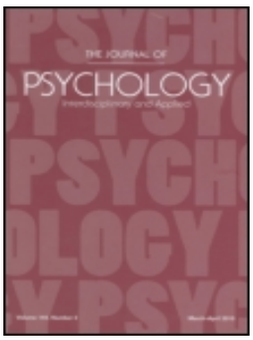

The Journal of Psychology

ISSN: 0022-3980 (Print) 1940-1019 (Online) Journal homepage: http://www.tandfonline.com/loi/vjrl20

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To cite this article: H. A. Abramson , M. E. Jarvik , M. H. Gorin & M. W. Hirsch (1956) Lysergic Acid Diethylamide (LSD-25): XVII. Tolerance Development and its Relationship to a Theory of Psychosis, The Journal of Psychology, 41:1, 81-105, DOI: 10.1080/00223980.1956.9916206

To link to this article: http://dx.doi.org/10.1080/00223980.1956.9916206

Published as a separate and in *The Journal of Psychology*, 1956, 41, 81-105.

LYSERGIC ACID DIETHYLAMIDE (LSD-25): XVII. TOLERANCE DEVELOPMENT AND ITS RELATIONSHIP TO A THEORY OF PSYCHOSIS*[1]

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A. INTRODUCTION

The first observations recognized as the development of tolerance to lysergic acid diethylamide (LSD-25) are apparently those of Isbell *et al.* (6) who studied drug addicts at the NIMH Addiction Research Center. From these data it can be said that LSD-25 is its own best antidote.

The purpose of the present experiment was to determine how lysergic acid diethylamide antidotes itself, that is, evokes tolerance under two conditions: (*a*) high doses repeated daily and, (*b*) low doses increased on successive daily administration Another purpose was to determine whether administration of d-l-brom lysergic acid diethylamide (BOL-148), an LSD-25 derivative, would evoke tolerance to LSD-25 given the following day. We have found a marked diminution of response to successive administrations of LSD-25 as measured by direct observation and by our questionnaire (2). BOL-148, however, did not noticeably inhibit the usual LSD-25 response.

Savage (8) studied the therapeutic effects of LSD-25 on depressed patients. Starting them "on an oral dose of 20 micrograms, which was increased daily to a point where a definite psychophysiological effect could be observed," he then gave that dose daily for one month and drew the following conclusion: "Improvement obtained during the course of LSD therapy was not greater than that obtained without its use in comparable cases." Our findings in the present experiment suggest that the anticipated therapeutic effects of LSD-25 did not appear due to the development of tolerance.

Lovell *et al.* (7), in reporting no side effects from LSD-25 given in increasing doses for 9-11 days, apparently were not aware of the "autodoting" effects of the drug. This phenomena can also be found by a careful study of the work of Frederking (4). Hoch, Cattell, and Pennes (5) found that

*Received in the Editorial Office on September 7, 1955, and published immediately at Provincetown, Massachusetts.

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This investigation was aided in part by a grant from the Josiah Macy, Jr. Foundation, New York City.

some patients who received LSD-25 responded inconsistently from experiment to experiment, while others gave similar responses. The variant results may be related to the time interval between experiments and development of tolerance.

B. Method

1. *Subjects*

Three subjects were used in this experiment. All had served as subjects at least six times and as many as 50 times before the present experiment. Subject *A* was a 26-year-old female weighing 145 pounds. Subject *B* was a 38-year-old male whose weight was 170 pounds. Subject *C* was a 39-year-old female, weight 132 pounds. All subjects were in good health, and all were college graduates.

2. *Experiments*

Subject *A* received 100 micrograms of LSD-25 at 10:00 A.M. on six consecutive days. Five days later she received 100 micrograms of LSD-25 at 9:25 A.M.

Subject *B* received 100 micrograms of LSD-25 at 7:00 P.M. on three consecutive days. In a second series of experiments he received five micrograms of LSD-25 at 9:30 A.M. and at 8:00 P.M. of the first day, 10 micrograms at 9:45 A.M. of the second day, and 25 micrograms at 9:45 A.M. and at 8:30 P.M. of the third day. On the fourth day he received 75 micrograms at 10:30 A.M., and on the last day, at 10:40 A.M., he received 100 micrograms of LSD-25.

Subject *C* also participated in two series of experiments. In the first series she received increasing doses of LSD-25 beginning with five micrograms administered at 9:00 A.M. and 5:30 P.M. The following day she received 10 micrograms of the drug at 8:30 A.M. and 5:30 P.M. On the third day she received 20 micrograms of the drug at 9:00 A.M. and 4:30 P.M. On the fourth day, she received 50 micrograms at 10:30 A.M., and on the last day, 75 micrograms at 9:00 A.M. In the second series of experiments the subject received 100 micrograms of BOL-148 at 11:30 A.M. and 6:30 P.M. The next day she received 100 micrograms of BOL-148 at 9:00 A.M. and 10:00 P.M. She received 25 micrograms of LSD-25 at 9:00 P.M. of the third day.

C. Procedure

The subjects had little or no food before receiving the drug which was given orally in 75 cc of tap water. Following ingestion of the drug the subjects responded to a questionnaire ½ hour after receiving the drug and,

in most cases, at four hourly intervals thereafter. The questionnaire contained 47 questions inquiring about the subject's physiological and perceptual state and is reproduced in a previous paper (2). Positive responses ranged from + to +++++, indicating the severity of the symptom present. Subjects also indicated whether normal or not, in the following psychic areas: motor behavior, control, consciousness, concentration, mood, attitude toward environment, orientation, memory, and hallucinations.

D. Results

The number of responses given during each experiment and the specific responses made are summarized here. The results obtained from each subject will be reported separately. Statistical analysis and grouping of the data is not warranted with so few subjects.

1. *Subject A*

This subject received 100 micrograms of the drug on six successive days and once again five days later. Table 1 indicates the psychic areas in which changes were reported and the total number of times psychic changes were

TABLE 1
NUMBER OF TIMES SUBJECT *A* REPORTED CERTAIN PSYCHIC CHANGES
(Subject was questioned six times during each of seven experiments with 100 micrograms of LSD-25.)

Area	Number of times changes were reported Day 1*	2	3	4	5	6	11
1. Motor behavior	4	0	0	0	0	0	0
2. Control	0	0	0	0	0	0	0
3. Consciousness	0	0	0	0	0	0	0
4. Concentration	0	0	0	0	0	0	0
5. Mood	0	0	0	0	0	0	0
6. Attitude toward environment	0	0	0	0	0	0	0
7. Orientation	0	0	0	0	0	0	0
8. Memory	0	0	0	0	0	0	0
9. Hallucinations	3	1	0	0	0	0	0
Total	7	1	0	0	0	0	0

*Subject was questioned only five times on this day.

reported during the day. The subject was questioned six times. There were hallucinations on the first two days and changes in motor behavior on the first day. On subsequent days the subject was normal in all areas.

