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# Psychopathology and Psychophysiology of Minimal LSD-25 Dosage

A Preliminary Dosage-Response Spectrum

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Despite 14 years of investigation, as intensive as accorded any biologically active chemical, a gap remains in the systematic description of human response to lysergic acid diethylamide (LSD-25). The dramatic schizophrenic-like symptoms after doses of  $40\mu g$  to  $100\mu g$  have drawn the main interest. The threshold for activity is placed at  $20\mu g$  by general consensus, while perfunctory administration of smaller doses has left their effect uncertain.

Accompanying those pharmacologic demonstrations has been the controversy whether LSD symptoms simulate the psychopathology of schizophrenia <sup>1</sup> or can be better explained as a toxic organic psychosis.<sup>2</sup> One of these alternatives might be favored by its resemblance to the complete dosage-response relationship of LSD. It is unfortunate for analogical comparison that early stages of toxic psychosis have rarely been described in a psychopathological framework <sup>3</sup>; on the other hand, there is a firm basis for comparison with various schizophrenic processes.

This preliminary note reports the response to 24 doses of LSD-25, graduated in size to emphasize the relationship of symptoms to dosage.

### Methods

Fourteen young men without apparent emotional problems volunteered as subjects. Extensive

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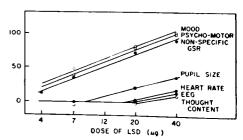
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physiological measurements on the subjects reclining alone in a dark room took 20 minutes of each hour. Another third of each hour was absorbed in psychological and psychiatric observation. In the remaining intervals subjects occupied themselves in any way they chose. Conscious mood was assessed by two questionnaires constructed from our initial experiments. On one questionnaire, the subject estimated deviation from his usual state in matters of perception, body image, alertness, emotion, and thought. On the other, the subject placed himself along the scale between pairs of adjectives describing opposite extremes of mood.

A psychiatric interview preceded the dose and was repeated every hour during the experimental day. While the subjects were generally aware of LSD symptoms in usual dosage, none knew the size of their oral dose, or whether they had taken a placebo of plain purified water U. S. P. The "double-blind" system prevailed, in that all measurements and judgments were made without knowledge of the dose.

#### Results

Physiological changes in general were absent with doses below  $20\mu g$ . The exception was the nonspecific component of the galvanic skin response (GSR), which was activated after  $7\mu g$  (Figure).



Effect of LSD dosage on psychiatric and physiological measures. The relative intensity of LSD effects on an arbitrary ordinate are plotted against dose on a logarithmic scale. Measurements are described in the text.

The two questionnaires were marked by four subjects who received  $20\mu g$  and four other subjects receiving  $7\mu g$ . After  $20\mu g$  there were deviations from normal in body image, thought, and emotion at the second and third hours. In contradistinction, after  $7\mu g$  the subjects did not record departure from their ordinary state during the experimental day.

On the bipolar dimensions of the second questionnaire the four subjects receiving 20µg marked the scales in such a way as to give a decrease in dimensions labeled alertness, motility, control, thought, and sociability. These remained below the initial level for the entire experimental day. On the other hand, after 7µg the bipolar dimensions shifted rapidly. For alertness and motility a dip at the third hour was followed by a climb above the initial value for the rest of the day. Control and thought sank gradually for the first three hours, returning to the initial level at the fourth hour. Sociability increased for the first two hours, dipped sharply at the third hour, and recovered to remain far above the predrug value. The sixth dimension, hedonic tone, also dipped sharply at the third hour and bounced far above the initial level for the rest of the day. These average results from the two questionnaires are described as background for the changes noted during interview.

Psychiatric information elicited each hour was summarized, and symptoms are presented here as representing a "syndrome" if they occurred at a given time in at least half of the subjects who received that dose. Six subjects received the 20µg dose. One hour later they exhibited hypomanic behavior with euphoria, increased psychomotor tension, and distractibility. By the second hour there was indifference with physical retardation and social withdrawal, irritability, and frequent forced laughter without pleasure. At the third hour withdrawal continued with prominent shifts in affect, and changes in thought process, including feelings of inferiority, obsessive thinking, strange unreal thoughts, and one early idea of reference. By the fourth hour most of the subjects were mildly hypomanic and continued that way, with occasional waves of depression or irritability.

In the case of six subjects who received 7µg psychiatric interview in the first and second hours recorded hypomania with expansive euphoria, increased psychomotor activity and tension, and irritability. By the third hour there appeared sudden profound tiredness with an appropriate degree of indifference and depression of mood. At the fourth hour, when subjects were convinced that the drug effects were over, hypomania of a characteristic egosyntonic type developed. Several subjects described this feeling as "rebirth" or "cleansing." Hypomania continued through the rest of the day with occasional waves of depression. There were no changes either of thought processes or of thought content after  $7\mu g$  (six subjects). after 4µg (two subjects), or after 12µg (two subjects). However, 9 of those 10 subjects displayed cycles of sudden and profound shifts in affect. They ranged toward both extremes of mood during the day; no one experienced severe euphoria who did not also have a high degree of dysphoria at some other time.

The three subjects who received purified-water placebo reported isolated symptoms of tenseness, preoccupation, and change in body image, particularly in the first two hours. The only "50%" symptom for the group was mild sleepiness during the third and fourth hours. In the five subjects receiving doses above  $30\mu g$ , symptoms were consistent with many reports in the literature, including depersonalization, visual illusions, and suggestions of hallucination.

#### Comment

The general acceptance of 20µg as the threshold dose of LSD was confirmed for common peripheral autonomic measurements and for dramatic psychic symptoms. However, effects did appear from still lower doses. Though the meating of the physiological change, nonspecific GSR activation,

is not clear, it has been linked indirectly with neurophysiological arousal by two lines of evidence: the effect of pharmalogic agents <sup>4</sup> and simultaneous estimates of behavioral alertness.<sup>5</sup>

Cycles in affect and in psychomotor activity were elicited by psychiatric interview and by one adjective check list. It is noteworthy that subjects under low doses of LSD were not completely aware of these cycles, for they were not recorded on the other questionnaire, which measured deviations from the usual state. Affect changes have been noted in most human studies of LSD: Stoll's original report 6 includes alternating phases of euphoria and depression from usual doses. The present report distinguishes shifting affect as the mental consequent of low-dose LSD.

Symptoms from LSD in a range of minimal dosage reflect various levels of psychopathology, which cannot be rigorously differentiated from those toxic organic changes occurring before clouding of consciousness. Pending more complete descriptions of early organic symptoms, the spectrum reproduces that of schizophrenia in the following detail. At  $7\mu g$  rapidly shifting affect simulates the most dependable sign of "trace" schizophrenia, described by Lewis and Piotrowski,7 In the 20µg range symptoms approximate the pseudoneurotic form of schizophrenia delineated by Hoch. Only above 30µg do classical schizophrenic-like symptoms of visual illusion and hallucinations begin to evolve.

## Summary

This preliminary report presents physiological and psychiatric changes in man from doses of lysergic acid diethylamide (LSD- 25) below the usual range. Seven micrograms activated the nonspecific galvanic skin response and induced cycles of rapid and profound shifts in affect. Between  $7\mu g$  and  $40\mu g$  the dosage response of LSD is consistent with the spectrum of psychopathology associated with the ill-defined group of "borderline" schizophrenic processes.

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