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Studies on Lysergic Acid Diethylamide (LSD-25)

I. Effects in Former Morphine Addicts and Development of Tolerance During Chronic Intoxication

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The striking mental changes induced by the diethylamide of lysergic acid (hereafter referred to as LSD) have been studied extensively in Europe,* Great Britain,† and the United States.‡ In minute doses (20γ to 120γ) LSD induces a peculiar mental state characterized by anxiety, signs of autonomic dysfunction, perceptual distortion (chiefly visual), alterations in mood and affect, synesthesias, feelings of depersonalization, and hallucinations. The drug is apparently the most effective and safest agent for inducing an experimental, but reversible, psychosis in nonpsychotic subjects.

Various interpretations have been placed on the mental state produced by LSD. Some European authors refer to it as a "toxic psychosis of the exogenous reaction type" or a "diencephalosis,"§ presumably because the autonomic signs suggest effects on the hypothalamus. The resemblance of some of the psychic manifestations which follow LSD to symptoms of the major psychoses has been stressed by others.‖ The LSD reaction has been referred to as "experimental schizophrenia" or "experimental psychiatry." Because some of the symptoms induced by LSD also occur in schizophrenia, it has been suggested that schizophrenia may be due to a toxin,[21] to a deficiency of some metabolite necessary for brain function,¶ or to some metabolic tissue disturbance.# A defect in the degradation of epinephrine involving either adrenochrome[25] or adrenoxine[26] has been postulated. Another hypothesis, based on competitive actions of serotonin and LSD in excised smooth muscle preparations, postulates either a deficiency or an excess of serotonin in the brain.[23] Recently it has been shown that both reserpine and serotonin prolong the sleeping time of mice treated with hexobarbital.[27] LSD abolishes the prolongation of sleeping time induced by either substance.* Since reserpine causes depletion of serotonin stores in the brain,† some relationship between serotonin and mental function is inferred. Further, LSD is presumed to cause mental symptoms by "competing with" serotonin for neuronal receptor sites.

All of these theories are based on resemblances between the LSD reaction and the major psychoses. The effects of LSD last only a few hours, and practically all experiments with the drug have been "acute"; i. e., single doses of LSD were given at intervals of days or weeks. The

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* References 1-5.
† References 6-9.
‡ References 10-20.
§ References 1, 21.
‖ References 4, 12, 14.
¶ References 22, 23.
# References 5, 24.
* References 27, 28.
† References 28, 29.

chronic experiments that have been done involved administration of the drug to psychotic patients in whom the LSD response was difficult to assess. It, therefore, seemed desirable to determine whether resemblance of the LSD reaction to the major psychoses, which are chronic diseases, would become more or less prominent when the drug was administered chronically to nonpsychotic persons. It is the purpose of this paper to describe the reaction induced by LSD in former morphine addicts, to show that the intensity of the reaction is measurable, and to report the rapid development of tolerance (loss of effect) to LSD when the drug was administered daily for 3 to 85 days.

Characteristics of the LSD Reactions in Former Opiate Addicts

The patients who volunteered for the experiments were male drug addicts who had been abstinent from opiates for three months or more when the studies were carried out. None of these patients was psychotic; all had either character disorders or inadequate personalities, and the majority were Negroes. Because of the great differences in economic and ethnic backgrounds and personality types, and, possibly, physiological differences resulting from antecedent opiate addiction, it was necessary to determine whether the LSD reaction in these subjects was similar to the reactions observed by other investigators in other kinds of people in different environments. Preliminary experiments were, therefore, carried out using 12 white and 12 Negro male subjects.

