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RESISTANCE TO LYSERGIC ACID IN SCHIZOPHRENIC PATIENTS*

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The present study was instituted to compare the sensitivity of schizophrenic patients to the administration of lysergic acid diethylamide (LSD-25), with that of normal individuals. A variety of reports on normal subjects indicate that they exhibit clinical psychiatric effects of LSD-25 in doses of 10-100 mcg.[1-12] While most clinical studies show effects from 25-50 mcg., the careful psychologic studies of Abramson, et al.[9-11] show that in comparison with placebo administration, 100 mcg. is more consistent than lower doses in demonstrating psychological abnormalities.

So far as schizophrenic patients are concerned, the literature is controversial. Some investigators have noted abnormal behavior, using the same range of doses which are efficacious in producing changes in normal subjects.[3, 4, 13-17] Others, however, state that schizophrenic patients show milder reactions in this range of dosage, or need larger doses to produce psychological changes, both findings indicating some degree of resistance to the drug.[1, 4, 12, 15, 18]

There has been published no quantitative investigation of the problem of an elevated threshold to the drug in this psychosis, and it is for this reason that this study was organized.

The subjects studied were 34 men and women admitted to Worcester (Mass.) State Hospital with a diagnosis of schizophrenia. The data on the sub-type, sex and duration of illness are shown in the accompanying table. There were 18 men and 16 women—hospitalized from one month to 19 years, the average being 5.6 years. Two-thirds of the population were institutionalized for more than two years, so that the population is essentially one in which the psychiatric condition has become chronic.

The patients were tested on their own wards to maintain familiarity of environment and were permitted to engage in routine ward activities whenever feasible during the period of observation.

In determining the degree of reactivity of the patients, various autonomic phenomena were noted, such as trembling, flushing,

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Sub-type, Sex and Duration of Hospitalization of 34 Schizophrenic Patients

Diagnosis	Number	Sex	Years of Hospitalization
Schizophrenic Reaction			
		M	.08
		M	.24
		F	.64
		M	.72
		M	1.0
		M	1.0
Acute Undifferentiated	7	M	2.0
		M	1.0
		F	1.0
		F	9.0
Simple	4	M	12.0
Catatonic	1	F	.5
		M	5.0
Hebephrenic	2	M	7.0
		M	2.0
		M	3.0
		F	5.0
		M	7.0
		F	10.0
Paranoid	6	F	19.0
		F	5.0
		F	5.0
		F	5.0
		F	7.0
		F	10.0
		M	10.0
		F	12.0
		M	15.0
		F	15.0
Chronic Undifferentiated	10	M	19.0
		M	.08
Residual	2	F	.08
		F	.64
Schizophrenic Affective	2	F	1.0
Total	34		
No. of Males		18	
No. of Females		16	
Average Hospital Duration of Group			5.6
Average Hospital Duration of Males			4.8
Average Hospital Duration of Females			6.7

sensations of cold and warmth, numbness, paresthesias, hunger and nausea. These symptoms and signs were observed either just before psychological changes occurred, or they coincided with them. The criterion for a threshold dose, however, was that at which psychic changes occurred, such as alterations in the behavior or thought content of the individual, including the admitted presence of delusions, illusions, hallucinations and other sensory misperceptions. This depended, of course, largely on the ability or willingness of the patients to communicate their unusual sensations. In all patients who were considered to have responded to LSD-25, some autonomic responses were noted. In the others, who did not reveal any psychiatric changes at the dosages used in this study, such phenomena were seen in three.

Method

Since in normal subjects the usual effective dose of LSD-25 ranged from 20-90 mcg., the initial procedure was to start with a dose of 50 mcg. and increase this by 50 mcg. daily until psychic changes were noted, up to a maximum of 300 mcg. In view of the fact that many patients did not respond to the lower doses, the initial dose was later increased to 150 mcg. and finally to 200 mcg. When a psychological reaction occurred at this higher initial dose,

