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Lysergic Acid Diethylamide in Patients with Excess Serotonin

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In contrast to other lysergic acid derivatives, lysergic acid diethylamide (LSD) is an extremely potent "hallucinogenic" agent.* Considerable attention has been given to Gaddum's suggestion that the psychological effects of LSD might be due to an antagonism of 5-hydroxytryptamine (serotonin) in brain. This amine is present in the central nervous system with particular localization in the hypothalamus, mesencephalon, and medulla.† The observation that LSD is antagonistic to the stimulant effects of serotonin on various types of smooth muscle in vitro [5] led Gaddum to speculate that "it is possible that the H-T (serotonin) in our brains plays an essential part in keeping us sane and that the effect of LSD is due to its inhibitory action on the H-T in the brain." [6] A similar notion was expressed by Woolley and Shaw,[7] who found that harmine, a potent hallucinogen,[8] is also a serotonin antagonist. The observation of Shore, Silver, and Brodie [9] that LSD antagonizes serotonin potentiation of barbiturate hypnosis in mice supports this suggestion. Evarts and coworkers ‡ have found that the pharmacological effects of bufotenine (N-dimethyl serotonin) are similar to those of LSD in several respects; both compounds block synaptic transmission in the lateral geniculate nucleus of the cat and cause disturbances of certain sensory functions in the monkey. The similarity of action of LSD and bufotenin suggested that "LSD and bufotenin may owe their neuropsychological effects to the fact that they are serotonin analogues." [11] The speculation to date implies that if increased amounts of serotonin were available at the site of LSD action, there would be a decrease in the effects of LSD.

The availability of patients with elevated blood serotonin levels seemed to offer an opportunity to test the hypothesis that the effects of LSD in man are due to serotonin antagonism. The patients used in this study exhibited the syndrome associated with malignant carcinoid of the small intestine with metastases to the liver.§ This syndrome is chiefly manifest by cutaneous flushes, diarrhea, asthma, and valvular heart disease. The demonstration of large amounts of serotonin in carcinoid tumors ‖ and in the blood of such patients ¶ implicates overproduction of serotonin by the tumor in the pathogenesis of the syndrome. A greatly elevated urinary excretion of a serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), is another constant finding and is useful in establishing the diagnosis.# In seven patients studied at the clinical center, blood serotonin levels were shown to range from 0.5γ to 2.7γ/ml. compared with normal values of 0.1γ to 0.3γ/ml., and the urinary

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* References 1 and 2.

† References 3 and 4.

‡ References 10 and 11.

§ References 12 and 13.

‖ References 14 and 15.

¶ References 15-17.

References 17 and 18.

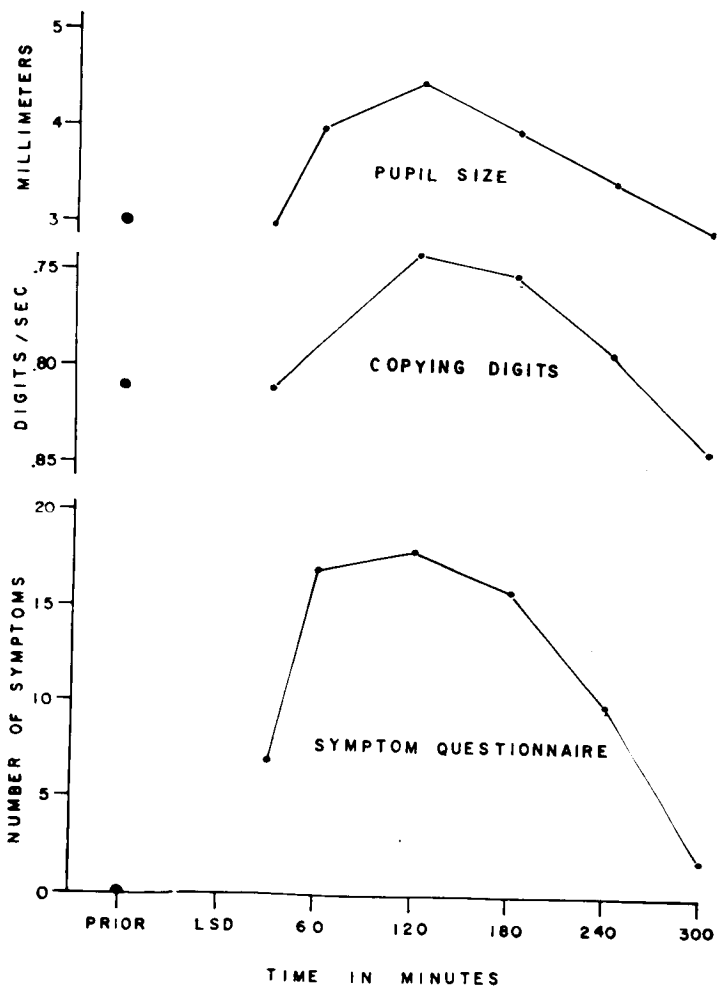
excretion of 5-HIAA ranged from 160 to 580 mg/day, compared with 2 to 9 mg/day in normals. Although one of these patients showed poor concentration and marked emotional lability, in no case was there any evidence of psychotic behavior.