Methods.—The experiments were conducted in a closed ward devoted to clinical research. The subjects were observed in individual rooms but were free to leave between observations and to mingle with other patients in a common dayroom. The drug was always given orally, and the subjects were fasting. Doses of LSD varied from 20γ to 300γ (total dose), or approximately 0.25γ to 5γ per kilogram of body weight. Results were controlled by using placebos and a randomized order of administration of LSD and placebos in all experiments. Pulse rate, systolic and diastolic blood pressures, respiratory rate, and rectal temperature were determined at hourly intervals, after 10 minutes' rest in bed, and 2 hours before and 8 hours after administration of either placebo or LSD. Brief psychiatric examinations were carried out approximately two, four, and six hours after administration of the drug. Pupillary diameter was determined once hourly, as follows: The patient was taken into a dark room, seated in a chair under constant light, and asked to look at a white spot on a wall 10 ft. (3 meters) away. The size of the pupils was compared with those of black circles of known diameter on a card which was held alongside the patient's eyes. Neurological examinations, including pupillary reactions to light and accommodation, station and gait, coordination, deep tendon and superficial skin reflexes, and tests for abnormal reflexes were carried out hourly.

Results.—Response to Various Doses: Reactions to zero dosage (placebo) were generally negligible. Doses of LSD of less than 1γ/kg. of body weight induced only mild effects. Autonomic changes were slight. Mental effects consisted chiefly of anxiety and mood changes, primarily in the "euphoric" direction. Perceptual distortion was rare, and no hallucinations were reported. Doses of 1γ to 2γ per kilogram induced more striking effects. The autonomic and neurological changes became definite and measurable. Mental changes, including anxiety, mood changes, and perceptual distortion, occurred in all patients, and many reported "elementary" hallucinations (kaleidoscopic patterns of light and color with the eyes closed) and occasionally "true hallucinations" (perception of something that could be described as a definite thing, animal, or person). Feelings of unreality and symptoms of depersonalization were common.

Doses of 3γ/kg. or more induced a reaction which was too severe to be tolerated on more than one occasion by most patients. A dosage range of 1γ to 2γ per kilogram was adopted for most work, and the descriptions below are based on doses of this order.

Time Course: The effects of 1γ to 2γ of LSD per kilogram were apparent within 30 minutes after oral administration, became maximal in one and one-half to two hours, remained maximal to the fourth or fifth hour after administration, and thereafter gradually declined. Usually, eight hours after the drug patients had recovered except for some residual nervousness and anxiety. All symptoms disappeared completely within 16 hours.

"Nonmental" Effects: Statistical analysis of the data showed no significant change in temperature, pulse rate, or respiratory rate. Systolic and diastolic blood pressures were significantly elevated.

The only consistent neurological changes were dilatation of the pupils and accentuation of the deep tendon reflexes. Occasionally, twitching of the muscles and tremors involving muscle clonus occurred in patients who had severe mental reactions. Waves of goose flesh were noted in some patients.

"Mental" Effects: The mental effects seemed to be identical with those described in the literature in nonaddicts. Changes in mood in the direction of either euphoria or depression, difficulty in concentration, feelings of strangeness, anxiety, nervousness, and dream-like states were reported. Motor activity varied. Some patients were constantly active; others became very quiet and withdrawn.

Various alterations in all sensory modalities were described: acute or dull hearing, "sandpaper" feel of clothes, metallic tastes, bad odors, sensations of the body being light or heavy, and a great variety of visual changes. Actually, alteration in vision was the only sensory change reported by all patients. The subjective visual phenomena included blurring; changes in perception of depth and distance; distortion in size, shape, and color of objects, persons, and the patient's own body; lights and colors on closing the eyes or looking at the wall, which formed kaleidoscopic patterns not suggestive of any real thing ("elementary hallucinations"), and, rarely, "true hallucinations" (perception of persons or things not really present). Frequently, patients saw their hands or feet transformed into animal paws or into the extremities of a dead person. Similar sensations were experienced on looking at other persons. Auditory hallucinations were infrequent. The sensorium was clear, and insight (realization that the effects were due to the drug) was usually maintained. Affect, though difficult to judge, generally seemed appropriate. During marked reactions most patients expressed fears of dying or of becoming permanently insane.

Symptoms which might be classed as "depersonalization" included the changes in the appearance of the extremities described above, "feelings" of being outside one's own body, and difficulty in recognizing oneself in a mirror. Patients also mentioned difficulties in deciding whether a thought referred to a real event or object or was merely a thought. Such experiences, while puzzling, did not form a part of an organized delusional system. Patients usually stated that such phenomena had not really occurred and were due to the drug.