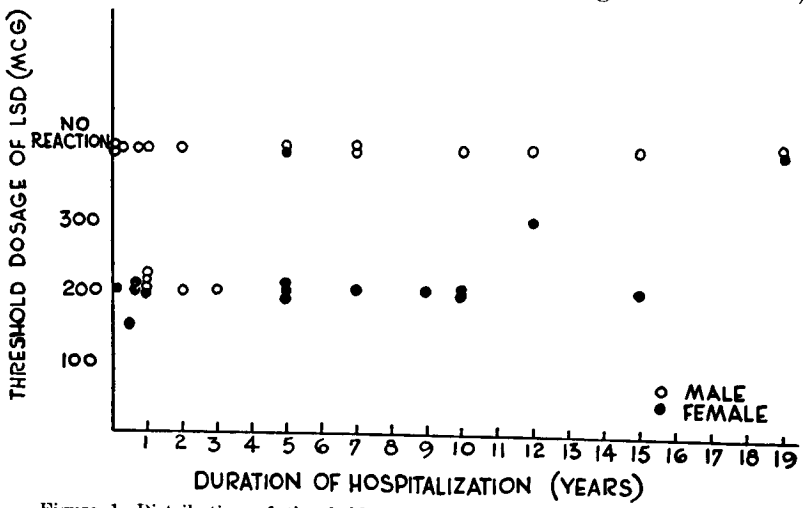

Figure 1. Distribution of threshold dosage of LSD by sex and duration of hospitalization

subsequent dosages were reduced by increments of 50 mcg. until the threshold dose was reached.

Results

The results of the threshold dosage study are shown in Figure 1. Of the 34 schizophrenic subjects, 19, or 56 per cent, showed psychiatric reactions at a dosage level up to 300 mcg. Of these 19, one showed a reaction at 300 mcg., 17 showed reactions at 200 mcg., and one at 150 mcg. In this group of patients only one showed a reaction at a dosage lower than 200 mcg. Larger doses than 300 mcg. were not administered in this study. Thus, in 15, or 44 per cent, of the patients, there was no deviation noted in behavior from that observed previous to the administration of the drug. It is apparent that these results indicate that schizophrenic patients react only to higher doses of the drug than are reported to be effective in normal individuals and, in fact, almost half of them show no change at three to four times the effective normal dose. Thus, a definite resistance to the drug is evident.

The relationship of the threshold dose to the duration of illness was examined. In Figure 1, is shown the length of hospitalization of the individual patients and the threshold doses of the drug necessary to produce psychiatric changes in behavior. No relationship was noted between the two factors. There are non-reactors in the early cases as well as in the late cases. Savage[4] has noted lesser reactions in chronic, than in acute, schizophrenic patients in doses up to 100 mcg. but the present data do not seem to bear this out.

There is a curious relationship between the reactivity of the individual and sex (Figure 1). Of the 19 reactors, 14 were women and five were men. Of the 15 non-reactors, two were women and 13 were men. Thus, a greater sensitivity to lysergic acid is noted in women. The distributions of age and duration of hospitalization were essentially the same for both sexes. There was some difference in the distribution of the sexes by sub-types (Table 1). In the acute undifferentiated group, there were six men and one woman. In the chronic undifferentiated group, there were three men and seven women. Thus, in the two largest groups, the acute cases tended to be males, and the chronic cases, females. Since in the two groups, the men tended to be non-reactors (eight out of

nine) and the women tended to be reactors (seven out of eight) the chronic group seemed to be the more reactive because of the predominance of females. This conclusion can only be verified, however, by the accumulation of a larger series of each sex. Hoch, et al.[16] noted a greater reaction to a given dose in the well-preserved, than in the deteriorated, group, which seems contrary to the present findings, but again, the writers' data on this point are complicated by the difference in response of the two sexes. At present, the writers have no explanation for the apparently greater sensitivity of the female organism to LSD.

A question arises as to whether the present technique of administering LSD in increasing doses every day produces a tolerance to the drug which might invalidate the conclusions. Savage[4] has stated that, on repeated daily administration, a tolerance usually develops. Isbell, et al.[19] noted a tolerance to the drug after daily administration for seven days, but one which was lost after discontinuance of the drug for three days. Since this factor would especially affect the results obtained in those patients who did not react to the maximum dose of 300 mcg., seven of the 15 non-reactors were again tested with two doses of the drug, 100 and 300 mcg., one week apart, one to six months (average three months) after the original threshold study was made. None of these pa-