Figure 1 shows the total number of questions receiving positive responses during each question period on each experimental day and the total number of responses made each day.

The subject responded at ½, 1½, 2½, 3½, 4½, and more than 4½ hours after receiving the drug, except on the first day when there was no response during the last interval The boxed insert on the figure shows that the total number of responses went from 30 to 13, to 15, and to 7 on the

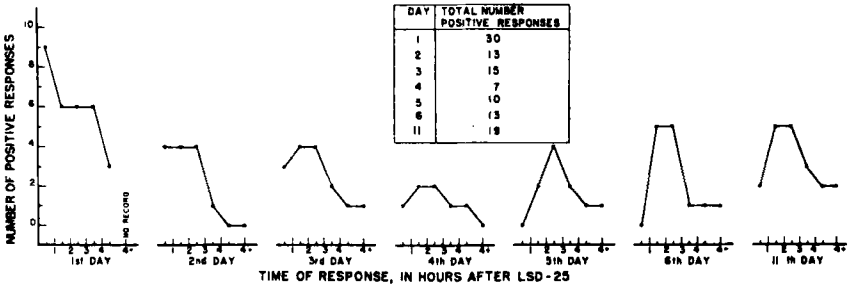

FIGURE 1

Total number of positive questionnaire responses given by Subject *A* on Section I during each of seven experiments. The subject received 100 micrograms of LSD-25 on six successive days and again after five days.

first four days, and then up to 10 on the fifth, and 13 on the sixth. Five days later, when the subject again received 100 micrograms of LSD-25 she gave a total of 19 responses. On the fifth day a decreased response occurred only during the first ½ hour. The maximum number of responses given during the last three intervals was two on all but the first day. On the eleventh day the number of responses given was greater than on the second day (except for the first ½ hour) but not as great as on the first day.

The hourly responses to each question on each experimental day are graphed in Figure 2. Where the same response was given on more than one day, the curves appear beneath each other. Only those questions receiving at least one positive response appear on the graph. Two questions received positive responses during every experiment, but with varying frequency: (No. 35) "Is your eyesight blurred?," and (No. 42) "Do you tremble inside?" Blurred eyesight was least frequent on the sixth day, while inner trembling was least prominent on the fourth day. The greatest response was given on the first and seventh days. Some symptoms, awareness of heartbeat (No. 19), heartbeat faster than usual (No. 20), and moist palms (No. 24), were reported only during the first experiment. Others, lips drawn back as if smiling (No. 12), diplopia (No. 37), and shapes and colors altered (No. 38), reported during the first few days disappeared completely in the middle days and reappeared on the sixth day. One symptom, objective vertigo (No. 14), was reported only on the first and fifth days.

Two symptoms, headache (No. 13) and dizziness (No. 15), appeared only in the later experiments. The magnitude of the responses seemed to vary with their frequency.

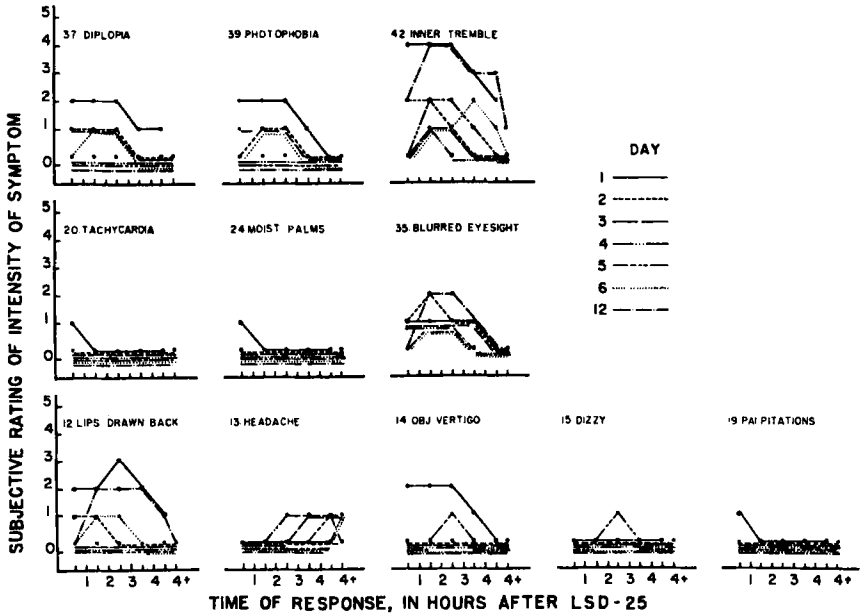

FIGURE 2

Subjective rating of intensity of each symptom reported by Subject *A* on Section I of the questionnaire. The subject received 100 micrograms of LSD-25 on six successive days and again after five days.

2. *Subject B*

This subject received 100 micrograms of LSD-25 on three successive days. Table 2 shows that during the first two there were changes in all psychic areas but one: no hallucinations occurred. On the third day there were alterations only in consciousness, concentration, and mood.

Figure 3 gives the number of positive responses made each day. There was a total of 64, 37, and 21 positive responses on the three days, respectively. Comparison of the time curves for these days clearly demonstrates the daily decline. Specific hourly responses made to each question appear in Figure 4. Only those questions receiving at least one positive response are graphed. The symptoms reported on all three days were: feeling of choking (No. 3), headache (No. 13), moist palms (No. 24), blurred eyesight

(No. 35), difficulty in focusing vision (No. 36), inner trembling (No. 42), weakness (No. 43), and fatigue (No. 44). Some symptoms were reported only on the first two days: decreased salivation (No. 5), objective vertigo (No. 14), dizziness (No. 15), unsteadiness (No. 16), sweating (No. 21),

TABLE 2
NUMBER OF TIMES SUBJECT *B* REPORTED CERTAIN PSYCHIC CHANGES
(Subject was questioned five times during each of three experiments with 100 micrograms of LSD-25.)

