments with psychotomimetic drugs, within-subject studies of those who were placebo negative and essentially anxiety-free take precedence over involved statistical techniques without these considerations. The response index is defined as the number of positive responses to the questionnaire divided by the dose in μg. In this way the order of LSD, congeners, and derivatives is listed. LSD is the strongest of the group whereas UML (Sansert) is the weakest but has the strongest antiserotonin activity. LSD rapidly produces tolerance to itself. A mathematical theory of tolerance has been partly tested and found to be adaptable to a theory pertaining to the nature of schizophrenia. Derivatives and congeners of LSD, as well as psilocybin, produce cross-tolerance.

A content analysis of the neurotic and psychotic symptoms is outlined as

well as a distinction between psychoanalytic and psychedelic therapy. A brief report is made of the effect of LSD in the communication processes in both nonpsychotic and psychotic subjects. It is believed that the study of drugs like LSD may be of value in recall of forgotten memories, but it is believed that the feelings connected with memories are not measurable at present and that from the viewpoint of psychodynamics (Freud) forgetting is always due to unconscious, unmeasurable processes.

If one attempts to study the reaction of the mind in the conscious human organism, he encounters certain methodological difficulties which confront all of those working with psychotomimetic drugs like LSD.* When I began the research on LSD, its derivatives and congeners 15 years ago, it appeared that to measure the influence of any drug on mental processes always introduced a compromise. This compromise embodied a requirement for replicability even though the experimental frame of reference was thereby narrowed. For this reason it was decided not only to observe the subjects but also to employ a questionnaire to determine their reactions.[5] At that time there existed the same or perhaps more of the confusion that is present today in evaluating the effects of LSD on man. Experiments in the literature at that time—for example, those of Hofmann[17]—did not produce results identical to those in my laboratory, probably because the setting and the method of observation were different; for example, my group and I rarely observed hallucinations. As a matter of fact, I am still wondering why these drugs are called hallucinogenic. The pseudohallucinations usually produced by doses up to ten times the threshold level of 25 μg in nonpsychotic subjects may be accompanied by many other symptoms of a toxic psychosis, with disturbances in motor behavior, concentration, orientation, memory, mood, control, level of consciousness, and attitude toward environment, but rarely are there true hallucinations. Replicability in this complex experimental milieu was also important, because it was necessary to devise a technique of quantitative comparison of the action of LSD with closely related compounds like LAE and less closely related compounds like psilocybin.

* Abbreviations used in this chapter are: ALD-52 (1-acetyl *d*-lysergic acid diethylamide); BOL-148 (2-brom *d*-lysergic acid diethylamide); LAE (*d*-lysergic acid ethylamide); LSD-25 (*d*-lysergic acid diethylamide); MLD-41 (1-methyl *d*-lysergic acid diethylamide); OML (oxymethyl *d*-lysergic acid diethylamide); UML (Sansert) (1-methyl *d*-lysergic acid butanolamide).

PART I QUESTION	½ Hr.	1½ Hrs.	2½ Hrs.	3½ Hrs.	4½ Hrs.	4½ Hrs.
1. Do you feel ill in any way?						
2. Are you nauseated?						
3. Have you a feeling of choking?						
4. Is salivation increased?						
5. Or decreased?						
6. Is your appetite increased?						
7. Or decreased?						
8. Do you have a "dry" taste in your mouth?						
9. Do you have a funny taste in your mouth?						
10. Is it a bitter taste?						
11. Are your lips numb?						
12. Or drawn back as if you were smiling?						
13. Does your head ache?						
14. Are things moving around you?						
15. Do you feel dizzy?						
16. Or unsteady?						
17. Is there difficulty in breathing?						
18. Do you pass more urine than usual?						
19. Are you aware of your heart beat?						
20. Is it faster than usual?						
21. Are you sweating?						
22. Are you hot?						
23. Or cold?						
24. Are your palms moist?						
25. Or dry?						
26. Or cold?						
27. Is your skin sensitive?						
28. Do you have funny feelings on your skin?						
29. Do your hands and feet feel peculiar?						
30. Do they feel heavy?						
31. Or light?						
32. Is there pressure in your ears?						
33. Is your hearing abnormal?						
34. Is it more acute than usual?						
35. Is your eyesight blurred?						
36. Do you have difficulty in focusing your vision?						
37. Do you see double?						
38. Are shapes & colors altered in any way?						
39. Does light bother you?						
40. Do things seem too close?						
41. Or too far away?						
42. Do you tremble inside?						
43. Do you feel weak?						
44. Or fatigued?						
45. Do you feel drowsy?						
46. Do you feel as if in a dream?						
47. Are you anxious?						

FIG. 7-1. *Part I*, Half an hour after administration and at hourly intervals thereafter, these direct questions are put to the subject. His rating is accepted, if possible, on a + to +++++ basis. *Part II*, Half an hour after administration and at hourly intervals thereafter, these qualitative ratings are made on the subject by the experimenter aided by the subject's comments. (From Abramson[3])

The Questionnaire

At the beginning of the project a questionnaire was compiled from the symptoms and signs reported in the literature. This questionnaire is still used by my coworkers and me and was also used by Dr. Harris Isbell while he was conducting his studies at Lexington, Kentucky.[18] In this way, it was possible to compare the effects of a

PART II

1. Motor Behavior:	2. Control:	3. Consciousness:
½ Hr.	½ Hr.	½ Hr.
1½ Hrs.	1½ Hrs.	1½ Hrs.
2½ Hrs.	2½ Hrs.	2½ Hrs.
3½ Hrs.	3½ Hrs.	3½ Hrs.
4½ Hrs.	4½ Hrs.	4½ Hrs.
Later	Later	Later
Concentration:	5. Mood (Euphoria - Depression):	6. Attitude to Environment:
½ Hr.	½ Hr.	½ Hr.
1½ Hrs.	1½ Hrs.	1½ Hrs.
2½ Hrs.	2½ Hrs.	2½ Hrs.
3½ Hrs.	3½ Hrs.	3½ Hrs.
4½ Hrs.	4½ Hrs.	4½ Hrs.
Later	Later	Later
7. Orientation:	8. Memory:	9. Hallucinations:
½ Hr.	½ Hr.	½ Hr.
1½ Hrs.	1½ Hrs.	1½ Hrs.
2½ Hrs.	2½ Hrs.	2½ Hrs.
3½ Hrs.	3½ Hrs.	3½ Hrs.
4½ Hrs.	4½ Hrs.	4½ Hrs.
Later	Later	Later

group of LSD derivatives and congeners on normal subjects with the effects of these compounds on drug addicts. Fig. 7-1 is the questionnaire devised at that time. Jarvik preferred to modify the questionnaire by regrouping essentially the same questions under physiological, perceptual, and cognitive reactions.[19] However, this modified grouping robbed the questionnaire of the randomization and tended to channel

