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Editorial

Antiserotonin Action of LSD-25 and other Lysergic Acid Derivatives: Fact and Fiction

In recent months the dangers of using d-lysergic acid diethylamide (LSD-25) have been highlighted in the lay press. Unfortunately these warnings for the most part show more anxiety than experience in the use of this compound by the writers. In addition, these reports do not discriminate between the effects of the drugs when prescribed by a physician and the unpredictable results of self-administration. Indeed the most authoritative warnings have been written by those who have had the least direct investigational experience using LSD-25. There is, however, a considerable body of evidence showing that compounds like LSD-25 and Sansert are safe to use when administered by physicians. Thus in a careful statistical survey Cohen[1] points out that *no instance of serious prolonged physical side effects* was found either in the literature or in the answers covering more than 25,000 administrations of LSD or mescaline. He points out that the literature records directly only one suicide in a schizophrenic patient and a small number of short self-limited psychotic reactions. He concluded that the administration of LSD is safe when given to a healthy selected group. With the application of certain safeguards, many side effects can be avoided.[2] Ditman, Hayman and Whittlesey[3] studied the effect of the administration of 100 mcg of LSD-25 orally in a permissive but non-treatment setting. Using a questionnaire they studied the effect of the LSD experience without psychotherapy. Claims of therapeutic value of the LSD experience were made by 74 of their 87 subjects. The early claims of the subjects were comparable to the most optimistic claims of other investigators who used it with prolonged and intensive psychotherapy. For one and a half years after exposure to LSD a very high percentage of alcoholic patients claimed to have decreased their drinking and about one third claimed complete abstinence. *There is no evidence of brain damage in this group, only improvement occurring in a very large fraction.* The writer has worked with these compounds continuously since 1951 and has administered them hundreds of times without noting the deleterious effects either in "normals", neurotics or hospitalized psychotics. It seems important to stress at this time that many derivatives of d-lysergic acid play a most important role in medical treatment.[4] To label any one of these derivatives as the cause of "chronic brain damage" without direct evidence, validated statistically, constitutes a disservice to science and to the practice of medicine. It is the purpose of this editorial to balance anxiety with some of the more positive and statistically valid aspects of the actions of these drugs.

Experience with children hospitalized for intractable asthma indicate that a small fraction of these children overtly show symptoms of autistic or schizophrenic behavior. Although the fraction is small and probably constitutes less

than 5% of the hospitalized children, the disturbances created by this group always upset the orderly therapy of the other children in residence. Recent studies with d-lysergic acid diethylamide (LSD-25) and 1-methyl d-lysergic acid butanolamide (Sansert) by Bender and her coworkers[5] indicate that both of these compounds are of great value in the treatment of hospitalized disturbed children. Thus Bender, Faretra and Cobrinik report the results of treatment of autistic children, showing all degrees of severity of symptoms of anxiety. When treated with both LSD and Sansert (UML-491) they showed definite positive changes in response to their environment. They became gay, happy and laughing, especially early in the treatment program. Nearly all of them were more alert and interested in watching other persons. Some showed changes in facial expressions in appropriate reactions to situations for the first time. In another group, verbal children 6 to 12 years of age, there was a change in superficial interpersonal relationships with improvement. Thus childish flights into fantasy and distortions gave way to more controlled reality in both reactions. Many of the children became aware of the realistic situation of their hospitalization, of family problems and achieved new insights into their psychological deviations. The results of psychological testing confirmed the improvement in the level of functioning from an overall point of view. *There was no evidence of increased brain damage in these children.* Indeed they were helped adapting to life. *It is important to emphasize that the dosages of LSD given daily were well above the adult threshold levels.*

What has this to do with allergic mechanisms? For many years the dominant notion in the therapy of the allergic state was based on neutralizing the effects of histamine. There were many contradictions and paradoxes to this view, especially the failure of the antihistamines in the treatment of asthma. More recently serotonin (5-hydroxytryptamine) has been brought into the picture not only as an agent possibly connected with emotional disturbances, but also as a mediator in the symptoms of allergic phenomena.[6] Thus Waalkes[7] and his coworkers have shown that serotonin is released in vitro from rabbit platelets following antigen-antibody reactions and in vivo during anaphylaxis because clumped platelets and white cells collect in pulmonary vessels during the anaphylactic response. In the rabbit the quantity of both serotonin and histamine in the lung is increased.

