Published as a separate and in *The Journal of Psychology*, 1960, 49, 151–154.

PRODUCTION OF CROSS-TOLERANCE TO PSYCHOSIS-PRODUCING DOSES OF LYSERGIC ACID DIETHYLAMIDE AND PSILOCYBIN*

Biological Laboratory, Cold Spring Harbor, New York; and South Oaks Psychiatric Hospital, Amityville, New York

H. A. ABRAMSON, A. ROLO, B. SKLAROFSKY, AND J. STACHE[1]

It has been previously demonstrated (4, 5) that 1-methyl-d-lysergic acid diethylamide (*MLD*-41) produces in man a marked cross-tolerance to d-lysergic acid diethylamide (*LSD*-25). *MLD*-41 is less toxic than *LSD*-25, having about one-third of its psychotomimetic activity (1). Production of cross-tolerance to *LSD*-25 by *MLD*-41 occurs not only in nonpsychotic subjects but also in hospitalized schizophrenic patients (9). These data focus on the possibility that, if the schizophrenias are produced by a disturbance in biochemical mechanisms analogous to that resulting from the administration of mescaline, *LSD* and similar substances, comparatively nontoxic molecules might be administered therapeutically to produce tolerance to the endogenous chemicals that might originate schizophrenic states. In accordance with this concept, developed mathematically with Gorin (3), our present studies on cross-tolerance have been conducted not only using lysergic acid derivatives, but also employing a new psychotomimetic compound recently synthesized by Hofmann (8). He first isolated it from the Mexican mushroom, Psilocybe. The active principle, called Psilocybin by Hofmann, is a phosphoric acid ester of 4-hydroxy-dimethyltryptamine. The indole ring is possessed by Psilocybin in common with lysergic acid.

Exposure of Siamese fighting fish to concentrations of 100 μg of Psilocybin in the outside liquid showed nothing worthy of note. However, when the fish are injected intraperitoneally with 25 μg of Psilocybin, their reactions are identical with those produced by *LSD* itself. The nose up-tail down position, excitation and kink in the tail are all readily observed (2, 7). Thus, *LSD* and Psilocybin in the fish may affect the same enzyme systems as do the respiratory enzyme poisons (6, 10).

In man, studies on cross-tolerance were carried out as heretofore. The

* Received in the Editorial Office on November 20, 1959, and published immediately at Provincetown, Massachusetts.

[1] This investigation has been aided in part by a grant from the Josiah Macy, Jr. Foundation, New York, N. Y. We are indebted to Sandoz Pharmaceuticals for the supplies of Psilocybin and LSD-25.

effect of Psilocybin itself and production of cross-tolerance by *MLD*-41 and *LSD* on man were obtained by giving it to the same group of five nonpsychotic test subjects who have been used in the study of *LSD*-25 and its derivatives for the past five years. All the compounds were administered orally either in distilled water or, in the case of Psilocybin, in capsules containing up to 2 mg of Psilocybin per capsule. Development of cross-tolerance to *LSD* by Psilocybin or to Psilocybin by *MLD*-41 and *LSD* was achieved by administering these drugs at home for five to 12 days ahead of time in increasing doses. In general, the procedure followed was that described heretofore (4, 5). Although Psilocybin produces tolerance to itself, symptoms developed during the pretreatment period at home, and our subjects were cautioned not to drive or to engage in any outdoor occupation while under the influence of the drug. Our most sensitive subject to Psilocybin (C.G.) developed tolerance to 4 mg of Psilocybin within six days and was able to take 15 mg on one day, in divided doses, without serious symptoms. Another subject (M.Z.) took 103 mg of Psilocybin in increasing doses for 14 days and was able to take 6 mg of Psilocybin with only minor symptoms. The method of measurement of responses to all drugs was that described heretofore. A questionnaire consisting of a first part containing 47 questions and a second part used as a short mental rating test of nine reactions was employed. Positive responses to the questionnaire are added, irrespective of the intensity of the response. Because *MLD* can be more safely administered to subjects at home during the pretreatment period, we have used that in preference to *LSD*. *MLD* produces tolerance to itself very rapidly, and for this reason large doses of *MLD* may be safely administered. We have summarized for this preliminary report only those experiments on cross-tolerance (Table 1). Actually, in this particular series of experiments on the group of five (now six) subjects, 101 experiments were needed for obtaining controls, randomization, cross-over design, and placebo data. These data will be published in full elsewhere. Inspection of Table 1 shows that in all six subjects and in all 15 experiments that have been performed on production of cross-tolerance between *LSD*, *MLD*, and Psilocybin, cross-tolerance was observed, using our questionnaire method of observation in every case. It is our impression that Psilocybin is more effective in producing cross-tolerance to *LSD*, with the dosages and method employed, than the cross-tolerance produced by *MLD* and *LSD* to Psilocybin. Perhaps a better indication of our criteria of cross-tolerance production is given by the fractions following the words listed in Column 4 of Table 1. The numerator of each of these fractions is the total number of responses to the questionnaire when the test