Marked quantitative variations in the degree of reaction of different subjects to the drug were noted. A dose of 2γ/kg. might induce only nervousness in one subject, while another subject might experience perceptual distortion and true hallucinations with loss of insight on the same dose. The same subject, however, responded each time to the same degree and in the same way as long as the testing situation was held constant.

Psychological Tests: In a preliminary exploratory experiment, six Negro males were given a battery of psychological tests (Wechsler-Bellevue Intelligence Scale, Goldstein-Scheerer Cube and Color-Form Sorting Test, the Rorschach test, and the Minnesota Multiphasic Personality Inventory [MMPI]) while receiving no drug and again at the height of the LSD reaction, after receiving a dose of 1γ to 2γ/kg. of LSD.

Comparison of the Wechsler-Bellevue subtest scores and the intelligence quotients obtained under control conditions (no drugs) with those following LSD showed a decrease in all verbal subtest scores. Scores on all performance tests, except the digit symbol, increased slightly, but the increases were less than those expected from the practice effects. When corrected for the expected practice effects, all subtest scores showed some decrease after LSD. When

the intelligence quotients after LSD were corrected for the expected practice effect, the verbal I. Q. decreased 8.63 points, the performance I. Q. 6.07 points, and the full-scale I. Q. 7.43 points. Although the number of subjects is small, these decreases probably represent a substantial impairment of intellectual function.

No loss of conceptual or abstract ability was found on repetition of the Goldstein-Scheerer Cube and Color-Form tests during LSD intoxication. However, it was apparent that patients exerted a great deal of effort in order to complete the tasks. Much of the effort took the form of acquiring a "set," i. e., making bodily adjustments indicating an attitude of attention. Possibly, this effort was related to difficulty in concentrating.

When responses on the Rorschach test before and after LSD administration were compared, some variation in several of the scoring categories was observed in each patient. However, the basic pattern of the test responses remained the same. When the Rorschach tests of all six patients were analyzed as a group, changes were noted in several factors under LSD: There was a decrease in total number of responses (R), in F+ per cent, and in Z (organizational activity), and a trend toward a D approach at the expense of W. Perhaps the most significant effect was a decrease in the use of form and an increase in the use of factors other than form. In every subject, either Sum C or Sum Y was increased. Although the changes can be considered only as trends because of the small number of subjects, they seem to indicate increased emotionality and a breakdown or loosening of intellectual control in patients who characteristically maintained rigid control.

Such striking changes were observed in the MMPI profiles after LSD in the original six subjects that it appeared the MMPI might be more sensitive than other psychological tests in measuring the LSD response. A separate study, which is being reported in detail elsewhere,‡ was therefore undertaken. Briefly, 24 subjects were tested in random balanced order under no drug, placebo, and LSD (50γ-130γ) conditions. The MMPI was given one and one-half hours after administration of placebo or LSD. Statistically significant elevations were found in the Psychasthenia ($P<0.01$), Schizophrenia ($P<0.01$), Paranoia ($P<0.05$), and Taylor Anxiety Scales ($P<0.05$).

Methods of Measurement and Analysis

On the basis of the preliminary work described above, methods for measuring both the "mental" and the "nonmental" aspects of the reaction were developed. Pupillary diameter, systolic blood pressure, and change in patellar reflexes were chosen as objective and measurable signs of the LSD reaction. Systolic blood pressure was measured after 10 minutes' rest in bed, using the standard auscultatory method. Pupillary diameter was estimated as described above. Patellar reflexes were graded according to the following system:

Grade 0: No response elicitable, even with reinforcement

Grade 1: Response elicitable only with reinforcement

Grade 2: Response elicitable without reinforcement; excursion after light tap less than a 6-in. arc and not repetitive

Grade 3: Response elicitable with light tap; excursion greater than 6-in. arc

Grade 4: Response very quick, forceful, and repetitive; almost complete extension of leg

These measurements were made at hourly intervals for two hours before and eight hours after administration of LSD. Data obtained were plotted on graph paper and the area under each curve measured with a planimeter, thus summarizing the data for each particular measurement in one figure. The average of the pre-drug measurements was used as the base line in each case.