O'Brien, Hughes and Newberne[8] point out that serotonin is known to be involved in the anaphylactoid reaction elicited by dextran and egg white. The same authors showed that d-lysergic acid diethylamide (LSD-25) blocked the course of experimental allergic encephalitis. Fifty mcg triweekly reduced the incidence of paralysis, the mortality rate and the severity of the histopathologic lesions in guinea pigs with allergic encephalitis.

The experiences just briefly cited are amongst a host of others which have been reported correlating the antiserotonin action of d-lysergic acid derivatives like LSD and Sansert with their antiserotonin actions.

If the antiserotonin era is about to supplement the antihistamine and steroid eras, physicians should become aware of the nature of the action of drugs like

LSD-25 and Sansert. These two drugs together with 1-methyl derivatives of LSD-25, namely, 1-methyl d-lysergic acid diethylamide (MLD), are amongst the most powerful antiserotonin drugs studied in the group of compounds related to d-lysergic acid. All three of these produce important psychic effects in nonpsychotic subjects although the dosage varies considerably. Thus the threshold dose of 1-methyl d-lysergic acid diethylamide in non psychotic subjects is about three times that of LSD-25 while that of Sansert is about 150 times that of LSD-25 at its threshold of activity.[9]

Of particular interest to the readers of this Journal is the remarkable effect reported for Sansert in the treatment of migraine.[10] Certain cases of migraine are well know to be caused by allergic reactions to foods. The published side effects of Sansert are very similar indeed to the effects of LSD 25 although at times the autonomic and psychic side effects may be overshadowed by the vasomotor phenomena of the high dosage of the ergot derivative compared with the threshold activity of LSD-25 or MLD. It is unfortunate that the similarity of the side effects of Sansert to those of LSD is denied by some of the workers in the field. In spite of the alleged danger of LSD and similar compounds, there are no valid data showing any correlations between the use of any of these drugs and permanent psychic injury. For example, Sandison[11] has pointed out that in 500 cases of LSD therapy, only one conceivable case could probably be considered to be deleteriously effected. Contrary to rumor these drugs are not addictive.[2, 12] As a matter of fact I have given LSD-25, its derivatives and congeners over a period of seven years to subjects for twenty-seven weeks every winter without any indication of the development of addiction. Indeed one of my subjects received LSD-25 eighty times.

It is important to note that important antiserotonin effects are present in other d-lysergic acid derivatives. Thus it is surprising that systematic investigation of 1-methyl d-lysergic diethylamide (MLD) which has an antiserotonin action approximately equal to that of Sansert, has not been studied more intensively.[13] It has been safely taken in high dosages without psychic effects by ambulatory subjects in my studies of tolerance to LSD. Certainly the side effects of the 1-methyl derivative of LSD should be no greater, and indeed much less, than those of the butanolamide (Sansert).

Table 1 illustrates some of the compounds which have been studied in nonpsychotic subjects and their antiserotonin values. The first column indicates the relative strength in regard to LSD as determined by the Cold Spring Harbor questionnaire, and the second column indicates the anti-serotonin effects as reported by Cerletti and his coworkers.

The investigation of the compounds under discussion in disturbances of mental and allergic states is bound to open new avenues for research and treatment. It is to be hoped that the restrictions placed on the study of compounds of this type by the Food and Drug Administration will soon be removed and that the practicing physician will once more play his important role in the evaluation of drugs in the therapy of human diseases. Without the help of the practicing physician we shall have to look again to Europe for guidance in the study of

TABLE I

A comparison of psychotomimetic and antiserotonin activity. Note that MLD has an antiserotonin activity similar to UML (Sansert). Antiserotonin data after Cerlette et al.[13]

	Activity	Anti-Serotonin Activity
d-lysergic acid diethylamide (LSD)	100	*100*
acetyl d-lysergic acid diethylamide (ALD)	91	210
oxymethyl d-lysergic acid diethylamide (OML)	66	59
1-methyl d-lysergic acid diethylamide (MLD)	36	*370*
d-lysergic acid morpholide (SLM)	11	2
2 brom d-lysergic acid diethylamide (BOL)	7.2	103
d-lysergic acid pyrrolidide (LPD)	5.3	5
d-lysergic acid ethylamide (LAE)	3.4	12
1-methyl d-lysergic acid butanolamide (UML)	.66	*400*

new drugs. This was the situation before World War I. We are rapidly regressing toward that period. Let us hope that the anxieties of a small group will be replaced by a more hardy spirit of inquiry and scientific investigation.