Area	Number of times changes were reported Day 1	Day 2	Day 3
1. Motor behavior	3	2	0
2. Control	3	3	0
3. Consciousness	2	3	1
4. Concentration	3	3	2
5. Mood	4	2	2
6. Attitude toward environment	3	2	0
7. Orientation	3	3	0
8. Memory	2	3	0
9. Hallucinations	0	0	0
Total	23	21	5

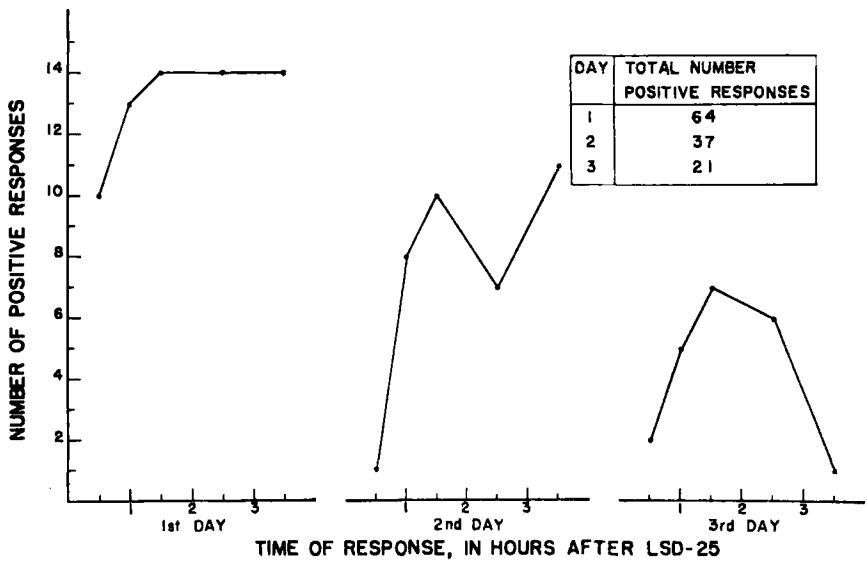

FIGURE 3
Total number of positive questionnaire responses given by Subject *B* on Section I during each of three experiments. The subject received 100 micrograms of LSD-25 on three successive days.

warmth (No. 22), photophobia (No. 39), apparent closeness of objects (No. 40), and a dream-like feeling (No. 46). On the first day, only, the subject reported dry taste in mouth (No. 8), lips drawn back as if smiling (No. 12), awareness of heartbeat (No. 19), pressure in ears (No. 32),

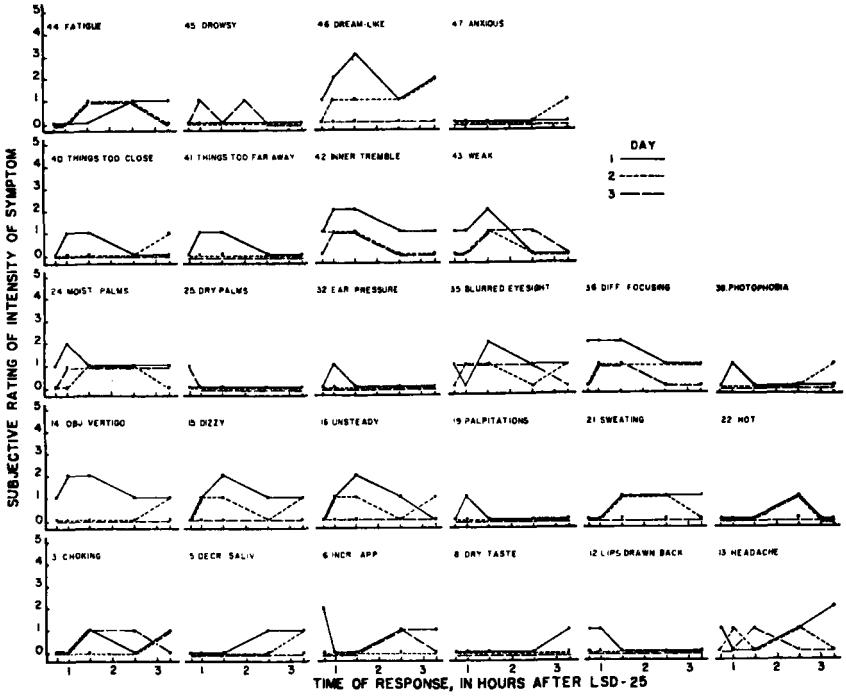

FIGURE 4

Subjective rating of intensity of each symptom reported by Subject *B* on Section I of the questionnaire. The subject received 100 micrograms of LSD-25 on three successive days.

and things seemed too far away (No. 41). Irregularly appearing responses were, increased appetite (No. 6), dry palms (No. 25), drowsiness (No. 45), and anxiety (No. 47). The responses generally appeared with less frequency and intensity on successive days.

In the second series of experiments for this subject he received increasing doses of LSD-25 on five successive days. The psychic changes which occurred are enumerated in Table 3. Not until the fourth day, when 75 micrograms of the drug was administered, was there a psychic change; the subject re-

ported a slight decrease in concentration. After 100 micrograms of LSD-25 a decrease in consciousness, slight confusion, and a feeling of remoteness from the environment were reported.

TABLE 3
NUMBER OF TIMES SUBJECT *B* REPORTED CERTAIN PSYCHIC CHANGES
(Subject was questioned six times during each of seven experiments with increasing doses of LSD-25.)

Area	Number of times changes were reported Day and dose 1-5 μg.	1a-5 μg.	2-10 μg.	3-25 μg.	3a-25 μg.	4-75 μg.	5-100 μg.
1. Motor behavior	0	0	0	0	0	0	0
2. Control	0	0	0	0	0	0	0
3. Consciousness	0	0	0	0	0	0	1
4. Concentration	0	0	0	0	0	2	1
5. Mood	0	0	0	0	0	0	0
6. Attitude toward environment	0	0	0	0	0	0	1
7. Orientation	0	0	0	0	0	0	0
8. Memory	0	0	0	0	0	0	0
9. Hallucinations	0	0	0	0	0	0	0
Total	0	0	0	0	0	2	3

Figure 5 shows the number of positive responses during each experiment. During four of the seven experiments there were none. After 75 and 100 micrograms the subject gave six positive responses. He did indicate that 2½ hours after receiving 10 micrograms of the drug he could detect its presence. The particular responses made are given in Figure 6. Under 25 micrograms of the drug, given in the morning, he reported drowsiness (No. 45) and awareness of the presence of LSD-25. Under 75 micrograms the subject reported difficulty in focusing his vision (No. 36), photophobia (No.

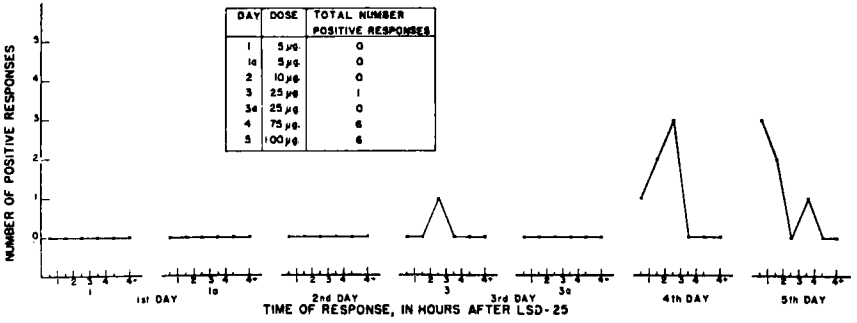

FIGURE 5

Total number of positive questionnaire responses given by Subject *B* on Section I during each of seven experiments. The subject received increasing doses of LSD-25 on successive days.