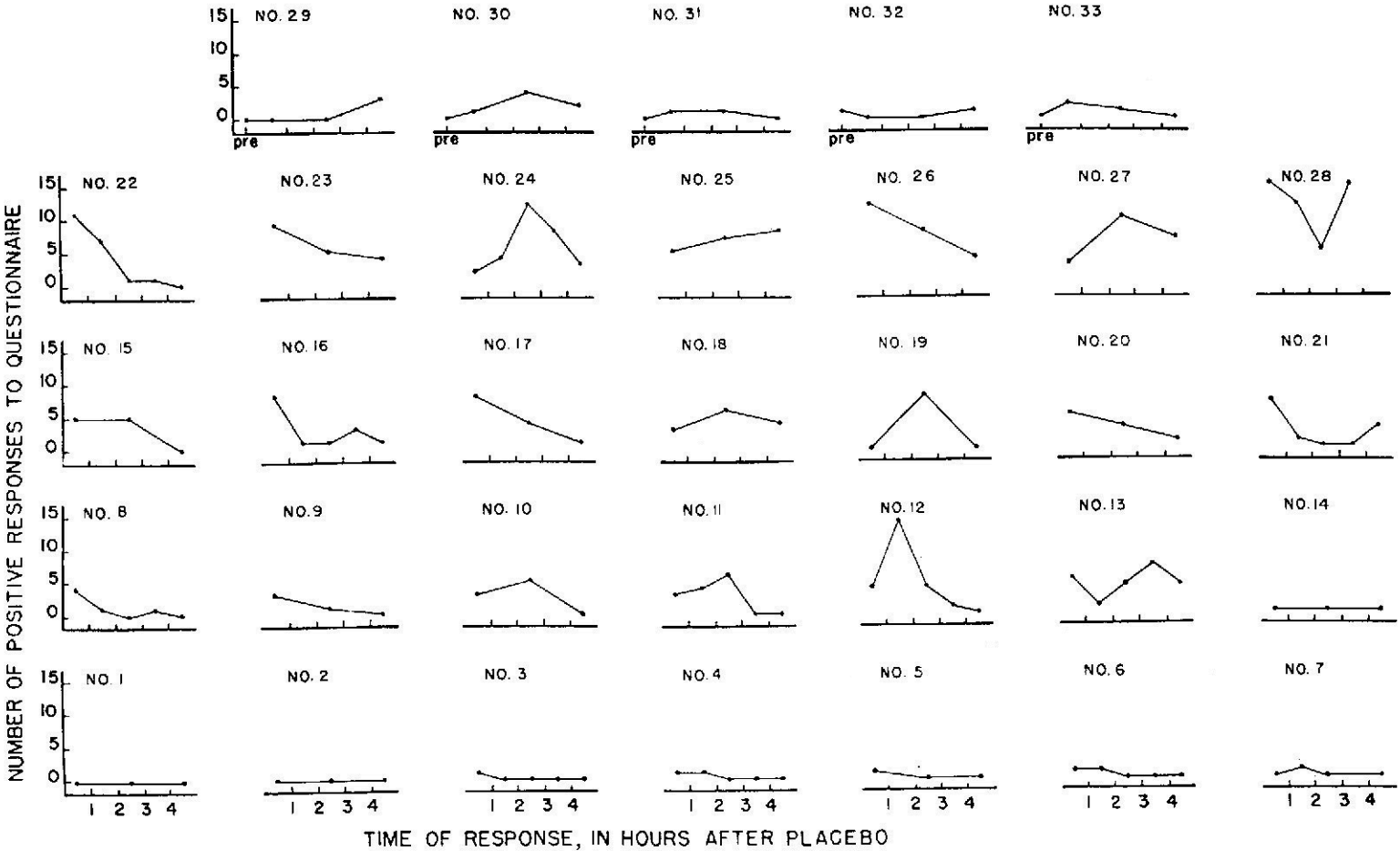


FIG. 7-2. Number of positive responses to the questionnaire at stated time intervals after the ingestion of a placebo. Subjects 1 through 28 are arranged in order on increasing number of different responses.

the responses. Note that Part II of the questionnaire is essentially a short mental rating test. Depending on the experimental design, subjects may fill in parts I and II themselves, or they may be questioned by the observer. The subjects themselves may make additional notes on the back of the cardboard test sheet. Using both parts of the questionnaire introduces some of the disadvantages often inherent in a strictly structured test situation, but provides the replicability of a questionnaire and the flexibility of a clinical assessment.

One of the objections to the questionnaire has been that the subject is aware of the nature of the response, and therefore, for various reasons, will provide positive responses because of previous knowledge. However, it was found that more replicable data could be obtained if the subjects knew in advance the nature of the experiment and if they were trained subjects who could be relied upon to be placebo negative. It was more important, therefore, in designing experiments, to have subjects who could detect a placebo than to have subjects ignorant of typical reactions to LSD and similar drugs. Incidentally, most important of all in the design of experiments with this type of drug is the reduction of anxiety on the part of the subject. Such reduction is much more significant than strict adherence to a system that may be statistically valid for other types of experiments.

Placebo Reactivity[6]

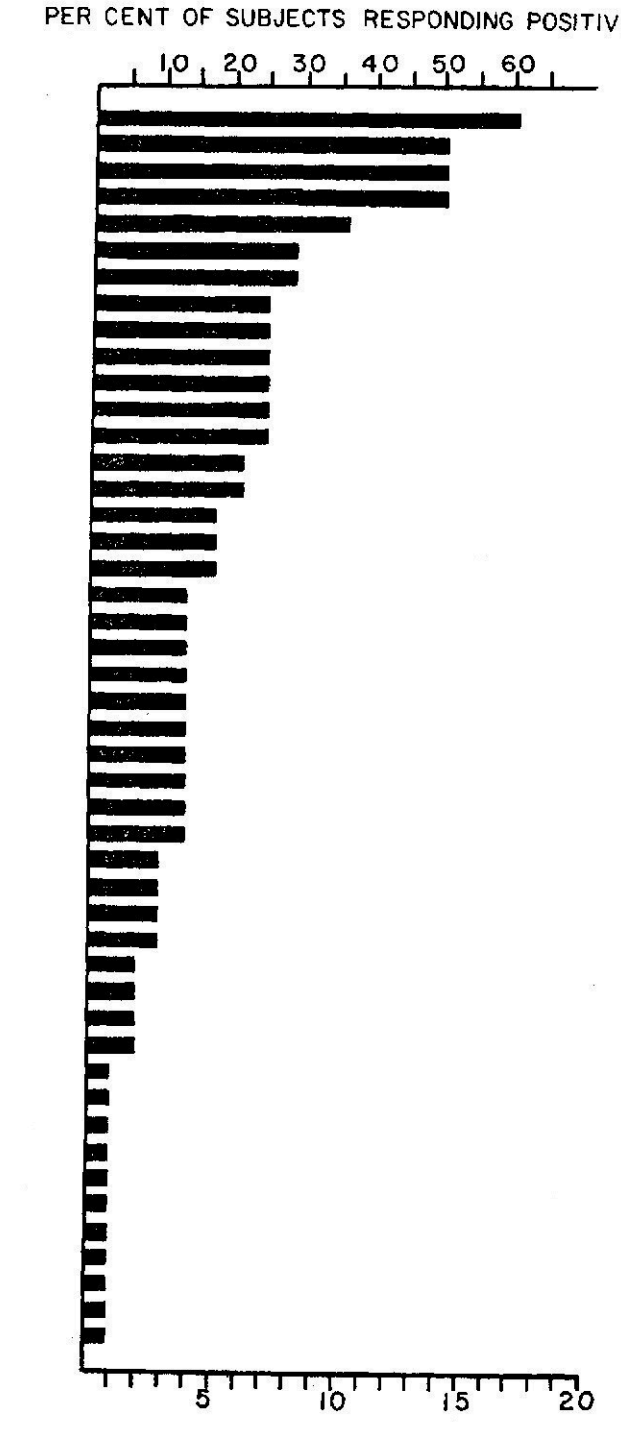
Only inadequate studies of psychotomimetic drugs can be made if poor communication exists between observer and subject. The data obtained on 33 randomly selected, essentially nonpsychotic subjects showed the frequency of placebo reactors to be high. Placebo responses may be obtained in essentially normal subjects. Data obtained with placebo-positive subjects is open to question.

Subjects were usually tested in groups of 2 to 5. Fig. 7-2 illustrates the number of positive responses to the questionnaire at stated time intervals for 33 subjects. Note the wide variation in placeebo activity. Fig. 7-3 illustrates the number and percentage of 28 subjects (given a placebo) responding positively to the items of the questionnaire. Most subjects who respond to a placebo tend to do so most markedly during the initial part of the experiment, and the greatest percentage

QUESTIONS

24. Are Your Palms Moist?
13. Does Your Head Ache?
44. Do You Feel Fatigued?
45. Do You Feel Drowsy?
47. Are You Anxious?
1. Do You Feel Ill in Any Way?
15. Do You Feel Dizzy?
46. Do You Feel as if in a Dream?
6. In Your Appetite Increased?
16. Do You Feel Unsteady?
22. Are You Hot?
30. Do Your Hands and Feet Feel Heavy?
43. Do You Feel Weak?
4. Is Salivation Increased?
29. Do Your Hands and Feet Feel Peculiar?
7. Is Your Appetite Decreased?
32. Is There Pressure in Your Ears?
35. Is Your Eyesight Blurred?
5. Is Salivation Decreased?
9. Do You Have a Funny Taste in Your Mouth?
18. Do You Pass More Urine Than Usual?
19. Are You Aware of Your Heart Beat?
20. Is it Faster Than Usual?
21. Are You Sweating?
23. Are You Cold?
26. Are Your Palms Cold?
39. Does Light Bother You?
42. Do You Tremble Inside?
2. Are You Nauseated?
3. Have You a Feeling of Choking?
8. Do You Have a "Dry" Taste in Your Mouth?
10. Is There a Bitter Taste in Your Mouth?
11. Are Your Lips Numb?
12. Are Your Lips Drawn Back as if You Were Smiling?
34. Is Your Hearing More Acute Than Usual?
38. Are Shapes and Colors Altered in any Way?
14. Are Things Moving Around You?
17. Is There Difficulty in Breathing?
25. Are Your Palms Dry?
27. Is Your Skin Sensitive?
28. Do You Have Funny Feelings on Your Skin?
31. Do Your Hands and Feet Feel Light?
33. Is Your Hearing Abnormal?
36. Do You Have Difficulty in Focusing Your Vision?
37. Do You See Double?
40. Do Things Seem Too Close?
41. Do Things Seem Too Far Away?

FIG. 7-3. The number and percentage of 28 subjects responding positively to a placebo. The items are arranged in order of decreasing percentage response.


PER CENT OF SUBJECTS RESPONDING POSITIVELY
10
20
30
40
50
60
5
10
15
20
NUMBER OF SUBJECTS RESPONDING POSITIVELY

of responses were related to anxiety and to phenomena which commonly occur without the presence of a drug, such as drowsiness, fatigue, or headache.