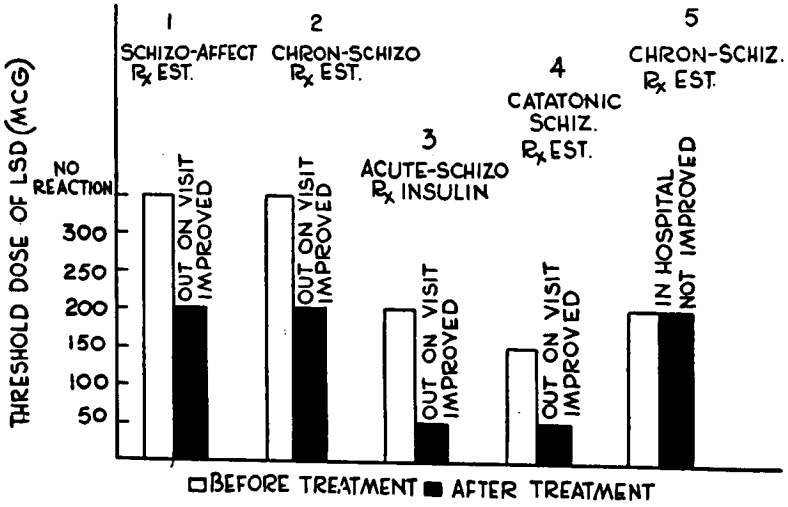

Figure 2. Effect of treatment on LSD threshold in five patients.

tients reacted to the drug. Thus, in these schizophrenic patients, the resistance to the drug was maintained and was not apparently due to the previous technique of daily administration.

A possible relationship between the clinical status of the patient and the sensitivity to lysergic acid was investigated. Five female subjects had threshold dosage measured before and after treatment with electric shock or insulin coma (Figure 2). The second test was done one month after cessation of therapy. In four women in whom there were clinical remissions sufficient to enable the patients to be sent out of the hospital on visit status, the threshold after treatment was distinctly lower than that before treatment. The fifth patient did not improve after electric shock treatment and showed no lowering of the threshold to LSD-25. This trend toward increased sensitivity to the drug with improvement in the clinical status is interesting, but a larger series must be obtained before any definitive statement can be made. It is, of course, possible that the parallelism between the two phenomena may have been purely coincidental, but the persistency of non-reactivity to 300 mcg. of LSD in seven patients whose psychiatric status was unchanged lends some support to the possible interrelationship of the two factors.

Discussion

The data indicate that the responsivity of schizophrenic patients to the administration of lysergic acid is less than that of normal subjects. The development of tolerance to the administration of the drug is not a factor. The data, however, are not conclusive in determining to what extent the lesser sensitivity to the effects of the medication is due to the patients' unwillingness or inability to communicate the presence of abnormal sensations. It would not seem likely that the increased tension built up by these large doses could be successfully suppressed so as not to be evident on careful psychiatric scrutiny, if it were assumed that the threshold was not increased. On the other hand, the question can be definitely settled only by further research to determine whether the material is adequately absorbed and affects the nervous system of the patients to the same degree as it does in normals.

The cause of resistance to the drug leads to speculative realms which are beyond the scope of this paper. Whether the insensitivity is part of the general lack of reactivity exhibited by these

schizophrenics to stressful situations, or is a special instance of abnormal enzymatic function in the central nervous system must await the further investigation suggested.

The diminution in threshold which occurred in the patients who improved presents another fascinating problem. While the series is too small to be anything but suggestive, the trends are at least in the right direction, and, if confirmed, certainly imply a physiological imbalance during a certain stage of the psychosis which is corrected as the patient improves. This phase is undergoing further study.

Summary

A study was made of the sensitivity of 34 schizophrenic patients (18 men and 16 women) to doses of lysergic acid diethylamide, varying from 50 to 300 mcg., to determine a threshold dose which would produce psychiatric changes. Nineteen (56 per cent) of the patients showed psychologic reactions after administration of the drug in dosages varying from 150 to 300 mcg. Fifteen (44 per cent) showed no effects at the highest dose given—300 mcg. Tolerance to repeated administration of the drug was not a factor, since repetition of the maximum dose, 300 mcg., to seven of the non-reactors three months later again resulted in no reaction. Women were more sensitive to the drug than men. There seemed to be a parallelism between the degree of sensitivity to the drug and the psychiatric status of the patients, since four patients who improved after shock therapy reacted at lower doses than during the acute psychotic stage.

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