39), inner trembling (No. 42), and drowsiness (No. 45). After 100 micrograms he reported a feeling of choking (No. 3), unsteadiness (No. 16), blurred eyesight (No. 35), inner trembling (No. 42), fatigue (No. 44), and drowsiness (No. 45).

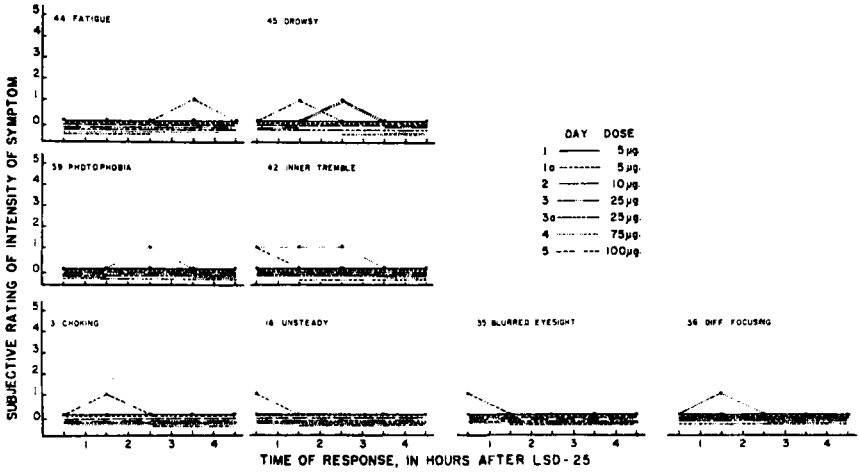

FIGURE 6

Subjective rating of intensity of each symptom reported by Subject *B* on Section I of the questionnaire. The subject received increasing doses of LSD-25 on successive days.

3. *Subject C*

Subject *C* also received increasing doses of LSD-25. The changes which occurred in the psychic areas appear in Table 4. No changes were reported until the fourth day, when the subject received 50 micrograms of the drug and reported impairment in motor behavior, control, concentration, and a detached attitude toward the environment. Under 100 micrograms she reported impaired coördination, decreased ability to concentrate, and a detached attitude toward the environment.

Figure 7 shows the total number of positive responses at each hour and each day. Under 5 and 10 micrograms of LSD-25 the subject gave no positive responses at either administration. Under 20 micrograms of the drug, taken in the morning, she gave a total of six responses. The same dose given in the evening evoked no positive response. Under 50 micrograms of LSD-25 on the following day, there was a total of 11 responses and under 75 micrograms there were 14.

The specific responses made under each dose are graphed in Figure 8. After the first dose of 20 micrograms of LSD-25 Subject *C* reported slight nausea (No. 2), dizziness (No. 15), heaviness of hands and feet (No. 30),

TABLE 4

NUMBER OF TIMES SUBJECT *C* REPORTED CERTAIN PSYCHIC CHANGES

(Subject was questioned five times during each of eight experiments with increasing doses of LSD-25.)

Area	Number of times changes were reported Day and Dose							
	1-5 µg.	1a-5 µg.	2-10 µg.	2a-10 µg.	3-20 µg.	3a-20 µg.	4-50 µg.	5-75 µg.
1. Motor behavior	0	0	0	0	0	0	1	1
2. Control	0	0	0	0	0	0	1	0
3. Consciousness	0	0	0	0	0	0	0	0
4. Concentration	0	0	0	0	0	0	1	3
5. Mood	0	0	0	0	0	0	0	0
6. Attitude toward environment	0	0	0	0	0	0	1	2
7. Orientation	0	0	0	0	0	0	0	0
8. Memory	0	0	0	0	0	0	0	0
9. Hallucinations	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	4	6

and weakness (No. 43). Under the second dose of 20 micrograms there were no positive responses. The symptoms reported after 50 micrograms of the drug were: unsteadiness (No. 16), peculiar feeling in hands and feet (No. 29), heaviness of hands and feet (No. 30), apparent alterations

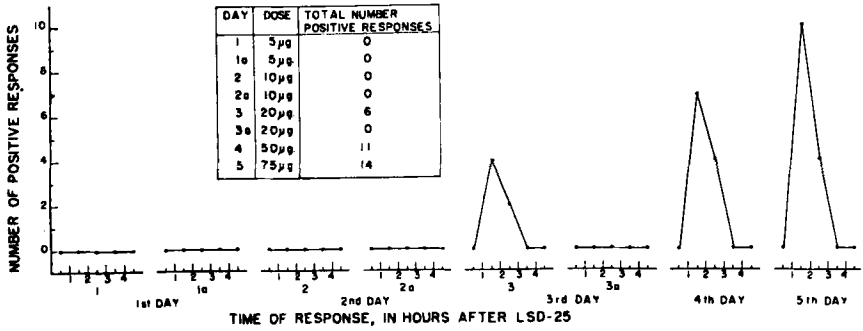

FIGURE 7

Total number of positive questionnaire responses given by Subject *C* on Section I during each of eight experiments. The subject received increasing doses of LSD-25 on successive days.

in shapes and colors (No. 38), inner trembling (No. 42), weakness (No. 43), and a dream-like feeling (No. 46).

Under the highest dose (75 micrograms) some symptoms appearing under 50 micrograms were reported: unsteadiness (No. 16), peculiar feeling