Subject-to-Subject Variability

The questionnaire is useful in detecting the fact that large differences in reactivity to LSD and its congeners exist from subject to subject.[1-3] The drugs may be given to each subject more than once,

TABLE 7-1. The Effect of Psilocybin on Two Nonpsychotic Subjects

Subject	*Experiment*	*Psilocybin (mg)*	*Questionnaire response (n)*
P. B.	1	3	4
	2	6	2
	3	6	14
	4	6	13
	5	6	23
D. V. G.	1	6	16
	2	6	10
	3	6	10
	4	8	14

and thus one may make two or three separate comparisons at separate dose levels for each drug, obtaining both subject-to-subject data and within-subject studies. Within-subject variability is illustrated in Table 7-1, which discloses the wide variability and the number of responses for Subject P. B. and the relative constancy of Subject D. V. G.'s responses. Our method of using the questionnaire enables us to compute a standard analysis of variance with three components:

(1) Average difference between drugs for all subjects.

(2) Subject-to-subject variation of psychotomimetic effects of the drugs.

(3) An overall estimate of experimental error for each subject.

Subject Sophistication and Anxiety

In experiments where the program included the use of a trained group of five essentially placebo-negative subjects to whom LSD and

other psychotropic drugs had been administered regularly each week during the winter periods for nine years, the subjects became more sophisticated and less anxious. However, anxiety was seen to crop up even in these sophisticated subjects under certain circumstances. It must be emphasized that the queries of the questionnaire are very different indeed from the usual therapeutic trial where the expectation of the patient is to be helped, not threatened, by a new psychosis-producing drug. Every effort must be made to eliminate anxiety, which inevitably is engendered by the test situation, no matter how dedicated or experienced the test subject may be. A social milieu containing no new factors with two or more subjects is fairly anxiety-free. Interaction by the members of the test group was encouraged, as was having wives or husbands present. Such arrangements may be permitted under certain conditions and definitely do diminish anxiety. No visitors were permitted unless unanimous consent was obtained from members of the group. Test subjects were encouraged to verbalize recent experiences which they felt might be anxiety-producing. It may be necessary to disclose to one member of the group information that partially destroys the blind or double-blind character of the experimental design. Ideally speaking, double-blind experiments may be desirable. However, in my test group, a single-blind design produced much less anxiety. Tension arises in a subject unless he knows that someone who is both capable and responsible for his safety is consciously aware of what is really happening to him during the experiment.

High Doses

As the dose increases, Part I of the questionnaire becomes more difficult to use because of difficulty in communicating with the subject or obtaining cooperation from him. The second part of the questionnaire must be emphasized under these circumstances, with the observer's evaluation often more important than the numerical value of the responses.

Within-Subject Studies

I first used the questionnaire in an attempt to obtain a study of subject-to-subject variability with different doses. However, the ques-

tionnaire was especially useful for comparisons of different psychotomimetic doses or compounds if studies were made within placebo-negative subjects rather than between subjects. The method becomes sensitive if each subject receives all of the compounds at all of the dosage levels unless, as occasionally happens, a subject has a very low threshold and very severe reactions at higher doses. With

TABLE 7-2. LSD-25: Threshold for Calculation of Group Average = μg

Subject	*Date*	*Dosage (μg)*	*Number responses*	*RI*	*Subject estimate*
C. G.	3/16/56	50	34	.68	50
	2/8/57	35	25	.71	25
	11/15/57	25	34	1.36	> 25
	1/3/58	25	19	.96	25
	5/16/58	35	22	.63	25
				Av. .86 ± .23	
P. B.	11/21/52	50	23	.46	
	1/9/53	75	47	.62	
	3/16/56	50	21	.48	
	3/29/57	50	23	.46*	
	5/16/58	50	17	.34	35
				Av. .47 ± .06	
D. V. G.	3/11/55	25	5	.20	
	3/16/56	50	14	.28	
	11/15/57	35	16	.46	35
				Av. .31 ± .10	
M. Z.	3/16/56	50	12	.26	25
	3/29/57	50	33	.66	25
	11/15/57	35	14	.40	25
	5/16/58	50	11	.22	35–50
				Av. .39 ± .15	
J. G.	3/11/55	50	24	.50	
	4/8/55	25	8	.32	25
	10/2/55	25	6	.24	25
	12/2/55	25	11	.44	25
	3/16/56	50	16	.32	> 25 but < 50
	11/15/57	35	9	.29	35
	5/16/58	50	10	.20	25–35
				Av. .33 ± .08	

GROUP AVERAGE RI = .47

* At 2 hr: "I was never so frightened in my life."

this method, variations within the response from subject to subject cancel out when response averages are compared.

Response Index[1-3]

Since the questions of the questionnaire are constructed so that a positive response constitutes one response, a number, n, is obtained by adding the number of responses for a given period. It is obvious that if the same drug is used in all experiments, different values of n may be compared. However, if LSD is to be compared with its congeners and derivatives, the significance of n becomes important only when the dose administered is introduced into the comparison. I have called the ratio of n divided by the dose in micrograms the Response Index (RI), or

$$\text{RI} = \frac{n}{\mu g}$$

For a given dose, therefore, the higher the value of RI, the greater the response to the drug. The use of the RI provides a suitable method of comparing psychotomimetic activity at threshold levels, or slightly above threshold levels, of various compounds related structurally. When the group average of the RI is obtained, a more representative value of psychotomimetic activity is established.

Table 7-2 illustrates, in a condensed form, data obtained on the same five test subjects from 1955 to 1958 at threshold levels of LSD-25 or slightly above. Note that even though the RI for single experiments varies somewhat, the subjects' estimates of the dose of LSD are fairly accurate. If the averages obtained for each subject are used

TABLE 7-3. A Comparison of Values of the Average RI for LSD-25 on Five Subjects with One Pretreatment (Placebo) Experiment

Subject	*RI (Placebo for 4 days)*	*Average RI data from Table 7–2*
P. B.	.56	.47
C. G.	.84	.86
J. G.	.31	.33
D. V. G.	.40	.31
M. Z.	.44	.39
Group RI	.51	.47

The agreement is better than anticipated.

to calculate a Group RI, the Group Average RI = .47. We obtain, thus, a number characterizing the response of this group under the specific nonstressful test conditions. The number (Group Average RI), we felt, eliminated many of the variables and gave a representative basic measure of psychotropic activity based on the questionnaire technique.

But this question arose: Did this Group RI fluctuate markedly under different test conditions and with these nonpsychotic subjects? Fortunately, other data were available. Table 7-3 illustrates an experiment in which the same subjects took a placebo (blind) for 4 days, three times daily, prior to taking LSD-25. This Group Average RI is .51. The average RI for each individual in Table 7-3 checks with the average RI in Table 7-2.

Experiments on test subjects included LSD derivatives. Some of these derivatives are illustrated in Fig. 7-4. Some of the results of ex-

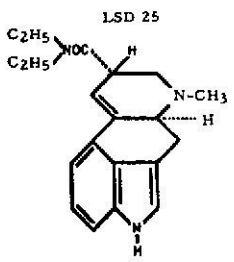
TABLE 7-4. ALD-52

Subject	*Date*	*Dosage (μg)*	*Number responses*	*RI*
P. B.	1/ 4 /57	25	10	.40
	1/18/57	50	12	.24
				Av. .32 ± .08
C. G.	12/21/56	25	10	.40
	1/ 4 /57	25	19	.76
	1/18/57	50	37	.74
				Av. .63 ± .16
M. Z.	12/21/56	25	19	.76
	1/ 4 /57	25	18	.72
	1/18/57	50	30	.60
				Av. .67 ± .07
J. G.	12/21/56	35	8	.23
	1/ 4 /57	35	8	.23
	1/18/57	70	29	.41
				Av. .29 ± .08
D. V. G.	12/21/56	35	10	.29
	1/ 4 /57	35	7	.20
	1/18/57	70	14	.20
				Av. .23 ± .05

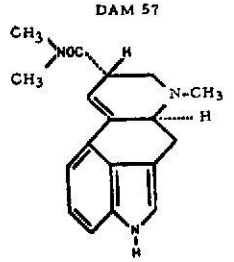
RI Group Average = .43

periments with these derivatives are to be found in Tables 7-4–7-6. For practical purposes, ALD-52, the 1-acetyl derivative of LSD, is as strong as LSD itself. However, two other compounds, OML and MLD, diminish in effectiveness. Changing the group on the amide linkage reduces the activity even further. The values show a more marked diminution in activity as the amide structure is varied.