Mental effects induced by LSD were assessed in two ways: 1. The questionnaire devised by Abramson and associates[19] was administered hourly for two hours before and for eight hours after LSD. The number of positive responses on the questionnaire was counted over the entire eight-hour period after administration of LSD, but answers to questions which were also scored positive before administration of the drug were eliminated. The questionnaire includes such items

‡ Belleville, R. E.: MMPI Score Changes Induced by Lysergic Reid Dithylamide (LSD-25), to be published.

as "I am trembling inside," "I am confused," "Things seem near or far away," etc. This questionnaire has several disadvantages—it may suggest symptoms; few positive responses are given to many of the questions, and it does not cover all the mental phenomena observed after LSD. The questionnaire, however, has the advantage that a systematic record of certain symptoms is obtained at definite intervals before and after administration of the drug.

2. The degree of mental effect was also assessed by conducting a short psychiatric examination between the second and fourth hour after administration of the drug. In carrying out this examination, special attention was given to anxiety, nervousness, perceptual distortion, presence or absence of hallucinations, and insight, and a "grade" was assigned to the reaction according to the following scheme:

Grade 1: Anxiety and nervousness, without perceptual distortion or hallucinations

Grade 2: Anxiety, nervousness, and visual perceptual distortion without "true" hallucinations

Grade 3: Anxiety, nervousness, perceptual distortion, and "true" hallucinations, but with insight maintained

Grade 4: Same as Grade 3, except that insight (realization that the effects are due to the drug) is lost

The grading system was based on the time course and on the response to increasing dosage observed in the preliminary work. The system has the disadvantage that the various grades may not form a continuous scale (Grade 2 may not be twice that of Grade 1). It gives no information concerning the quantitative aspect of the symptoms which go into determining the grades. Also, Grade 4 was seldom reached with doses of less than 3γ/kg.

These methods were tested by determining the response to graded doses and by determining the reproducibility of the reaction in the same subjects.

Response to Varying Doses.—Eight nontolerant Negro males were used in this experiment. They were given, under "blind" conditions and in randomized order at weekly intervals, a placebo and 0.25γ, 0.5γ, 0.75γ, 1γ, 1.5γ, and 2γ per kilogram of body weight of LSD. Two of the patients, who were very sensitive to LSD, did not receive the 2γ dose, and one did not receive the 1.0γ dose. Observations were carried out as described above. Results obtained with the various doses are shown in Table 1. Allowing for the omission of the sensitive patients in the 1.5γ and 2γ columns, the degree of change in all measurements increased with the dose. Peak effects were attained at the 1.5γ/kg. dose except for blood pressure. Statistical analysis, using a *t*-test for paired observations [30] showed that changes from placebo to LSD were significant ($P<0.05$) for all measurements at all doses except 0.25γ/kg. Differences between doses that varied as much as 1γ/kg., e. g., between 1.0γ/kg. and 2.0γ/kg., were statistically significant, whereas differences between doses varying 0.5γ/kg. or less, e. g., between 0.5γ/kg. and 1.0γ/kg., were not significant.

Although the number of patients used was small, the results showed that the degree of effect was related to the dose and that methods were useful in assessing the intensity of the LSD response.

TABLE 1.—*Effects of Increasing Doses of LSD-25*

Measure	Dose, γ/Kg.						
	0	0.25	0.5	0.75	1.0*	1.5	2.0†
Patellar reflex‡	0.5	1.18	1.60	1.89	2.10	2.04	1.93
Pupillary diameter‡	0.4	1.10	2.29	3.57	3.64	4.27	3.66
Blood pressure‡	1.82	2.91	2.93	4.00	4.24	4.87	5.35
Questions§	4	26	42	56	30	65	42
Grade§	0	0.2	0.63	1.5	0.7	1.6	1.5

* Data on seven patients only.
† Data on six patients only.
‡ Expressed as mean area under curve (square inches). See text.
§ See text for method.

Reproducibility.—Twelve Negro males received 60γ of LSD on three separate occasions at intervals of at least one week. Tests with LSD were interspersed in randomized order with placebos. The results were analyzed as described above and are shown in Table 2. Statistically, the results were identical on all three tests, thus proving that the measurements used in assessing the LSD reaction are reproducible in the same subjects from time to time, provided test conditions are held the same.