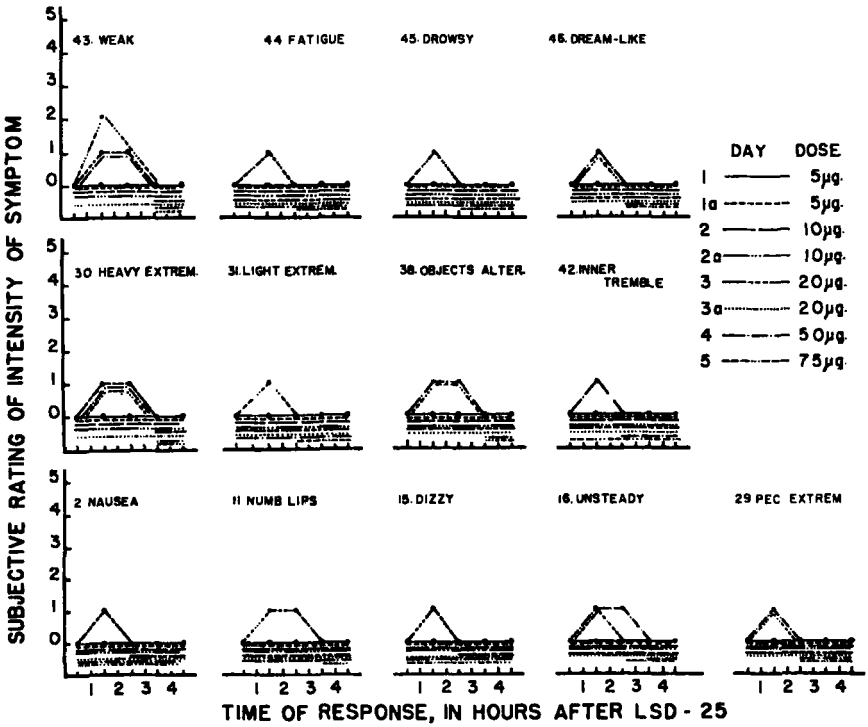

FIGURE 8

Subjective rating of intensity of each symptom reported by Subject *C* on Section I of the questionnaire. The subject received increasing doses of LSD-25 on successive days.

in hands and feet (No. 29), heaviness of hands and feet (No. 30) apparent alterations in shapes and colors (No. 38), weakness (No. 44), and dream-like feelings (No. 46). In addition to these responses, numb lips (No. 11), lightness of hands and feet (No. 31), fatigue (No. 44), and drowsiness (No. 45) were indicated. Most responses were made 1½ hours and some were made 2½ hours after the drug.

In the second series of experiments this subject received 100 micrograms of BOL-148 four times; then 25 micrograms of LSD-25. During the first

experiment there were changes in motor behavior, control, and concentration (see Table 5). There were no psychic changes during the subsequent experiments.

TABLE 5

NUMBER OF TIMES SUBJECT *C* REPORTED CERTAIN PSYCHIC CHANGES

(Subject was questioned six times during each of four experiments with 100 micrograms of BOL-148 and a fifth experiment with 25 micrograms of LSD-25.)

Area	Number of times changes were reported Day 1	1a	2	2a*	3
1. Motor behavior	3	0	0	0	0
2. Control	2	0	0	0	0
3. Consciousness	0	0	0	0	0
4. Concentration	3	0	0	0	0
5. Mood	0	0	0	0	0
6. Attitude toward environment	0	0	0	0	0
7. Orientation	0	0	0	0	0
8. Memory	0	0	0	0	0
9. Hallucinations	0	0	0	0	0
Total	8	0	0	0	0

*Subject was questioned only three times on this day.

Figure 9 shows that there were five positive responses following the first administration of BOL-148, nine after the second, five after the third, and none after the fourth. Under LSD-25 there was a total of 12 positive responses. No positive responses were given during the first ½ hour.

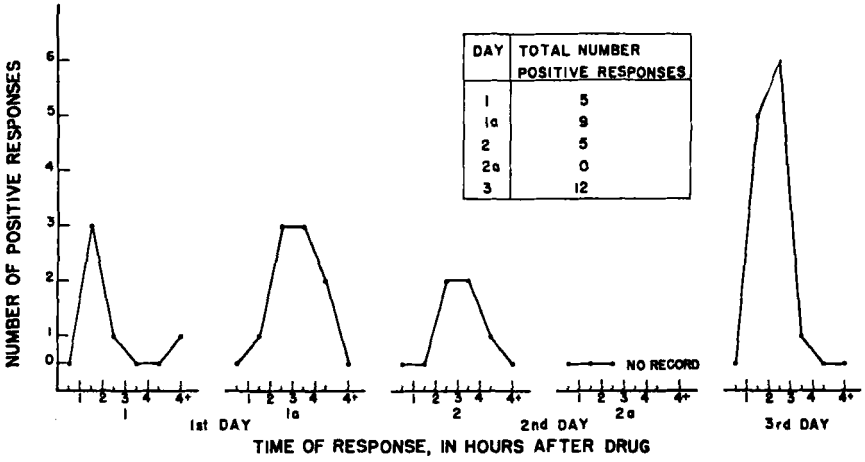

FIGURE 9

Total number of positive questionnaire responses given by Subject *C* on Section I during each of five experiments. The subject received 100 micrograms of BOL-148 twice daily for two days and 25 micrograms of LSD-25 on the third day.

Figure 10 indicates which questions received the positive responses during each experiment. After the first experiment with BOL-148 the subject reported a headache (No. 13), dizziness (No. 15), funny feelings on the skin (No. 28), and inner trembling (No. 42). Under the second dose

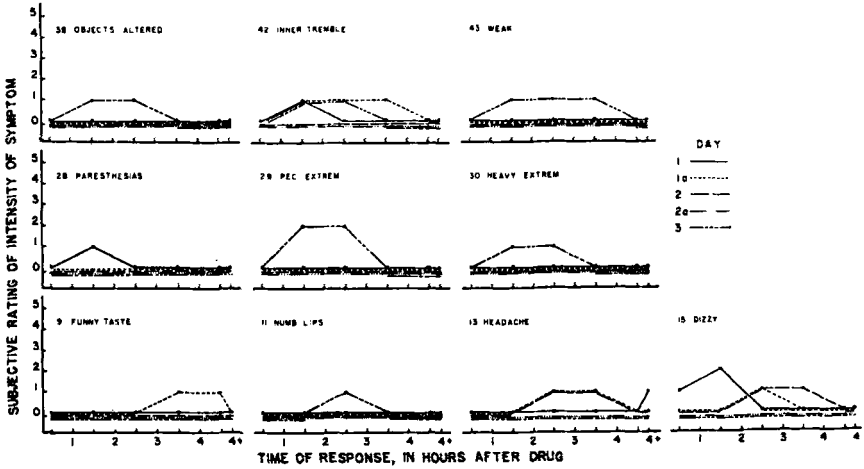

FIGURE 10

Subjective rating of intensity of each symptom reported by Subject C on Section I of the questionnaire. The subject received 100 micrograms of BOL-148 twice daily for two days and 25 micrograms of LSD-25 on the third day.

of BOL-148 in the evening of the first day she again reported a headache (No. 13), dizziness (No. 15), and inner trembling (No. 42), and also a funny taste in her mouth (No. 9). After BOL-148 given in the morning of the following day, headache (No. 13) and dizziness (No. 15) were reported. That evening she gave no positive responses to 100 micrograms of BOL-148. The next day the subject received 25 micrograms of LSD-25 and reported a total of six different symptoms: numb lips (No. 11), peculiar feeling in hands and feet (No. 29), heaviness in hands and feet (No. 30), apparent alterations in shapes and colors (No. 38), inner trembling (No. 42), and weakness (No. 43). All positive responses were given 2½ hours after receiving the drug and all symptoms but numb lips (No. 11) were also reported at 1½ hours.