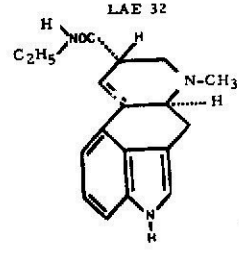
Table 7-7 gives the relative strengths, LSD = 100, of the compounds thus far studied with our method. Using this method we had hoped to obtain in man more quantitative measures in psychopharmacologi-



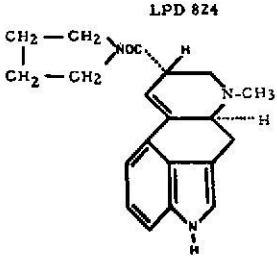
lysergic acid diethylamide



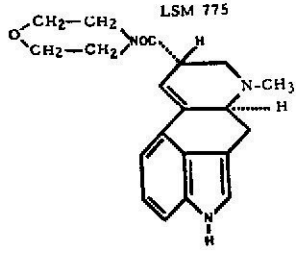
d-lysergic acid dimethylamide



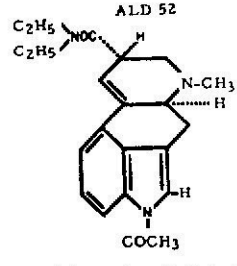
d-lysergic acid ethylamide



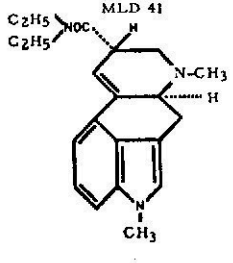
d-lysergic acid pyrrolidide



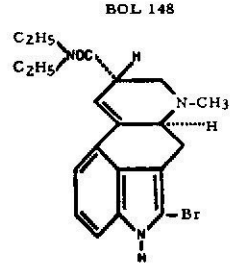
d-lysergic acid morpholide



d-1-acetyl-lysergic acid diethylamide



d-1-methyl-lysergic acid diethylamide



d-2-brom-lysergic acid diethylamide

FIG. 7-4. LSD and some related compounds.

cal experiments dealing with effectiveness of psychotomimetic drug effects, tolerance, cross-tolerance, antagonisms, synergisms, and therapy. Unfortunately, these experiments could not be continued because of the new regulations imposed by the Food and Drug Administration in 1963.

It should be emphasized that the derivatives and congeners listed in Table 7-7 have been studied only near the threshold dose. What

TABLE 7-5. OML-632

Subject	*Date*	*Dosage (μg)*	*Number responses*		*RI*	*Subject estimate LSD equivalent*
C. G.	1/10/58	35	16		.46	< 25
				Av.	.46	
P. B.	1/3/58	35	12		.37	25
	1/10/58	50	18		.36	35
				Av.	.37 ± .005	
D. V. G.	1/3/58	35	11		.31	< 25
	1/10/58	50	18		.36	> 35
				Av.	.34 ± .03	
M. Z.	1/10/58	50	16		.32	35
				Av.	.32	
J. G.	1/3/58	35	2		.07	< 25
	1/10/58	50	3		.06	35
				Av.	.07 ± .005	
			GROUP AVERAGE RI = .31			

Threshold for calculation of group average = 35 μg.

special values the different compounds may have in psychoanalytically oriented therapy or in psychedelic therapy is unknown. The two compounds LSD and UML are considered to differ widely in their ability to produce psychological reactions. However, when the dosage of UML is increased, psychological responses certainly occur. In my test group, for example, the reaction of the subject to doses of UML at or near the threshold dose, measured by the response to the questionnaire, was similar to their reaction to LSD. But 170 μg of UML are required to produce the effect of 1 μg of LSD. In other words, in terms of the questionnaire, the threshold dose of UML is about 4 mg.

It is pertinent that the dose of Sansert, clinically accepted for the treatment of migraine, was gradually reduced to 2 mg, i.e., one-half the threshold dose for psychic effects in certain patients. The argument that these effects are due to vasomotor responses does not eliminate the psychic end result.

TABLE 7-6. MLD-41

Subject	*Date*	*Dosage (μg)*	*Number responses*	*RI*	*Subject estimate*
C. G.	10/26/56	25	0	0	<15
	11/ 9 /56	50	23	.46	25
	11/16/56	25	0	0	0
				Av. .46	
P. B.	10/12/56	10	0	0	0
	10/26/56	25	0	0	0
	11/ 9 /56	50	0	0	0
	11/16/56	75	15	.20	15
	11/30/56	115	22	.19	35
				Av. .13 ± .086	
D. V. G.	10/12/56	10	1	.10	0
	10/26/56	25	0	0	0
	11/ 9 /56	70	0	0	0
	11/16/56	100	3	.03	0
	11/30/56	140	20	.14	35 ?
				Av. .056 ± .055	
M. Z.	10/12/56	10	0	0	0
	10/26/56	25	0	0	0
	11/ 9 /56	50	0	0	0
	11/16/56	75	2	.027	0
	11/30/56	115	33	.29	35
				Av. .11 ± .16	
J. G.	10/12/56	10	2	.20	
	10/26/56	25	0	0	
	11/ 9 /56	70	5	.071	
	11/16/56	100	7	.07	
	11/30/56	140	21	.15	
				Av. .097 ± .035	

GROUP AVERAGE RI = .17

Threshold for calculation for group average = 50 μg.

TABLE 7-7. A Comparison of Psychotomimetic and Antiserotonin Activity

Drug	*Activity*	*Antiserotonin activity*
d-lysergic acid diethylamide (LSD)	100	100
acetyl *d*-lysergic acid diethylamide (ALD)	91	210
oxymethyl *d*-lysergic acid diethylamide (OML)	66	59
1-methyl *d*-lysergic acid diethylamide (MLD)	36	370
d-lysergic acid morpholide (SLM)	11	2
2 brom *d*-lysergic acid diethylamide (BOL)	7.2	103
d-lysergic acid pyrrolidide (LPD)	5.3	5
d-lysergic acid ethylamide (LAE)	3.4	12
1-methyl *d*-lysergic acid butanolamide (UML)	.66	400

Note that MLD has an antiserotonin activity similar to UML (Sansert). Antiserotonin data after Cerletti.[14a]

Cross-Over Designs

It is feasible to use a cross-over design in the study of various derivatives of LSD, varying the compounds within the group. This method has been especially effective in preliminary comparison of LSD and psilocybin by administering both drugs to our test group double blind. It may be mentioned that our test subjects could not usually distinguish at the beginning of the series between LSD and psilocybin taken orally, unless doses were near the threshold level.

Experiments comparing LSD and psilocybin[8] were run blind in groups of six subjects. Some subjects received placebos while others received the drugs under discussion on the test run. One subject, C. G., was very sensitive to LSD and similar compounds. In order to make certain that he was placebo negative, two experiments were run with distilled water alone. The subject correctly estimated that placebos were present. The next experiment was with a subthreshold dose of BOL. In two other experiments, 25 and 35 μg of LSD were successfully estimated by the subject, but in spite of 22 positive questionnaire responses in another experiment, he did not feel that he had received LSD. For this reason he was then given a placebo. This was followed with 25 μg of LSD which the subject correctly estimated. When three congeners of LSD were administered, separately, the subject estimated the subthreshold dosage correctly. Having thus established in 11 experiments that the subject was suitable for evaluation of psilocybin, C. G. was then given psilocybin. With this subject 3 mg of psilocybin was equal to about 25μg of LSD; 6 mg of psilocybin

showed about a 35 μg LSD response. This experienced subject could not distinguish between 50 μg of LSD and psilocybin, although in later experiments the group of test subjects as a whole learned to distinguish between the two drugs by the course of reaction rather than by the symptoms. Subject C. G. took 50 mg of psilocybin at home for 7 days before taking 50 μg of LSD. He developed tolerance to 4 mg of psilocybin while taking this compound at home, and his response to 50 μg of LSD was subthreshold with cross-tolerance developing produced by psilocybin. It is of interest to mention that the subject was not confused by the scrambling of LSD and psilocybin in separate experiments and that his estimation of the dose of psilocybin or LSD or equivalent doses was remarkably accurate.

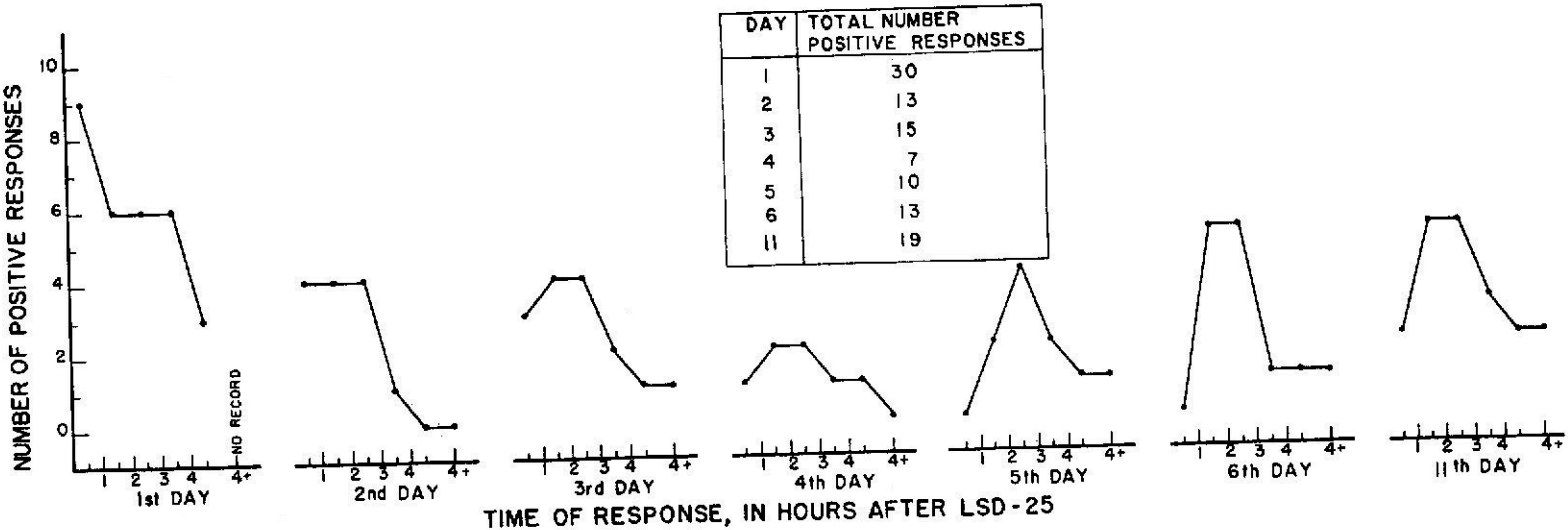
Tolerance[4]

LSD rapidly produces tolerance to itself. The rate of tolerance production depends upon the method of administration of the dose. The RI was a useful device to follow the way in which doses of LSD given on repeated days affected the LSD response in nonpsychotic, trained, placebo-negative subjects. A subject received 100μg of LSD-25 on 3 successive days. The response on the third day was so small that the subject felt that his mentation processes had been affected by the LSD, and that he no longer could judge the LSD effect.