TABLE 1

The effect of pretreatment of nonpsychotic subjects by 1-methyl lysergic acid diethylamide (*MLD*-41) and Psilocybin on test doses of Psilocybin and lysergic acid diethylamide (*LSD*-25) in a study of cross-tolerance production. Note that cross-tolerance was observed in all cases. The fractions in the fourth column are the ratio of questionnaire responses with and without pretreatment.

Subject	Pretreatment dose	Test dose	Tolerance to test dose	
R.B.	1175 μg MLD	6 mg PSI	Partial	(2/5)
	4325 μg MLD	8 mg PSI	Partial	(2/9)
	103 mg PSI	75 μg LSD	Almost complete	(< 3/7)*
J.G.	4300 μg MLD	8 mg PSI	Almost complete	(1/29)
	67 mg PSI	75 μg LSD	Almost complete	(3/20)
	600 μg LSD	8 mg PSI	Almost complete	(2/29)
D.V.G.	1175 μg MLD	6 mg PSI	Complete	(0/10)
	4325 μg MLD	8 mg PSI	Complete	(0/14)
	103 mg PSI	75 μg LSD	Complete	(> 0/8)
M.Z.	815 μg MLD	6 mg PSI	Almost complete	(3/10)
	4325 μg MLD	8 mg PSI	Partial	(9/18)
	103 mg PSI	50 μg LSD	Almost complete	(3/27)
C.G.	50 mg PSI	50 μg LSD	Almost complete	(4/25)
P.B.	1175 μg MLD	6 mg PSI	Complete	(0/10)
	103 mg PSI	75 μg LSD	Almost complete	(< 8/18)

* Seven responses were to 50 μg *LSD*.

dose was administered after pretreatment, while the denominator represents a value for the responses to the questionnaire given by control experiment with the test dose or less where no pretreatment dose had been administered the week before. Note that in every case, without exception, the value of the fraction is one-half or less. The data do not convey the remarkable blocking effect produced, for example, in Subject D.V.G., who has a most severe reaction to 75 μg of *LSD*-25 but who is able to take this dose of *LSD* with no symptoms whatsoever after pretreatment with Psilocybin. Table 1 illustrates that there is an important variation between subjects in the ability to develop cross-tolerance. What the mechanism is, we do not know, although Subjects J.G. and D.V.G. are the only two female members of the group.

It might be conjectured at first that the presence of the indole ring was primarily responsible for the production of cross-tolerance. This is not quantitatively borne out by our unpublished studies of cross-tolerance production by other similar compounds, *LAE*, *DAM*, and *UML*, which show a wide variation in effectiveness. Further experiments with d-lysergic acid, itself, and compounds similar to lysergic acid diethylamide and derivatives and congeners of the hydroxytryptamines are planned. In any event, these data indicate that there may be a common mechanism responsible for the

production of the induced psychotic states in man by compounds of this type. In other words, is the enzyme mechanism in the psychoses induced by *LSD* and Psilocybin the same? Further investigations of the nature of this mechanism, such as those we have begun, employing the respiratory enzyme poisons in Siamese fighting fish, may lead to a solution of the problem, not only of the genetic and enzyme processes connected with the experimental psychoses in man, but also those processes accountable for the schizophrenias themselves.

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Long Island Biological Association
Biological Laboratory
Cold Spring Harbor, New York

South Oaks Psychiatric Hospital
Amityville, New York