Further study of the figures shows the hourly changes in severity of response to each question.

E. Discussion

The pattern of rapid development of tolerance, and its correspondingly rapid decline as reported by Isbell (6) is not typical of either immuno-type mechanisms or detoxification mechanisms. To provide possible insight into the autodote phenomenon, a mechanism has been formulated which involves the concept of a tolerance factor stoichiometrically related to the drug itself, and formed as a direct consequence of its physiological action.

Isbell (6) reports that tolerance is essentially completely lost in three days. Our data on rate of loss of tolerance are meager, and confined to Subject *A*. In this subject considerable tolerance remained five days after the last administration of the drug. This is shown by the experiment wherein tolerance had been established by the administration of six 100-microgram doses spaced 24 hours apart, and tested by a seventh dose administered five days later (on the eleventh day). Indirect evidence from the analysis of the data on Subjects *B* and *C* indicates that their patterns may be like that of Isbell's subjects, even though they are psychologically different in some other respects.

In any event, studies of a wide variety of individuals to determine whether characteristic patterns with respect to rate of development and loss of tolerance can be established and reproduced are indicated. The mechanism to be proposed offers a way to correlate the data in terms of a single rate constant (k_4) for any one series of experiments.

While this is undoubtedly an over-simplification of a very complex mechanism, the rate constant appears to define a key factor in the systems.

The extremely low dosage at which initial reaction is obtained is of the order of that required for systemic reactions of histamine and epinephrine. It points to an intrusion of LSD-25 into psychic reactions as an analog of physiologic substances normally involved in these reactions; the unique feature of the action is that tolerance is so quickly established, and yet so rapidly lost. In this respect it differs in kind from histamine and epinephrine where tolerance to repeated administration has not been successfully demonstrated except over much longer periods, if at all. Yet caution is necessary in formulating any theory, for while LSD-25 may be a physiologic substance involved in the neurological phenomena or related to such substances, it is possible that the method of administration sets up an artificial situation. By distributing the material through the ordinary channels it comes into contact with tissues where normally it might have no metabolic function, but still could have metabolic consequences. This would set in motion a detoxification mechanism wherein the LSD-25 is destroyed or neutralized (eliminated) before it can reach the centers of its primary reaction. In other

words, the establishment of tolerance could be an artifact of the method of administration not intimately connected with the mechanism of the psychic reactions induced by the drug.

In the speculations which follow, we are taking the view that the establishment of tolerance and the rapid loss of tolerance are part of a unified mechanism which also involves the psychic actions of the drug. The motivating factor in this choice of routes is that the pattern of rapid establishment and loss of tolerance is unique and not typical of detoxification mechanisms.

Finally, the question arises whether all the symptoms observed are due to a primary reaction of LSD-25 at one particular neurological site, or to several independent reactions at different sites.

The fact that Isbell (6) obtains complete tolerance (zero reaction by the questionnaire) after several weeks of administration can be used to support the notion of one primary reaction being involved. We have not obtained complete tolerance to larger doses of LSD-25, but our periods of administration are shorter, and zero reaction might have been obtained if administration had been continued over longer periods for Subjects *B* and *C*.

For Subject *A* it appears that complete tolerance to large doses (100 micrograms) cannot be obtained, even though partial tolerance is very quickly established and relatively slowly lost. The mechanism to be presented is sufficiently flexible to cover cases of complete and incomplete tolerance without invoking more than one primary reaction step.

1. *Stoichiometric Relations for Tolerance*

In the case of Subject *A*, there is almost a 1/1 correspondence between LSD-25 administered and the development of tolerance. Thus, 100 micrograms given on Day 1 protects the subject almost completely against a 100-microgram dose on Day 2, even though a reaction greater than a threshold reaction is observed.

In the case of Subject *B*, there is approximately a ½ correspondence between LSD-25 administered and the development of tolerance. Thus, 100 micrograms given on Day 1 protects the subject against about ½ of a 100-microgram dose on Day 2. Also, a total of 45 micrograms given in four doses on Days 1, 2, and 3 protects completely against 25 micrograms given 12 hours later on Day 3.

Similar correspondence exists in Subject *C*, and in Isbell's subjects. Obviously, since tolerance is being rapidly lost as well as established, only in cases where the rate of loss is relatively slow can the ideal stoichiometric 1/1 correspondence be approached. In all actual cases it would have to be less

than 1/1. Subject *A* does show a slow loss of tolerance, and the nearly 1/1 correspondence between initial dosage and tolerance 24 hours afterward ties in with the slow loss, and offers confirmation for the theory.

2. *Mechanism*

The mechanism to be suggested for the phenomenon of tolerance has four essential steps. In Step 1, LSD-25 (designated by *L*) interacts with a neuro-metabolic system, *E*, to cause symptoms, and becomes modified by combination with a component of this system and is converted to *LE*. Reaction 1 (see below) is reversible so that as long as *LE* is present, some reaction of LSD-25 might be observed.

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

When E_T comes in contact with LSD-25, it reacts with it to form *LE*. This is Step 3 in the mechanism, and it follows that when tolerance is established LSD-25 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 of the drug.

Since tolerance disappears in time, a fourth step is postulated wherein E_T is eliminated.

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

$$L + E \underset{k_5}{\overset{k_1}{\longleftrightarrow}} LE \qquad \underset{\longrightarrow}{(1)} \quad \underset{\longleftarrow}{(5)}$$

$$LE \xrightarrow{k_2} E_T + \text{Decomposition Products or Excretion} \qquad (2)$$

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

$$E_T \xrightarrow{k_4} \text{Decomposition Products or Excretion} \qquad (4)$$

All four reactions proceed while symptoms are occurring, but when the effect of the drug wears off only Reaction 4 continues to go on. 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-25 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-25 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-25, 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-25 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 occur. This seems to correspond to the situation with Subject *A*.

3. *Quantitative Considerations*

The quantitative considerations are based on the idea that Reaction 4 is of the first order with respect to E_T, and therefore that in any given time period between administrations a constant percentage of E_T will be lost irrespective of the initial amount present. Further, the loss of E_T with time will follow the equation:

$$\log \frac{A}{A - x} = k_4 t \qquad (6)$$

where A is the initial amount of E_T present and x is the amount of E_T lost in time, t. To illustrate the way x varies with k_4 Table 6 was computed from Equation (7) for a value of t of 24 hours.

TABLE 6

VALUES OF k_4 AS A FUNCTION OF LOSS OF TOLERANCE

Per cent loss of tolerance in 24 hours, x	k_4, hours^{-1}	$1/k_4$, hours
10	0.0043	232
20	0.0095	105
40	0.0210	47.6
60	0.0378	26.5
80	0.0662	15.1
90	0.0905	11.0
95	0.219	5.57
99	0.288	3.47

The units of k_4 are reciprocal time. The reciprocal of k_4 (Column 3) represents the time in hours at which

$$\text{In}\ \frac{100 - x}{100} = 1 \qquad (7)$$

or at which $x = 63.5$ per cent loss of tolerance.