TABLE 2.—*Reproducibility of Response to 60γ LSD on Three Separate Occasions*

Measure	Trial		
	1	2	3
Patellar Reflex*	3.32±0.47	3.01±0.38	3.01±0.52
Pupillary Diameter*	3.02±0.20	3.73±0.37	3.02±0.18
Blood Pressure*	2.40±0.36	2.30±0.18	2.39±0.38
Questions†	101±24	97±29	93±19
Grade†	1.5 ±0.32	1.1 ±0.3	1.5 ±0.11

* Expressed as the mean ± the standard error of the area under curves (square inches).
† Means ± standard errors. For methods, see text.

Tolerance

Four experiments were carried out. In Experiments 1 and 2, the period of administration of LSD was relatively short, and questionnaires and assessment of the clinical degree of reaction were the only measurements obtained. In Experiments 3 and 4, administration of LSD was carried on for longer periods of time, and measurements included effects on blood pressure, pupillary diameter, and knee jerk. In the fourth experiment a special effort was made to assess the degree of tolerance and to determine the speed with which tolerance was lost on discontinuation of the drug.

EXPERIMENT 1.—Five Negro males and six white males received in randomized order for three days either a placebo or LSD twice daily. LSD was administered in doses of 10γ, 20γ, and 30γ at 9 a.m. and 9 p.m. on the first, second, and third days, respectively. On the fourth day all patients were given 75γ of LSD (approximately 1γ/kg.) at 9 a.m., and questionnaires and clinical rating were obtained as described above. During the following week the experiment was repeated except that those patients who had received LSD were given placebos and vice versa. Results are shown in line 1 of Table 3. The decreases in the number of positive questions and in the clinical grade observed after three days' pretreatment with LSD as compared with three days' pretreatment with placebos were significant ($P<0.05$) by the *t*-test for paired observations.[30]

EXPERIMENT 2.—Four white and 4 Negro males received in randomized order either placebos or LSD at 9 a.m. daily for seven days. The initial dose of LSD was 20γ, increasing stepwise to 75γ on the seventh day. On the eighth day all patients

TABLE 3.—*Tolerance to LSD After Administration for Three Days (Experiment 1) and Seven Days (Experiment 2)**

Experiment	Questions		Clinical Grade	
	Nontolerant†	Tolerant‡	Nontolerant†	Tolerant‡
1	98±25	22±9	1.95±0.35	0.6±0.2
2	88±31	18±5	1.7 ±0.5	0.6±0.2

* Figures are the means ± standard errors.
† After administration of placebo for three or eight days.
‡ After administration of LSD for three or eight days.

in both groups were tested with 75γ of LSD, and questionnaires were obtained and clinical grades assessed. In the second half of the experiment, the LSD and placebo groups were reversed. Results are shown in line 2 of Table 3. Significant decreases in both questions ($P<0.05$) and grade ($P<0.01$) were observed, which, however, were no greater than that seen after the three-day schedule described in Experiment 1.

EXPERIMENT 3.—Six Negro males served as subjects for this experiment. Five of these had been diagnosed as having character disorders and one as having an inadequate personality. No evidence of psychosis was found on psychiatric examination of any of these patients. Intelligence quotients ranged from 84 to 125. Prior to chronic intoxication, patients were tested at weekly intervals and in randomized order with doses of 0, 90γ to 130γ, 140γ to 150γ, and 180γ of LSD (approximately 1γ to 1.5γ, 1.5γ to 2γ and 2γ to 3γ per kilogram). Measurements were made as described above. Following completion of the initial testing, five patients were placed on a single daily dose of 90γ to 130γ of LSD once daily for seven to eight days. The dose was then increased to 150γ for three days and then to 180γ for three days. One of these five patients withdrew after the ninth day. The sixth patient, who had a very severe reaction to the 180γ test dose, began chronic intoxication with a dose of 50γ of LSD, which was gradually increased to 180γ by the 22d day of chronic intoxication. Questionnaires were obtained daily, and the clinical grade was assessed daily. Pupillary size, knee jerks, and blood pressure were measured at intervals of three to four days. At the end of the 14 days of chronic administration in four patients and of 22 days of chronic intoxication in one patient, LSD was discontinued without the patients' knowledge, water being given in its place. Five patients were tested with a single dose of 120γ to 130γ two to six days after discontinuation of LSD.