The question arose as to what type of response would occur if the LSD were given for longer than 3 days. Fig. 7-5 illustrates that Subject A, who received 100 μg of the drug on 6 successive days, and once again on the eleventh day after a lapse of 5 days, developed tolerance but seemed to lose the tolerance developed. For example, on the fifth day the number of responses started to increase. On the eleventh day, after the 5-day interval, the number of responses approached those of the first day. The administration of small doses, increased gradually for 5 successive days, produced some tolerance, but not so successfully as the use of larger doses to begin with.

Theory of Tolerance

It was important to make some attempt to develop a mathematical scheme to explain the rapid development of tolerance. With the help



DAY	TOTAL NUMBER POSITIVE RESPONSES
1	30
2	13
3	15
4	7
5	10
6	13
11	19

FIG. 7-5. Total number of positive questionnaire responses given by Subject A on Section 1 during each of seven experiments. The subject received 100 μg of LSD-25 on 6 successive days and again after 5 days.

of Dr. M. H. Gorin, a mathematical treatment of tolerance development was outlined, and an attempt was made to relate this to a theory of psychosis. Certainly, our theory is an oversimplification of a very complex mechanism. However, the mechanism to be proposed offers a way to correlate the data in terms of a single rate constant (k_4). The extremely low dosage at which the initial reaction to LSD is obtained is of the order of that required to produce systemic reactions to other drugs such as histamine and epinephrine. It points to an intrusion of LSD into psychic reactions as an analogue of psychological substances normally involved in these reactions. The unique feature of the psychic action is that tolerance is so quickly established and yet so rapidly lost. In the speculations which follow, the view is taken that the establishment of tolerance and its rapid loss are part of a unified mechanism which also involves the psychic actions. Briefly, the mechanism suggested has four essential steps and involves the following compounds.

Step 1: LSD, designated by L, interacts with a neuro-metabolic system, E, to cause symptoms. The compound LE is formed. As long as LE is present, some reaction of LSD may occur.

Step 2: LE is labile and splits into E_T and other products which are eliminated. E_T is the key substance in the mechanism and designates the tolerance factor.

Step 3: When E_T comes into contact with LSD it reacts to form LE. When tolerance is established L is preferentially reacting with E_T compared with the metabolic reaction which causes symptoms. It is postulated that LE is reformed because this allows E_T to be built up in time by repeated administration. Since tolerance disappears in time a fourth step is required.

Step 4: E_T is eliminated.

These four steps are represented by the equations below. The k's over the arrows are rate constants for each step.

$$\mathrm{L} + \mathrm{E} \underset{k_5}{\overset{k_1}{\longleftrightarrow}} \mathrm{LE} \qquad \begin{matrix}(1) & (5) \\ \longrightarrow & \longleftarrow\end{matrix}$$

$$\mathrm{LE} \xrightarrow{k_2} \mathrm{E_T} + \text{decomposition products and excretion} \qquad (2)$$

$$\mathrm{E_T} + \mathrm{L} \xrightarrow{k_3} \mathrm{LE} \qquad (3)$$

$$\mathrm{E_T} \xrightarrow{k_4} \text{decomposition products and excretion} \qquad (4)$$

All four reactions proceed while symptoms are occurring, but when

the effect of the drug wears off, only Reaction 4 continues. The psychic reactions appear to be over in hours, while the elimination of tolerance takes several days. It follows, therefore, as a first approximation, that when the psychic reaction is over, essentially all of the LSD which entered the site of reaction has been converted to E_T. Also, it is obvious that the intensity of the reaction to the next administration of LSD is primarily determined by the rate of loss of E_T by Reaction 4. Initially, enough E_T is present to protect against an approximately equal dose of LSD, but the longer the period between administrations (for a given value of k_4), the greater will be the reaction to the next dose.

Postulating that Reaction 1 is reversible brings in the feature of residual response to LSD after tolerance is established. A steady state between Reactions 1 and 5 reduces the effective concentration of L to a low level. If this is below the threshold for the individual concerned, zero reaction will be obtained. On the other hand, the steady state concentration in other individuals might be above their threshold level, and some symptoms therefore occur. This seems to correspond to the situation with Subject A.

Quantitative considerations were developed based on the idea that Reaction 4 is of the first order with respect to E_T. A constant fraction of E_T will be lost between administrations irrespective of the initial amount present. The loss of E_T with time will follow the equation

$$\log \frac{A}{A - X} = k_4 t$$

where A is the initial amount of E_T present and X the amount of E_T lost in time, t.

In our original communication the theory developed was discussed in relation to the data obtained. Application of the formula to the data demonstrated the relationship between the predicted effective dose of LSD-25 and the effective dose found. Further experimentation was suggested to verify certain predictions. The theory for development and loss of tolerance to LSD-25 was adapted to a theory pertaining to the nature of schizophrenia. A substance P, analogous to LSD-25, was suggested as giving rise to the mechanisms of tolerance which are either lost or altered during clinically psychotic reactions. It was proposed that both the P substance and anti-P substances (E_T) should be sought in the urine of clinically schizophrenic patients, and that

anti-P substances might also be found in the urine of nonschizophrenics.

Cross-Tolerance[10]

Since LSD produced tolerance to itself remarkably quickly, it was most important that the effect of derivatives and congeners of LSD be studied to ascertain if changing the spatial groups would produce cross-tolerance. The effect of MLD-41 on man was studied by giving increasing doses of MLD-41 to the group of test subjects who could assay the effects of LSD with a good deal of accuracy. The interview and test situation was the usual protected, social setting described previously. After determining the threshold level to MLD-41 for each member of the group, MLD-41 was taken at home by the test group 5 or 6 days ahead of time in increasing doses. The levels chosen for the first dose were below the threshold of response to MLD-41.

TABLE 7-8. Effectiveness (Corrected) of LSD Derivatives on Production of Cross-Tolerance

MLD	100
BOL	8
OML	2
DAM	0.5
LAE	0.4
UML	0.2

A typical experiment in C. G., our most sensitive subject, was conducted as follows: starting with 100 μg of MLD-41 in divided doses, C. G. reached a dose of 350 μg on the sixth day. Since MLD-41 is about one-third as active as LSD, this indicated that C. G. had developed tolerance to about 120 μg of LSD. The MLD-41 was first administered May 4th; on May 10th, 100 μg of MLD-41 was taken in the morning, with a total of 1450 μg of MLD-41 taken from May 4th to May 10th inclusive. At 7:45 P.M. on May 10th, 100 μg LSD-25 was administered orally in distilled water to this extremely sensitive subject. There was essentially no reaction to LSD-25.

We have seen that compounds like MLD-41 produce tolerance to LSD perhaps even better than LSD produces tolerance to itself. Of special significance is the fact that UML-491, according to the experiments

of Balestrieri[12] and myself, also produces cross-tolerance to LSD, but not very effectively. Table 7-8 illustrates the way in which preliminary data give the order of production of cross-tolerance by derivatives and congeners of LSD. It is not generally accepted that UML-491 belongs in this group of psychotomimetic compounds. However, the study of its side effects and the similarity of its action to that of LSD in autistic and schizophrenic children[14] make it likely that UML-491 and LSD-25 both belong to the same group of compounds as far as psychotomimetic activity is concerned. In support of this point of view are the data on fish,[15] which show similar surfacing properties, and snails, which go into regular convulsive seizures, produced by both compounds.

Balestrieri[9,12,13] has made a statistical evaluation of cross-tolerance produced by mescaline, BOL-148, JB-336, and psilocybin. The chemical structure of mescaline, of course, is very different from that of LSD. Balestrieri found that mescaline activity was reduced in subjects who had acquired a tolerance to LSD-25. However, cross-tolerance to LSD-25 was not as easily developed by mescaline. The work of Balestrieri was confirmed by Wolbach and coworkers in humans, and by Freedman and his coworkers in rats.

Content Analysis[7]

Kornetsky[7] systematized and analyzed the symptoms described by two different observers in 141 experimental sessions on 31 subjects who had taken LSD-25 in doses up to 225 μg. The subjects were paid, nonpsychotic adult volunteers, all of superior intelligence.