LSD was administered to two of these patients to ascertain the extent to which elevated blood serotonin levels might antagonize the effects of LSD.

MATERIALS AND METHODS

LSD was given orally in 100 ml. water with the subjects in the fasting state. Patient 1 received 20γ, 40γ and 80γ of the drug on May 30, June 6, and June 9, 1955, respectively, while Patient 2 received 40γ on June 10 and a placebo on June 14.

Psychological Observations.—The tests used to measure the psychological effects of LSD were a symptom questionnaire [19] and a test of digit-copying speed.[20] The effects of LSD on the performance of these tests by normal subjects had been determined previously. The symptom questionnaire consisted of 47 items which covered a variety of symptoms produced by LSD. In analyzing the subject's response, no attempt was made to grade the intensity of a positive answer to any of the items; the score was the number of positive responses. In the test of digit-copying speed, subjects were asked to copy 96 separate digits as quickly as possible; the score was the number of digits copied in one minute. The two tests were performed prior to and at 30-minute intervals after drug administration. In addition, the verbal reports of the subjects were evaluated in determining the over-all psychological effects of LSD.



Changes in pupil size, digit-copying speed, and symptom questionnaire responses after 80γ LSD in Patient 1.

Physiological Observations.—With the subject in the supine position, cuff blood pressure and radial pulse rate were measured every 10 minutes for 1 hour before and for 6 hours after drug administration. Pupil diameter was measured every 30 minutes. The subjects were observed closely for any untoward reactions.

REPORT OF CASES

PATIENT 1.—A 50-year-old housewife was first seen in March, 1955, complaining of "hot flushes" since 1946 and progressive enlargement of the liver since 1948. Liver biopsy in 1952 revealed carcinoid. Since 1952 the flushes had been accompanied by frequent vomiting and diarrhea, these symptoms becoming intractable prior to admission; there was a weight loss of 25 lb. Pertinent physical findings included cachexia, frequent erythematous flushes, blood pressure of 130/80 mm. of Hg, and a very large nodular liver. Blood serotonin levels ranged from 0.5γ to 1.5γ/ml., and urinary excretion of serotonin metabolite (5-HIAA), from 240 to 280 mg/day.

PATIENT 2.—A 55-year-old businessman was admitted in April, 1955, complaining of intermittent explosive diarrhea of two years' duration and frequent flushes since August, 1954. Two small carcinoid tumors were excised from the ileum in November, 1954, and numerous metastases were seen in the liver. During 1955 he developed dependent ankle edema and experienced several attacks of asthma. There was gradual weight loss of 10 lb. Relevant physical findings were general appearance of well-being, frequent erythematous flushes of the face and neck, blood pressure of 115/80 mm. of Hg, systolic pulsations of the neck veins, expiratory wheezes, enlarged nodular liver, and edema of the lower legs. Flushes could be produced by abdominal massage. Cardiac fluoroscopy revealed an enlarged right atrium, and a right atrial pressure curve was diagnostic of tricuspid insufficiency. Blood serotonin levels ranged from 1.2γ to 1.9γ/ml. and urinary excretion of serotonin metabolite (5-HIAA) from 380 to 580 mg/day.