Results.—The results are protrayed graphically in Figure 1. On the left, in individual blocks, are shown the mean responses of the six patients to the three doses of LSD and to placebo prior to chronic intoxication. The results on patellar reflex, pupillary size, and systolic blood pressure are expressed in terms of the area under the time action curves (see "Methods

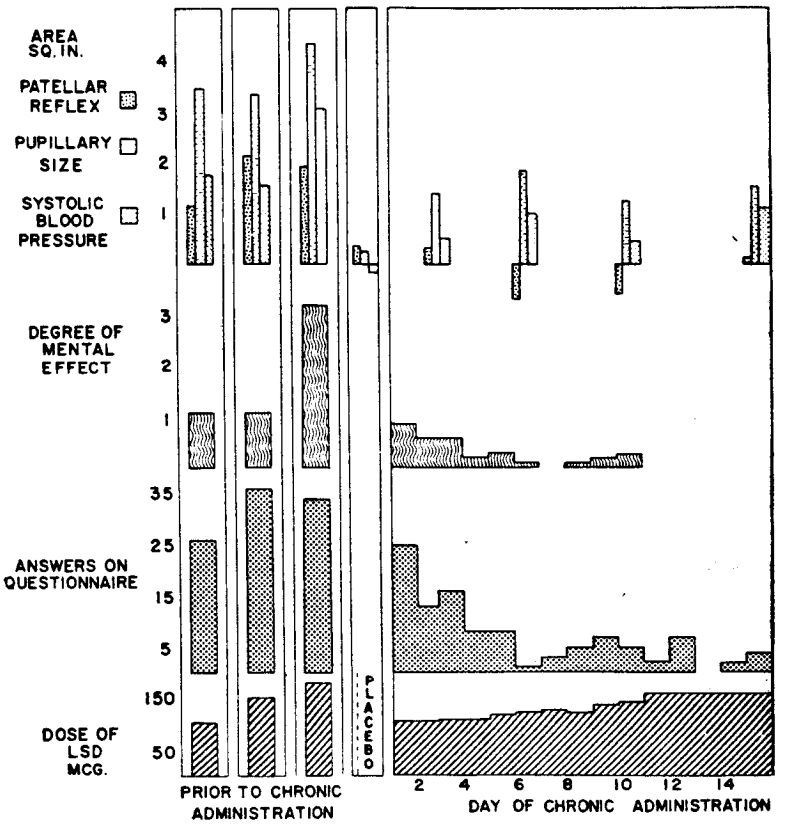

Fig. 1.—Tolerance to LSD in Experiment 3.

of Measurement"). Degree of mental effect and number of positive answers were assessed as described above. The mean responses to LSD during chronic administration are shown on the right, in the large block. In reading the Figure, it is necessary to remember that one patient withdrew after the ninth day and that the measurements obtained during only the first 14 days of chronic intoxication of the patient who received the drug for 22 days are included in the values shown. A rapid decline in the degree of response during chronic administration, despite the increase in the dose of LSD, is obvious. Statistical analysis, using a method for paired observations,[80] showed that the differences between the results before and after three days or more of chronic administration were highly significant statistically ($P<0.01$) for all measurements.

Patients did not notice the transition from LSD to water at the end of the period of chronic intoxication. The reaction was as intense three days after discontinuing LSD as prior to chronic intoxication.