The raw data used were the summaries of symptoms reported to, or observed by, the experimenters. These summaries were made by the two investigators separately on different subjects. They did not anticipate that a content analysis would be made. They merely reported their observations.

Subjects were administered LSD-25 orally in single doses up to 225 μg and observed for at least 4 hours. Nineteen of the subjects were used at more than one dose level. For convenience of analysis the data were grouped into six dose levels, 0 μg (water), 1–25 μg, 26–50 μg, 51–75 μg, 76–100 μg, and 101+ μg. The number of subjects at each of these dose levels was 20, 8, 25, 10, 15, and 6, respectively.

The analyses of the summaries were made by grouping the data

into a number of arbitrarily selected descriptive parameters: euphoria, dysphoria, distortions in perception, "neurotic," and psychotic. The signs and symptoms selected for each were:

(1) Euphoria: (a) fatuousness, (b) laughter, (c) elation.

(2) Dysphoria: (a) depression, (b) feelings of sadness.

(3) Distortions in perception: (a) auditory, (b) visual, (c) taste, (d) time.

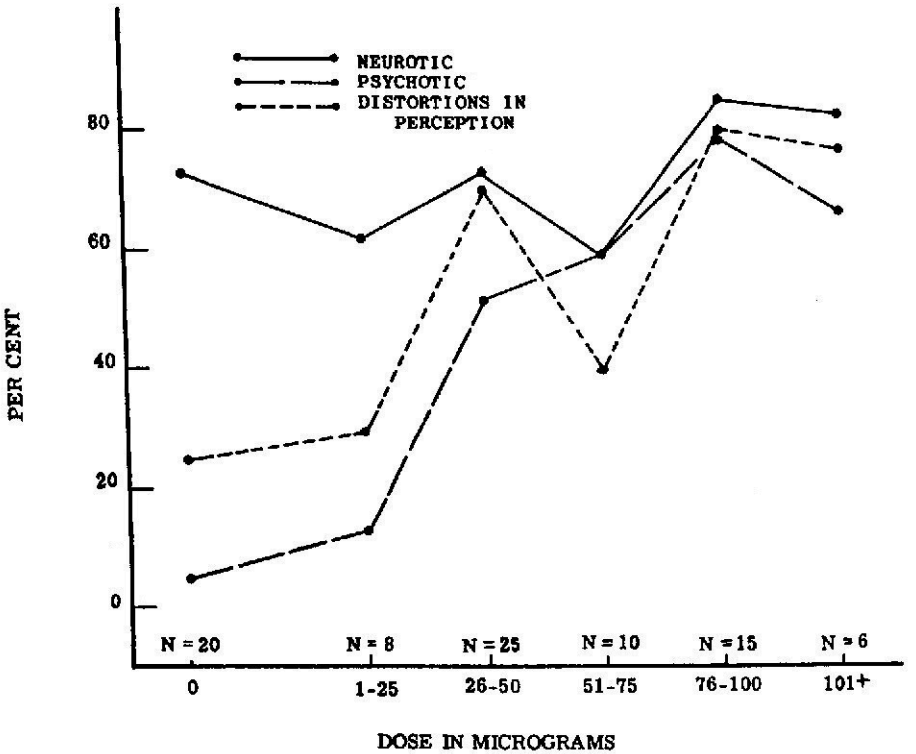


FIG. 7-6. As the dose of LSD increases there is a general increase in the number of subjects reporting psychoticlike phenomena. This relationship does not exist between dose and neurotic signs.

(4) "Neurotic": (a) nervousness, (b) anxiety, (c) inner trembling, (d) sweating, (e) moist palms, (f) palpitations–tachycardia, (g) difficulty in breathing, (h) trembling, (i) increased pulse rate, (j) feelings of hotness or coldness, (k) polyuria.

(5) Psychotic: (a) hallucinations, (b) delusions, (c) depersonalization, (d) illusions, (e) dreamlike feelings, (f) feelings of strangeness, (g) confusion, (h) suspiciousness, (i) uncommunicativeness.

Fig. 7-6 indicates that as the dose increases, there is a general increase in the number of subjects reporting psychoticlike phenomena and distortions in perception; however, there is not this positive relationship between dose and neurotic signs. Fig. 7-7 shows a nonlinear relationship between the dose and euphoric signs with optimum euphoria appearing between 51 and 75 μg. Optimum dysphoria

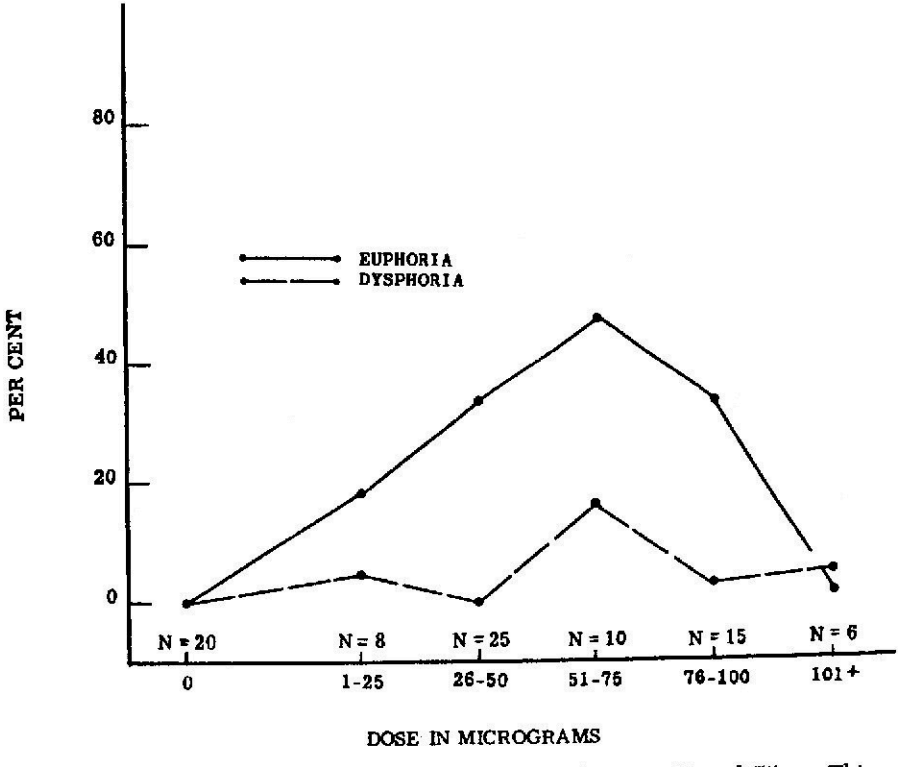


FIG. 7-7. Optimum euphoria and optimum dysphoria between 51 and 75 μg. This fits in with the use of this dose range of LSD in psychoanalytically oriented psychotherapy.

appears here between 51 and 75 μg. The finding of an optimum dose for the manifestation of euphoria is quite compatible with the reports of subjects who have been used at a variety of dose levels. In addition, this finding of an optimum dose for euphoria seems to coincide roughly with what is considered the optimum dose for the use of LSD-25 in psychotherapy.

Distinction between Psychoanalytic (Psycholytic) and Psychedelic Therapy[11, 16, 22]

The sociological aspects of the rather fantastic controversy precipitated by the discovery of LSD do not concern us here. However, the use of LSD and similar drugs is currently practiced in the Western world as a part of psychoanalytic therapy and as a method of psychedelic therapy, especially in the treatment of alcoholism. In psychoanalytic therapy the dose may be from 30–150 μg, perhaps higher. In psychedelic therapy the dose may reach 2000 μg. The difficulties involved in proving the value of the use of LSD and similar compounds in psychotherapy, *ipso facto* apply to studies of psychotherapy in general. A critical analysis of the use of any drug in psychotherapy includes, therefore, the problems of methodology of psychotherapy itself. It is not the scope of this presentation to discuss this aspect except to mention that at present statistical studies seem to be much less important than careful within-patient records and analyses. Verbalization, insight, recall, reliving, transference, and abreaction are all part of the psychoanalytically oriented therapy with LSD. Psychedelic therapy, on the other hand, produces a peak experience with a single high dose of LSD with the therapy built around this peak experience. Alnaes[11] of Norway stresses Johnsen's views on the value of the psychedelic experience. The patient becomes involved during the psychedelic experience in existential problems, searching for the meaning of life, for new values in adaptation and new orientations to his fellow man. There appears not only the release of unconscious material in connection with personal conflicts, and an unconscious re-evaluation of personal conflicts, but also experiences on the cosmic and archetypic levels.

To explain the meaning of the psychedelic experience as viewed by some of the workers, the plan of treatment is to bring the patient through certain levels of reaction where there is complete surrender to a deep and meaningful experience. As the high dose of LSD begins to work, it is held that at the first level of reaction there is ego depression accompanied primarily by psychosomatic symptoms. These symptoms are connected with the autonomic storm brought on by the drug. Before the loss of ego-feeling or ego-death, the patients

describe "wave energy flow, a feeling of biological life-flow, and the appearance of ecstatic visions."