Computations were based on a repetitive dose of LSD-25 of 100 micrograms every 24 hours. Three values of k_4 were used—one corresponding to 50 per cent loss of E_T in 24 hours, one to 40 per cent loss, and one to 60 per cent loss. Results are given in Table 7.

TABLE 7

E_T REMAINING ON SUCCESSIVE ADMINISTRATIONS OF LSD-25, WITH EACH OF THREE VALUES OF k_4

Admin. of LSD-25	1st	2nd	3rd	4th	5th	6th
Case I—k_4 Corresponds to 50 per cent Loss of E_T in 24 hours						
E_T Remaining*	0	50	75	87.5	93.75	97.88
Effective Dose of LSD-25**	100	50	25	12.5	6.25	2.12
Case II—k_4 Corresponds to 40 per cent Loss of E_T in 24 hours						
E_T Remaining*	0	60	96	117.6	130.6	138.4
Effective Dose of LSD-25**	100	40	4	— 17.6	— 30.6	— 38.4

Case III—k_4 Corresponds to 60 per cent Loss of E_T in 24 hours							
Admin. of LSD-25	1st	2nd	3rd	4th	5th	6th	7th
E_T Remaining*	0	40	56	62.4	65	66	66.4
Effective Dose of LSD-25**	100	60	44	37.6	35	34	33.6

*Twenty-four hours after most recent administration of LSD-25
**For this administration of LSD-25.

The three cases tabulated illustrate the critical effect of the value of k_4 on the build up of tolerance to the drug. A value of k_4 corresponding to 50 per cent loss of E_T allows build up of complete tolerance. If k_4 increases to 60 per cent, then only incomplete protection (tolerance) is obtained, and a 100-microgram dose will, after seven successive daily administrations, act like about 1/3 of this dose given initially. On the other hand, values of k_4 corresponding to less than 50 per cent loss allow build up of tolerance to more than the initial dose. Thus, for k_4 corresponding to 40 per cent loss per 24 hours a tolerance to 138.4 micrograms of the drug will build up in six days.

Another factor of interest is the effect of time between administrations.

An individual corresponding to Case III (60 per cent loss of E_T in 24 hours) would act like Case I (50 per cent loss) by reducing the time between administrations to 18 hours. This is computed from equation (6) as follows:

$$A = 100$$
$$x = 60$$
$$t = 24$$
$$\therefore \log \frac{100}{100 - 60} = 24k_4$$
$$\text{or } k_4 = \frac{\log}{24}\left(\frac{100}{40}\right) = \frac{\log 2.5}{24}$$
$$= \frac{0.398}{24} = 0.0167 \text{ hours}^{-1}$$

To calculate time for 50 per cent loss of E_T insert the value of k_4, 0.0167, into the equation and solve for t:

$$t = \frac{1}{0.0167} \log \frac{100}{100 - 50}$$
$$= \frac{\log 2}{0.0167} = \frac{0.300}{0.0167} = 18.0 \text{ hours.}$$

4. *Application of Model to Specific Cases*

a. Subject A. A value of k_4 corresponding to a 25 per cent loss of $E_T/24$ hours gives a pattern which is in reasonable agreement with the data. It predicts that the reactions on Days 2 and 11 should be roughly equivalent and slightly greater than those on Days 3, 4, 5, and 6.

TABLE 8

E_T REMAINING ON SEVEN SUCCESSIVE ADMINISTRATIONS OF LSD-25 AND EFFECTIVE DOSE PREDICTED

(k_4 corresponds to 25 per cent loss/24 hours)

Day	1	2	3	4	5	6	7	8	9	10	11
Dose	100	100	100	100	100	100	—	—	—	—	100
E_T*	—	75	131	173	204	228	246	185	139	104	78
Effective Dose	100	25	— 31	— 73	—104	—128	—	—	—	—	22

*Remaining from previous administration.

Note that after Day 2 complete tolerance to 100 micrograms is predicted, building up to a tolerance to almost 250 micrograms at the beginning of Day 6. It would be interesting to test this experimentally. Also, reactions on Days 3, 4, 5, and 6 should be equivalent.

b. Subject B. The two series on Subject *B* cannot be reconciled with the theory. In Series 1 wherein the 100 micrograms of the drug was administered in three equal doses 24 hours apart, the data correspond to a *k* value of 50 per cent, which predicts (Table 9).

TABLE 9
PREDICTED EFFECTIVE DOSE OF LSD-25
(k_4 corresponds to 50 per cent loss of E_T/24 hours)

Day	Effective Dose
1	100
2	50
3	25

In Series 2, a smaller rate constant of the order of 30 per cent loss/24 hours would have to be used to explain the data. This anomaly need not be explained with the present state of our knowledge, since sufficient data are not available to establish that either series are reproducible for a given individual. If this were established—then the model would have to be abandoned or modified.

In any event, in Series 2, this subject was made almost completely tolerant to a 75-microgram dose by the previous administration of only 70 micrograms in five doses over a three-day period.

c. Subject C. Computations based on a rate constant corresponding to 50 per cent loss per 24 hours gives a pattern similar to that observed in Subject *C*. For a 12-hour period the loss would be 29 per cent according to Equation (6). Results of computation with this value of k_4 are given in Table 10.

TABLE 10
E_T REMAINING WITH SUCCESSIVELY INCREASING DOSES OF LSD-25 AND EFFECTIVE DOSE PREDICTED
(k_4 corresponds to 50 per cent loss/24 hours)

Subject *C*	1st	2nd	3rd	4th	5th	6th	7th	8th
Dose, micrograms	5	5	10	10	20.0	20.0	50	75
Time elapsed since last administration, hours	—	12	12	12	12	12	12	24
E_T remaining from last administration	0	3.5	6.0	11.3	15.1	24.8	31.3	40.7
Effective dose, computed	5	1.5	4.0	— 1.3	4.9	— 4.8	18.7	34.3
Effective dose, found	*	*	*	*	*	*	**	***

*No reaction.

**Positive reaction somewhat less than that to 25 micrograms given in isolated dose.

***Positive reaction approximately like that found for 25 micrograms in isolated dose.

d. Isbell's Data. Isbell's (6) subjects, taken as a group, show correspondence with a k value of approximately 50 per cent loss per 24 hours (29 per cent loss in 12 hours). Carrying the computations through for his series, the following is obtained (Table 11), which predicts a 25-microgram response to the 75-microgram dose given in the seventh administration. By continuing to administer 75 micrograms/24 hours a build up of tolerance to a plateau value of 75 micrograms is predicted for this value of k_4. Having established this, if administration of LSD-25 is stopped, tolerance would decline according to a k_4 value of 50 per cent/24 hours (Table 12).