The development of tolerance can best be illustrated by comparing the reaction of one patient to a dose of 180γ before and during chronic intoxication. When this dose was given prior to chronic intoxication, the patient became extremely anxious and felt that he was being shocked with electricity. His body seemed to shrink and enlarge. His hands appeared to have extra fingers. People and objects changed size, shape, and color. The walls were a flickering mass of shadows and colors. He felt that he would die or would become permanently insane. Blood pressure was elevated 60 mm. of mercury; pupils were maximally dilated; knee jerks were very hyperactive; spontaneous tremors of large muscle groups were observed, and ankle clonus could be elicited. After recovery from this severe reaction, the patient wished to drop out of the experiment but, after considerable persuasion, agreed to continue. He was started on 50γ of LSD once daily, and this dose was increased until he again received 180γ of LSD on the 22d day. At this time he had no subjective effects, sat quietly, read, and watched television. His reflex, pupillary, and blood pressure changes were minor.

EXPERIMENT 4.—This experiment was similar to Experiment 3 but was more prolonged. Seven Negro male subjects, all of whom had been diagnosed as having character disorders, served as subjects. Intelligence quotients ranged from 71 to 128. None of the patients presented any evidence of psychosis on psychiatric examinations. In one patient the results of the Wechsler-Bellevue Intelligence Scale was suggestive of an organic intellectual defect. This patient had a history of a head injury with a period of unconsciousness for several hours. Neurological and spinal fluid examinations were completely negative in this patient.

Prior to chronic intoxication with LSD, all seven subjects were repeatedly tested with doses of 1γ to 2γ of LSD per kilogram. Intensity of the reaction was assessed as described above. Patients were then placed on one dose of the drug daily, the mean dose being 1.28γ/kg. daily. After seven days the mean dosage was increased to 1.55γ/kg. This level was maintained for 77 days, except as specified below. The degree of effect induced by the original mean dose of 1.28γ/kg. was assessed on the 7th day of chronic intoxication, and the degree of the effect induced by the mean dose of 1.55γ/kg. was measured on the 14th and 21st days. Thereafter the 1.55γ/kg. level was maintained, and at intervals of two weeks the patients were tested with a double (3γ/kg.), triple (4.5γ/kg.), and quadruple (6γ/kg.) dose in an effort to assess the degree of tolerance which had been developed. After these tests had been completed, the drug was withdrawn without the patients' knowledge for periods of one, two, and three days. The patients were then tested with the original mean dose of 1.28γ/kg. of LSD. Between withdrawals of LSD, the patients were made tolerant again by administration of the 1.55γ/kg. dose daily. The drug was finally withdrawn completely and the experiment terminated.

Results.—The results are shown in Figure 2. In this Figure the mean results prior to chronic intoxication are shown in the first block; the means of the tests carried out during the first 21 days of chronic intoxication are shown in the second, third, and fourth blocks. The fifth, sixth, and seventh sections show the results after the double, triple, and quadruple doses of LSD. The final three sections show the results after

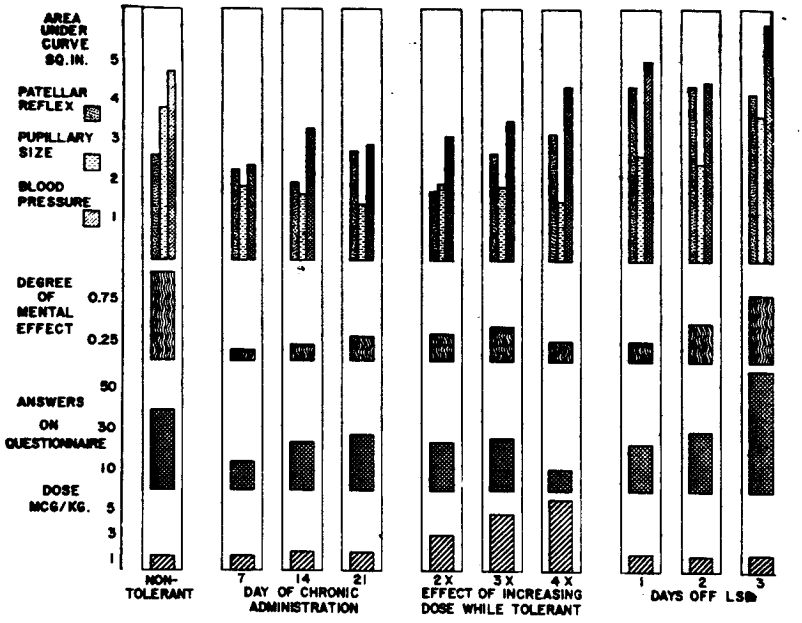

Fig. 2.—Tolerance to LSD in Experiment 4.