The second level is characterized by a feeling of separation between body and mind, accompanied by hallucinations—a constantly changing panorama of light impressions, new experiences and visions, a feeling of atom explosions and Sputniklike processes. The patient becomes a cosmonaut immersed in mystical and magic mythological experiences, with the appearance of archetypal figures and heroes and demons. It is an experience full of new realities in another world—in truth, a voyage into the vast inner space of the opening unconscious.

The third level is the event of "rebirth" and the coming back to the usual realities and "normal" ego functions.

It may interest the reader to have as an example a fragment of the verbalization of a 30-year-old successful artist who sought a psychedelic experience. He was given 300 μg of LSD. An abbreviated set of quotations from the first 2 hours of a verbatim recording follows:

Everything interpenetrates.
Cramps in left leg (four times in life before).
It is not only visual but beauty of meaning to Alice.
Let's put the room back in order.
I wonder where I have been when I wasn't here?
Walking back into the future.
To take this back into the real world to cut the shit.
I'm glad I'm finding out this nice stuff about me now.
Experiencing things I couldn't have imagined. I hope the physical structure of this room is adequate to take all this.
I wonder why I fabricated this kind of existence out of all the kinds. It must be a part of me.
I wonder why the universe would take such a complex way to unveil itself! Everything contained in this moment.

Effect upon Communication Processes[21]

Nonpsychotic Subjects

These experiments were done with Lennard[20,21] of the Bureau of Applied Social Research, Columbia University. Doses of 50 μg and 100 μg of LSD-25 were compared with a second experiment performed 5 months later. The following types of data were available for this preliminary analysis:

Condition 1: A typed script from a tape recording of a group of

four subjects (three female and one male) under the influence of LSD-25, discussing the topic "The Place of Women in Society."

Condition 2: A typed script from a tape recording of this group discussing the same topic after they had received placebos.

Condition 3: Typed scripts from tape recordings of group discussions in which members of our experimental group participated individually. The data used came from earlier sessions where the

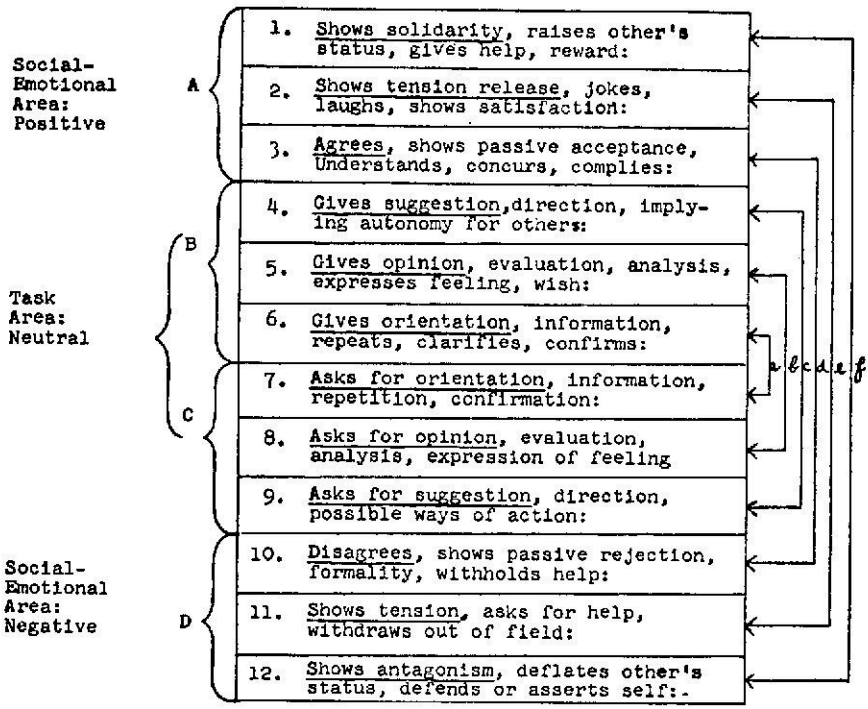


FIG. 7-8. The system of categories used in observation and their major relations: *a:* Problems of communication (6, 7); *b:* Problems of evaluation (5, 8); *c:* Problems of control (4, 9); *d:* Problems of decision (3, 10); *e:* Problems of tension reduction (2, 11); *f:* Problems of reintegration (1, 12); *A:* Positive reactions; *B:* Attempted answers; *C:* Questions; *D:* Negative reactions. (From Lennard et al.[21])

experimental member from the present group was under a placebo or "normal" condition, while the others in his group were under the influence of LSD-25.

The study of the effect of LSD-25 on group behavior was made through the utilization of certain basic and easily quantifiable variables present. Two types of variables were used:

(1) Formal characteristics of communication: *quantity of speech* (number of words, number of lines, number of thought units); *direction of communication* (who initiates; amount of communication; to whom addressed); *other characteristics of communication* (interruptions, unfinished thought units, etc.).

(2) A system of categories devised by Bales for the analysis of group interaction. Among the various methods of analyzing interaction now available, the Bales system has been most widely used, thus providing us with a body of comparative data. The system of categories employed is described in Fig. 7-8.

Some of the patterns of group communication under LSD-25 that were suggested by the exploratory study were as follows:

(1) Verbal output by the group members under the influence of the drug was restricted or shortened.

(2) In groups where some members had been given LSD-25 in the presence of group members who had not been given LSD-25, there was a tendency for those who had not received the drug to increase their communication output.

(3) When all group members were given LSD-25, there was a marked reduction in negative interpersonal responses. It would appear that disruptive social behavior may be reduced spontaneously when members of a group operate under a common threat, which here was the need to function socially under the effect of the drug.

(4) The ratio between the amounts of task activity and socioemotional activity did not differ for the group under condition "LSD-25" compared with condition "normal." The stability of this relationship under varying doses and conditions deserves further examination. The pattern of group communication seemed less impaired by the drug than the changes observed in individual functioning had led us to expect.

(5) The ratio of questions to answers, as well as the ratio of orientation to evaluative responses, is higher in the group under condition "LSD-25" than under condition "normal." This might have been an attempt on the part of the group to restore connective clarity despite the impairment felt because of the drug.

Communication in Schizophrenics[20]

A study of group processes was set up which involved contact of a schizophrenic patient only with nonpsychotic individuals. The group

consisted of the patient (chronic schizophrenic), a volunteer of the same sex and of about the same age as the patient, and the interviewer. These experiments were conducted at the State Hospital, Central Islip, N.Y.

Three elements were used to structure the interview: (1) the patient was given either a placebo or LSD-25 orally; (2) the questionnaire previously employed to study LSD in nonpsychotics was used as a basis for interrogation; and (3) selected pictures of the Thematic Apperception Test were discussed. Free discussion by the patient was preferred. Games were used to establish contact.

The taped interviews were transcribed and a content analysis of the group interactions was made (double blind) by content analysis technique and by modification of the Bales categories. The general nature of the technique used was the same as that in the foregoing description of the analysis of the group process in nonpsychotic individuals.

The experiments were performed on schizophrenics who were well enough to communicate in the group situation and who usually reacted to 50 μg of LSD-25 when taken orally. (The questionnaire has not been found to be as useful with schizophrenic patients as with nonpsychotic subjects.) Data for two series were partly analyzed. Each series involved one schizophrenic patient over a period of several months. All of the group sessions were recorded and transcribed. The findings reported here are based upon eight sessions for Patient A (four placebo and four LSD) and on seven sessions for Patient B (three placebo and four LSD). The transcript of some individual sessions exceeded 100 pages.

Our data covered only a small fraction of the things which ought to be done in this type of experiment. We could have studied posture, movements, gestures, and tonal characteristics of the interaction. However, verbal patterns were emphasized, and the unit of analysis was the sentence. Our data illustrate a finding in connection with a very simple variable: the ratio of the number of times that the patient talked to the number of times the volunteer talked. If the ratio is studied over time, there is an upward movement, as shown; the patient talks somewhat more, relative to the other people, but then some tolerance may develop, and the ratio decreases. The number of patient actions and the number of volunteer actions for the hour were tabulated. The ratio of one to the other is an index of the patient's participation relative to that of the volunteer. It may mean, for ex-

ample, that the patient talked about four times as often as the volunteer during the first MLD hour. As time goes on, the patient does talk more, relative to the others in the group. How much this is due to the LSD and how much to the continued interaction with people the patient knows, I don't think we can say.

Other variables, which show an increase in patients' references dealing with feelings, were studied. The findings are similar to those in psychotherapy groups in which both the therapist and the patient exhibit more affective communication as therapy proceeds.

Schizophrenic patients made many comments dealing with social expectations, role relationships (especially problems of sex-role identification) and discussion of what is proper behavior and what is not. Under LSD, during later sessions, there were many comments about contradictory signals given to patients by their parents. There was not much childhood or very early material, but there was a good deal of material concerned with adolescence and early youth.