TABLE 11
E_T REMAINING WITH SUCCESSIVELY INCREASING DOSES OF LSD-25 AND EFFECTIVE DOSE PREDICTED
(k_4 corresponds to 50 per cent/24 hours)

Isbell's subjects	1st	2nd	3rd	4th	5th	6th	7th
Dose, micrograms	10	10	20	20	30	30	75
Time elapsed since previous administration, hours	—	12	12	12	12	12	12
E_T remaining from previous administration	0	7.1	12.1	22.8	31.8	41.9	50.1
Effective dose	10	2.9	7.9	— 2.8	— 1.8	11.9	24.9

TABLE 12
PREDICTED LOSS OF TOLERANCE WHEN LSD-25 IS NO LONGER GIVEN

Day	Tolerance	Effective dose
0	75	0
1	37.5	37.5
2	18.7	56.5
3	9.3	65.3

A value of k_4 of 50 per cent thus predicts that tolerance would be lost in approximately three days.

5. *Application of Mechanism to Schizophrenia*

In offering a mechanism for the development and loss of tolerance to LSD-25, the question naturally arises whether this mechanism contains some clue to the nature of schizophrenia. Such a question contains at least three assumptions; namely: (*a*) That there is a substance analogous to LSD-25 involved in schizophrenia, and designated here as *P*. (*b*) That *P* has some normal function in the physiology of the emotional processes, but the metabolism of *P* is disturbed in schizophrenia. (*c*) That the substance *P* is regulated by a mechanism like the one proposed here for the development and

loss of tolerance to LSD-25, and that a breakdown of this mechanism is involved in *P* getting out of control.

Thus, we would have the mechanism:

$$P + E \underset{k_5}{\overset{k_1}{\rightleftharpoons}} \text{Symptoms } PE \qquad \underline{(1)}\ \underline{(5)}$$

$$PE \xrightarrow{k_2} E_T + \text{Decomposition Products} \qquad (2)$$

$$E_T + P \xrightarrow{k_3} PE \qquad (3)$$

$$E_T \xrightarrow{k_4} \text{Decomposition Products or Execretion} \qquad (4)$$

where the normal function of *P* might be involved, for instance, in the accommodation of the organism to stress situations. E_T would be the ballast against emotional explosion while the reaction k_5 would be the "safety valve" to bring about the necessary emotional response. Without such a safety valve E_T could act to eliminate *P* before the organism could make the necessary response.

There are data on the action of LSD-25 on schizophrenics. For instance, Cholden (3) found that schizophrenics become tolerant to LSD-25 and lose that tolerance in a manner approximately parallel to that of normals. Thus, the k_4 value (rate of elimination of E_T) is not outstandingly different in schizophrenics, compared with normals.

Further studies on normals and schizophrenics might result in the demonstration of differences in k_4. This would be important for classification and diagnosis. It would not seem to be the key to the problem of schizophrenia.

A more tenable hypothesis is that while schizophrenics show a relatively normal tolerance pattern, this pattern is ineffective in protecting against psychic reactions because of an abnormally high value of k_5. This would lead to a steady state concentration of the *P* factor above the value required to induce psychotic reactions even though large amounts of the tolerance factor, E_T are present. Building up E_T to larger values would prevent the reactions to the massive doses of LSD-25 as observed by Cholden (3), but the effect of small doses would not be observable in the psychotic patient over their usual symptoms.

Another rate constant in the mechanism which would have a profound effect on the nature of the response to *P* is k_2, the conversion of *PE* to E_T. If *PE* is reversing into *P* and *E*, and thus causing recurring symptoms, the

chain is broken only by Reaction 2, by which means *PE* goes to E_T, the tolerance factor. A subject with a high k_5, and a high k_2 would show bursts of psychotic behavior of short duration, within the approximately normal range. A low value of k_2 would prolong the psychotic state induced by the "secretion" of *P*.

It would be of interest to test this hypothesis by experiments in which the duration of the psychic reactions induced by LSD-25 are compared in normals and schizophrenics.

6. *Application of Theory to Biochemical Studies*

Experimental work is being instituted (1) to detect agents in the urines of clinically schizophrenic patients which might be the cause of clinical schizophrenia in man (*P* substance). The ideas developed above indicate that anti-*P* substances (E_T) should also be sought in such urines and in the urines of non-schizophrenics.

Referring back to the mechanism, if *P* is formed ("secreted") only at the site of its primary action it would not be eliminated as *P* but would end up as decomposition products of E_T, the tolerance factor, formed by Reaction 4. E_T might also be directly eliminated from the sites of neurological action and be found in the urine.

Another possible chemical clue in the urines would be the decomposition products of *PE* formed in Reaction 2, wherein *PE* is converted to E_T.

F. Summary and Conclusions

1. Three subjects with considerable experience in LSD-25 experiments were tested with LSD-25 on six and three consecutive days, respectively. The response to a questionnaire diminished rapidly from day to day. On the fifth and sixth days an increase appeared. Five days after the sixth day the response to 100 micrograms of LSD-25 by Subject *A* was not as great as on the first day but was greater than on the other days. The lowest number of responses resembled a 25-microgram response. The symptoms reported at that time were more typical of high dose symptoms but appeared less frequently.

2. Subjects *B* and *C* received increasing doses of LSD-25 on successive days, beginning with doses of five micrograms and gradually increasing to 100 and 75 micrograms, respectively. Subjects exhibited marked tolerance. Their responses to the highest doses were less than their usual responses to a 25-microgram dose of LSD-25.

3. Subject *C* demonstrated tolerance to 100 micrograms of BOL-148

given twice daily for two successive days, but showed only slight, if any, tolerance to 25 micrograms of LSD-25 given the following day.

4. All of the foregoing data were coördinated with the theory of the development and loss of tolerance to LSD-25. The mechanism suggested has four essential steps:

a. LSD-25 interacts with a neuro-metabolic system, *E*, to cause symptoms, and becomes modified, and is converted to *LE*. This is a reversible reaction and as long as *LE* is present some LSD-25 reaction might be observed.

b. *LE* splits into E_T (the tolerance factor) and other products which are eliminated.

c. When E_T comes into contact with LSD-25 it forms *LE*.

d. With the loss of tolerance in time, E_T is eliminated as a decomposition product or excretion. The loss of E_T will follow the equation:

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

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

5. 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.

6. 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.

7. It was proposed that both the *P* substance and anti-*P* substances (E_T) should be sought in the urines of clinically schizophrenic patients, and that anti-*P* substances might also be found in non-schizophrenic urines.

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