withdrawal of LSD for one, two, and three days, respectively. Decline in the LSD effects during the first 21 days of chronic intoxication is apparent. All decreases from preintoxication means are statistically significant. In this experiment, the degree of tolerance to the effects of LSD on knee jerks, pupillary size, and blood pressure, while definite, seemed less than in Experiment 3. Almost complete tolerance to the "mental" effects was developed, since the double, triple, and quadruple doses of LSD did not restore the original degree of mental reaction. Tolerance, however, was lost as rapidly as it was gained, since the original degree of mental reaction had been restored by the third day after discontinuation of LSD.

No abstinence symptoms followed withdrawal of LSD in either Experiment 3 or Experiment 4. In fact, none of the patients realized that LSD had been replaced by a placebo.

Comment

The effects induced by LSD appear to be the same in former opiate addicts as in nonaddicts, despite great differences in ethnic backgrounds, socioeconomic status, life history, personality patterns, and the environment in which testing with LSD was carried out. This fact indicates that the LSD reaction is, to some extent, independent of these variables. The LSD reaction appears to be a specific toxic psychosis which is mimicked only by intoxication with mescaline. It differs in its clinical features from the toxic psychoses induced by scopolamine, cannabis, cocaine, or withdrawal of alcohol and barbiturates.

Under the conditions of these experiments, the LSD reaction, when viewed *in toto*, had only a superficial resemblance to the chronic forms of any of the major psychoses. Symptoms suggesting schizophrenia which occurred in various patients included depersonalization, derealization, confusion, withdrawal from other persons, and changes in response to psychological tests. Affect, however, usually seemed appropriate, and auditory hallucinations were rare, as were ideas of reference and control. Systematized delusions were never observed. The outstanding change after LSD appears to be visual perceptual distortion. The kaleidoscopic changes in size, form, and color of objects, persons, and the patient's own body are very characteristic of the

LSD psychosis and are not a common part of the symptomatology of schizophrenia. The neurological signs induced by LSD are also not found in schizophrenia.

If it had been possible to maintain the original degree of effect throughout the experiment, the resemblance of the LSD psychosis to schizophrenia might have become more pronounced. It is conceivable that schizophrenia is associated with some chronic perceptual disorder and that a person who is having peculiar sensory experiences may develop peculiar explanations for these experiences. Such explanations might be interpreted by a person who is not experiencing such distorted perception as delusional thinking, and hence as evidence of schizophrenia.

The data establish the development of tolerance to LSD unequivocally. Two other laboratories § have also demonstrated this phenomenon in human subjects, and another has shown tolerance to the pyretogenic effect of LSD in rabbits.[33] Tolerance to LSD develops more rapidly, is greater in degree, and is lost more rapidly than is tolerance to any other drug with which we are familiar. Tolerance to LSD is not associated with the development of physical dependence (symptoms on withdrawal of the drug) as it is in morphine, barbiturates, and alcohol addictions. The data shed no light on the mechanisms of the tolerance. Further neurophysiological, biochemical, and psychological studies will be necessary to elucidate the reason for the declining effect of LSD on chronic administration.

Summary

In former opiate addicts, the diethylamide of lysergic acid (LSD-25) induced anxiety, mood changes, feelings of unreality, visual perceptual distortion, optical hallucinations, depersonalization, and derealization. Concomitantly, resting blood pressure was elevated, pupils were dilated, and the tendon reflexes were accentuated. Characteristics of the LSD reaction appeared to be the same in former opiate addicts and in nonaddicts.

The degree of both the "mental" and the "nonmental" changes increased with the dose of LSD. The intensity of the reaction induced by LSD remained the same when the same dose was repeated after an interval of a week or more.

When LSD was given daily, tolerance was evident after administration for only three days. After tolerance was well developed, administration of as much as four times the standard dose of LSD did not restore the original intensity of the reaction. On discontinuation of LSD, tolerance was lost as rapidly as it was developed.

§ References 31, 32.

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