relative protein synthesis, varies inversely as the length of the stalks at the beginning of the experiment. The difference in relative area, on the other hand, does not show any significant variation among stalks that differ greatly in length. This offers even more convincing evidence that an increase in surface area does not play a significant role in the higher rate of protein synthesis in the shorter stalks. Moreover, since all stalks have been subjected to a similar amount of injury, the operative procedure can be eliminated as a factor in the phenomenon.

These experiments are considered to reveal additional evidence of the independence of the cytoplasmic protein synthesis from the presence of a nucleus as described by Brachet and co-workers (*5*) and Stich and Plaut (*6*). The cytoplasm and not the nucleus must be regarded as playing an essential role in determining the amount of synthesized proteins. The simplest interpretation of our results would be made by assuming an intracellular inhibitory effect which increases with cell growth and which is reversible if the cytoplasm is divided into smaller units. The higher activity of smaller cytoplasmic fragments may explain the surprising results obtained by Brachet (*5*) and Beth (*7*) that cytoplasmic fragments synthesize proteins and differentiate at a faster rate if the nucleus containing rhizoid is removed.

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Production of Tolerance to Psychosis-Producing Doses of Lysergic Acid Diethylamide

It has been shown that 2 mg of crude beef brain extract per milliliter blocks the usual effect of 2 μg of lysergic acid diethylamide (LSD-25) per milliliter in the outside liquid on the Siamese fighting fish (*1*). This report (*2*) describes a study of a blocking effect that is probably produced by another mechanism: the development of tolerance to LSD-25 in man (*3*) by the prior administration for a period of days of a compound similar to LSD-25, 1-methyl lysergic acid diethylamide (MLD-41) (*4*).

Table 1. Comparison of production of tolerance to lysergic acid diethylamide (LSD-25) by 1-methyl lysergic acid diethylamide (MLD-41) and 2-bromo lysergic acid diethylamide (BOL-148).

Date of experiment	Total preparatory dose of MLD-41 (μg)	Pretreatment period	Total preparatory dose of BOL-148 (μg)	LSD-25 (μg)	Responses (No.)
29 March 1957	0		0	50	35
12 April 1957	1100	7 to 12 April	0	80	0
10 May 1957	700	4 to 10 May	0	100	7
7 June 1957	0	1 to 7 June	1450	50	14
21 June 1957	0	16 to 21 June	1000	50	21

1-Methyl lysergic acid diethylamide produces in man and the Siamese fighting fish reactions that are essentially indistinguishable from those produced by LSD-25, but there are higher reaction thresholds. In the fish, MLD-41 is about one-tenth as effective as LSD-25; it is approximately one-third as effective in man, as judged by our questionnaire technique. The questionnaire consists of a first part containing 47 questions and a second part containing nine reactions, which are rated both by the subject and by the observer. Positive responses to the questionnaire are added irrespective of the intensity of the response. Thus, in Table 1 the total of positive responses to the questionnaire refers to the sum of both parts of this questionnaire (*5*).

The effect of MLD-41 on man was obtained by giving it to a group of five nonpsychotic test subjects who have been used in the study of LSD-25 and its derivatives for the past 3 years. Both LSD-25 and MLD-41 were administered orally in distilled water or tap water with no essential differences observed between the two. Development of tolerance to LSD-25 was achieved by administering MLD-41 for 5 or 6 days in increasing doses, starting with 100 μg on the first day and reaching 350 μg on the fifth day. Since the threshold to MLD-41 is approximately 70 μg orally, tolerance to MLD-41 itself was developed rapidly. It appears that approximately 1000 μg of MLD-41 administered in this way protects against approximately 80 to 100 μg of LSD-25 taken orally 8 hours after the last dose of MLD-41.

Table 1 illustrates a typical series of experiments on one of our subjects. Although 2-bromo lysergic acid diethylamide (BOL-148) produces some tolerance to LSD-25, its effect for equal weights is much less, approximately one-third of that of MLD-41. The highest doses of LSD-25 varied from 1.1 to 1.6 μg/kg of body weight. These doses invariably produced a severe typical LSD-25 reaction in our test group. Note in Table 1 that, whereas 50 μg of LSD-25 in this subject, without pretreatment by MLD-41, produces 35 positive responses to the questionnaire, there were no positive responses to the questionnaire following a 50 μg dose of LSD-25 when this subject had been pretreated for 5 days with 1100 μg of MLD-41.

A similar experiment in which BOL-148 was substituted for MLD-41 resulted in 21 positive responses to the questionnaire (21 June 1957). The 21 positive responses obtained represent the equivalent of at least a 25-μg response to the LSD-25 administered. The subject himself estimated that he experienced a 35-μg LSD response.

The fact that a substance like MLD-41, which is less toxic than LSD-25, can produce a marked tolerance to LSD-25 lends hope to the possibility that if the schizophrenias are produced by a disturbance in biochemical mechanisms analogous to that resulting from the administration of mescaline, LSD-25, and similar substances, there is good reason to believe that comparatively nontoxic molecules might be administered to produce a similar tolerance to the chemicals that originate the schizophrenic state.

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References and Notes

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