Measurement of Feelings

The application of these data and concepts to the consideration of the mind as a tissue meets with certain difficulties. The brain has often been compared to a computer. But the human brain is characterized not only by its ability to store information, but also by its capacity to forget the infinite number of sensory inputs which occur constantly and which began at the moment of birth. The forgetting mechanism of the brain operates in a most spectacular way. A moment's reflection will show that the eye itself, on observing any scene, receives an infinite number of signals; yet the individual invariably forgets the infinite number of details of the scene unless a particular event is of special importance to the observer. The psychological development of the individual is organized so that the forgetting mechanism may be in one sense more important, in numbers at least, and often in quality, than the retrieval of stored information. For example, the forgetting mechanism in patients is inexplicably somewhat extraordinary at times. I can readily think of four patients who function very well in their daily lives, but who have the following amnesias:

Patient 1: A married man of 38, president of his company, who

had no memory of his father and mother before age 9. However, during that period he remembered all of his relatives—uncles, cousins, aunts —without difficulty. During analysis he remembered one incident connected with his mother: she locked him in a closet when he was about 7 years old. He remembered muttering quietly, "You son-of-a-bitch."

Patient 2: A married man of 40 with no memory of either his father or his brother before 8. There were vivid memories of his mother, as well as other members of the family. Using Sansert to break the amnesia, he regressed to age 4, when the single memory of his father appeared during a session. He recalled being beaten with a cat-of-nine-tails by the father and feeling the leather over his bare legs. He knew that he was 4 because of remembering exactly the way he was dressed. His mother stood by, shouting "Give it to him, give it to him."

Patient 3: A pregnant woman of 25, mother of two children, who had no memory of her mother before 8, when her father died.

Patient 4: A student of 22 with asthma who spent most of his life before age 10 with his mother in Florida. He had few memories of that part of his life. There were no memories of his mother. I was able to obtain motion pictures of his life with his mother before age 10. Neither the analytic procedure nor his seeing the motion pictures was able to resurrect any memories of his mother during that period.

One of the striking characteristics of forgetting from the Freudian point of view is that it is always due to unconscious, at present unmeasurable processes. One cannot consciously decide to forget. Another interesting mechanism of forgetting that the brain has is illustrated by what I very often see during the psychoanalysis of patients. The patient will come in saying, "I have a dream that I want to go over," and then, in an instant, says, "I can't remember anything about the dream." It is almost as if a switch were thrown within the brain, a forgetting switch, which in a subsequent session may be reversed. Or even in the same interview, the patient may say suddenly, "It has all come back to me now." Certainly, all of us have similar things happen, but to have a lengthy dream, full of unconscious conflicts, suddenly be forgotten and then remembered in this spectacular way, shows how important the mechanism of forgetting is and how important it is for us to develop drugs like LSD-25 to help us reverse the forgetting process and to enable the conflict between id,

ego, and superego to be scrutinized by the patient himself. Flash forgetting and flash recall are both worthy of investigation, especially in connection with unconscious conflicts.

Finally, a very important differentiation must be made between the brain as a tissue and the brain as the source of feelings. When we speak of the brain as a tissue, we at once think of measurable things:

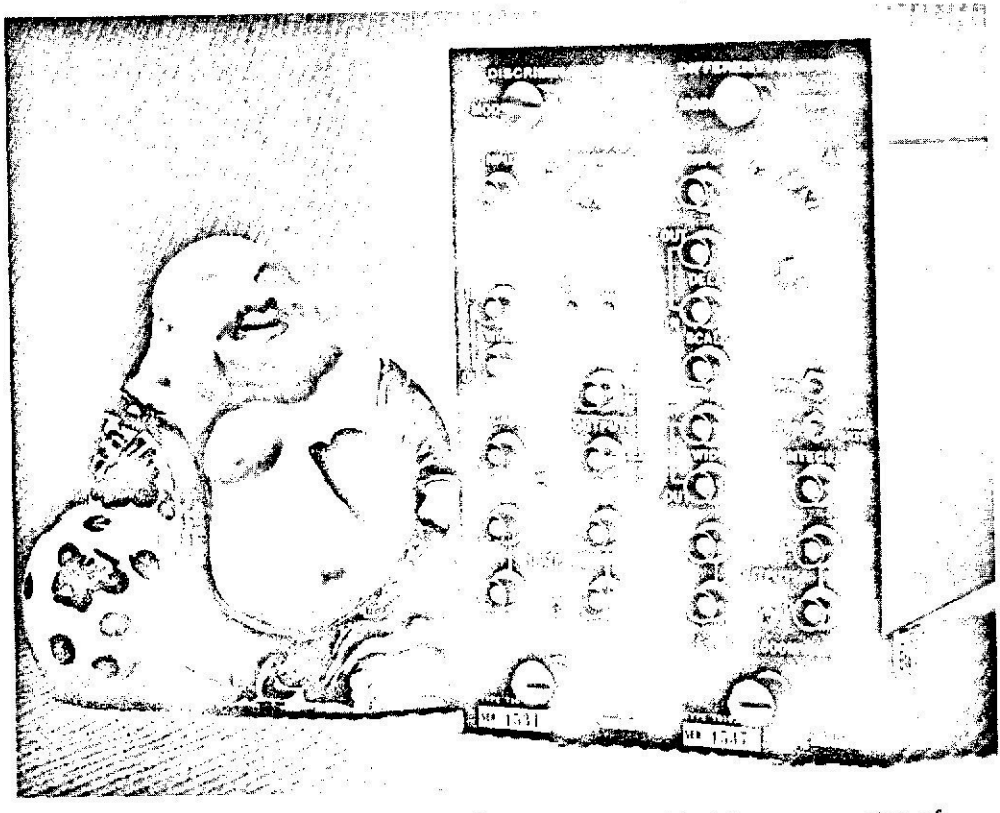


FIG. 7-9. "Counting Happiness" perhaps represents pictorially an expression of what difficulties the investigator faces when he attempts to measure feelings. (Courtesy of EG&G Company, Salem, Mass.)

the size of cells, the discharge of electrical energy, the metabolism of cells, and so on. When we speak of consciousness, that part of the brain which stores and assesses the feelings of the individual (the loves, the hates, the frustrations, the anxieties) and integrates these, we are confronted with a system which, up to now, has not yet been

measured. We cannot measure feelings. Any attempt at measurement always refers to a frame of reference involving similar feelings.

Fig 7-9 illustrates perhaps more poignantly the difficulty of considering the mind as a tissue. The difference between the complicated feelings of happiness of the porcelain god Hotei* and the predictable behavior of the instrument panel beautifully demonstrates all of the difficulties involved in measuring feelings.

The significance of events in terms of feelings always includes the past, present, and future significance of an event to the individual. The integration of these feelings by man, which I consider to be a definition of consciousness, has a frame of reference very different from the measurable quantities of the brain itself.[23] I don't believe that at present we can build a bridge between the measurable qualities of the brain and the unmeasurable qualities of the mind. I cannot, I confess, visualize how this can be done in the future.

Dr. Manuel H. Gorin has written:

I've had your letter before me for several days trying to comment constructively on the concluding sections of your paper for the *Mind as a Tissue* conference. My problem is that I am lost when you bring in "id, ego, and superego." To me these are nonphenomenal concepts and as such cannot be "measured" or "classified" in a biological sense. I have no difficulty in conceiving in a phenomenal manner the states of anxiety, frustration, depression, euphoria, fear, empathy, etc.

Nor am I pessimistic about developing a phenomenal approach toward "memory recall" or "amnesia," and can conceive of complex phenomena involving mental processes that require the presence of a particular individual or its symbol to occur (i.e., mother and asthma). If the sequential relationship of amino acids in proteins can be unraveled, I can hope that the sequentially important "imprinting" processes in biological systems can also be unraveled. They are probably rather limited in number since by definition they would be completed rather early in the development of the brain. From the point of view of completion of the imprinting processes, the processes of "learning," "memory recall," "feelings," etc. would all seem amenable to phenomenal treatment.

* Hotei was a Zen priest of the Shu period of China and is said to have died in March, 917, at the temple of Gokurin while he was seated on a rock in the midst of his prayers. The people call him Hotei Osho. He is conspicuous for his potbelly, and he nearly always carries a staff across his shoulder on which is slung a big bag containing all his personal belongings. He goes out begging for alms and all that is given him he puts into this bag. He is very fond of children, and his expression when playing with them is one of delight and pleasure. It is because of his delight in playing with children that he is included among the Seven Gods of Fortune.

Application of chemical kinetics to these concepts does not necessarily lead to phenomena involving monotonically (smoothly) increasing or decreasing concentrations. The significant factor may be a chemical switch (or shunt). Thus, a site occupied by LSD may send an impulse in one direction while that same site unoccupied would send that impulse down another path. A complex circuit of such switches in series and parallel, lock in or release a memory. Always lurking around the corner is E_T which steps in to moderate or eliminate the action of LSD. Since the half-life of LSD on the site is about an hour or less, and that of E_T about 24 hours, the opening or closing of such switches might occur in very complicated time sequences. A memory can be completely buried if insufficient LSD is secreted by ordinary arousal mechanisms to overcome the protective presence of E_T or that of more reactive sites.

While the above may be sheer speculative nonsense, the relationship of LSD (or more broadly L) and E_T is phenomenal, and I would assume that the release of deep-seated memories by LSD is phenomenal. Experimental work designed to connect these phenomena might in a sense "measure" feelings.

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