RESULTS

PATIENT 1.—This patient showed no apparent effects following 20γ and 40γ of LSD. She experienced moderately severe psychological effects after 80γ. The Figure shows the onset, peak, and regression of the effects of the 80γ dose of LSD as measured by the symptom questionnaire, digit-copying speed, and pupil size. Thirty minutes after administration of LSD the patient reported that she felt nauseated, unsteady, and hot and that her heart was beating faster than usual. At one hour she reported that her mouth felt puckered, and she thought that her voice had changed. Formications were present, her hands and feet felt peculiar, and she had difficulty in talking. She did not perceive the environment accurately and reported that she could "hardly see." She thought that the skin on her face was drawn into all sorts of "weird shapes." The patient became depressed, frightened, and tearful. At two hours, she felt better, although some symptoms were still present. At six hours, she was "back to normal" except that she felt she did not look like herself. Several striking physiological effects were observed. Within 30 minutes she exhibited almost continous profuse perspiration and erythematous flushing, which subsided gradually after six hours. At one hour the blood pressure and pulse rate increased from control values of 170/110 mm. Hg and 90/minute to 200/130 mm. Hg and 120/minute. By two hours the tachycardia had subsided, but the blood pressure remained at a level of 190/120 throughout the six-hour period of observation. During the second hour, marked edema of the face developed, being particularly pronounced in the lip and periorbital areas. The facial edema subsided gradually over a period of three days. The physiological reactions were similar to spontaneous attacks in this patient except for their increased severity and the hypertensive rather than the usual hypotensive response accompanying flushes.

PATIENT 2.—Because of an asthmatic attack which occurred following 40γ of LSD, a higher dose was not given. The verbal report of the subject following 40γ of LSD indicated a definite psychological effect, although this effect was less evident on formal psychological testing. At one and one-half hours, he thought that the walls were closing in on him, that there was a tight band around his chest, and that his field of vision was constricted bitemporally. After this initial unpleasant effect, he reported that he

was "very much at peace with world." There was no impairment in the patient's ability to copy digits. However, when given a test of addition consisting of 48 problems of 5 digits each, his speed of addition was 65 digits per minute, as compared with his control score of 110 digits per minute. There was a 1 mm. increase in the size of his pupils. At about six hours, the patient reported that he felt tense and that he seemed to have a "great deal of energy" that had to be "dissipated." Following a placebo, the patient responded only slightly, his reaction not approximating that seen with LSD. The patient appeared normal during the control period, but within one-half hour after LSD he began to have numerous erythematous flushes which continued for about five hours. At one hour he developed an acute asthmatic attack (the first in six weeks) which was relieved by inhalations of an (Isuprel) aerosol. There was no significant change in the blood pressure or pulse.

COMMENT

Although there is considerable variation of individual response to LSD, some symptoms are experienced by almost all subjects who receive the drug. These symptoms consist primarily of changes in the perceptual field, dream-like states, peculiar feelings of the extremities, paraesthesias, dizziness, unsteadiness, feelings of heat or cold, pressure in ears, inner trembling and weakness.[19] Although both patients exhibited most of these symptoms, they were more pronounced in Patient 1. Patient 2 experienced a more relaxing, pleasant, and less threatening effect, a response which was not atypical for a 40γ dose.

The results of this study indicate that a high level of blood serotonin does not alter the psychological effects of LSD and suggest that infusions of serotonin would not decrease the intensity of LSD effects in man. There is uncertainty as to the levels of brain serotonin in these patients. In this regard, when large amounts of serotonin (5 to 10 mg/kilogram) are injected intravenously into dogs and guinea pigs, no increase in brain serotonin is observed.* The striking peripheral effects, consisting of bronchospasm, facial edema, and aggravation of flushing reactions, have not been observed following the administration of LSD to normal patients and were the reverse of what would be expected to follow the administration of a serotonin antagonist to a patient with excess serotonin. The interaction of LSD and serotonin on smooth muscle in vivo may be different from that observed in vitro.

Because of uncertainty as to the brain levels of serotonin in carcinoid patients, these experiments do not refute the hypothesis that the psychological effects of LSD are due to a blockade of some central action of serotonin. However, pharmacological antagonism of serotonin in smooth-muscle systems is not a sufficient index on which to predict hallucinogenic effects in a given chemical agent. Potent serotonin antagonists such as ergotamine, 2-bromlysergic acid diethylamide,[21] and chlorpromazine [22] do not cause hallucinations. More direct evidence must be produced before it is established that the central effects of LSD are due to serotonin antagonism.

SUMMARY

The effects of lysergic acid diethylamide (LSD) were studied in two patients whose blood serotonin levels were elevated as the result of malignant carcinoid. The psychological changes produced by LSD in these patients are of the order which have been observed in normal subjects receiving LSD. It is concluded that elevation of blood serotonin levels does not alter the central effects of LSD.

* Udenfriend, S.: Personal communication to the authors.

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