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References

1. COHEN, S., Lysergic acid diethylamide: side effects and complications. *J. Nerv. and Ment. Dis.*, **130**:30 (1960).
2. ABRAMSON, H. A., Ed., The Use of LSD in Psychotherapy, Josiah Macy, Jr. Foundation, N. Y. (1959).
3. DITMAN, K. S., HAYMAN, M. AND WHITTLESEY, J. R. B., Nature and frequency of claims following LSD. *J. Nerv. and Ment. Dis.*, **134**:346 (1962).
4. HOFMANN, A., Chemical, Pharmacological and medical aspects of psychotomimetics. *J. Exp. Med. Sci.*, **5**:31 (1961).
5. BENDER, L., GOLDSCHMIDT, L. AND SANKAR, D. V. S., Treatment of autistic schizophrenic children with LSD-25 and UML-491. Recent Advances in Biological Psychiatry. **4**:170 (1962). BENDER, L., FARETRA, G. AND COBRINIK, L., LSD and UML treatment of hospitalized disturbed children. Recent Advances in Biological Psychiatry, **5**:84 (1963).
6. HARRIS, M. C., Serotonin. Its possible relationship to allergic disease. Cal. Med., **9**:68 (1959).
7. WAALKES, T. P., AND COBURN, H., The role of platelets and the release of serotonin and histamine to anaphylaxis in the rabbit. J. Allergy, **31**:395 (1960). WAALKES, T. P. AND COBURN, H., The role of platelets and the release of serotonin and histamine during anaphylaxis in the rabbit. J. Allergy, **30**:394 (1959).
8. O'BRIEN, D. J., HUGHES, F. W. AND NEWBERNE, J., Influence of lysergic acid diethylamide on experimental allergic encephalomyelitis (27832). Soc. for Exp. Biol. and Med. **111**:490 (1962).
9. ABRAMSON, H. A., Lysergic acid diethylamide (LSD-25): XXIX. The response index as a measure of threshold activity of psychotic drugs in man. J. Psychol., **48**:65 (1959).
10. DALESSIO, D. J., On migraine headache: serotonin and serotonin antagonism. J.A.M.A. **181**:318 (1962). FRIEDMAN, A. P. AND ELKIND, A. H., Appraisal of methysergide in treatment of vascular headaches of migraine type. J.A.M.A., **184**:125 (1963). GRAHAM,

J. R., Methysergide for prevention of headache. Experience in five hundred patients over three years.

11. SANDISON, R. A., In Hallucinogenic drugs and their psychogenic use. Ed. Crockett, R., Sandison, R. A., and Walk, A., Chas. C Thomas, Springfield, Ill.
12. ABRAMSON, H. A., ROLO, A., SKLAROFSKY, B., AND STACHE, J., Production of cross-tolerance to psychosis-producing doses of lysergic acid diethylamide and psilocybin. J. Psychol., **49**:151 (1960). ABRAMSON, H. A., SKLAROFSKY, B., BARON, M. O., AND FREMONT-SMITH, F., Lysergic acid diethylamid (LSD-25) antagonists. II. Development of tolerance in man to LSD-25 by prior administration of MLD-41 (1-methyl-d-lysergic acid diethylamide). Arch. Neurol. & Psychiat. **79**:201 (1958). ABRAMSON, H. A., HEWITT, M. P., LENNARD, H., TURNER, W. J., O'NEIL, F. J., AND MERLIS, S., Lysergic acid diethylamide (LSD-25): XXIV. The stablemade concept of therapy as affected by LSD in schizophrenia. J. Psychol., **45**:75 (1958). ABRAMSON, H. A., Ed., The use of LSD in psychotherapy, Josiah H. Macy, Foundation, N. Y. (1959).
13. CERLETTI, A., AND DOEPFNER, W., Comparative study on the serotonin antagonism of amide derivatives of lysergic acid and of ergot alkaloids. J. Pharm. Exp. Therap., **122**:124 (1958). CERLETTI, A., SCHLAGER, E., SPITZER, F., AND TAESCHLER, M., Psychopharmaka. Med. und Pharm., Shweiz. Apoth.-Ztg., **101**:210 (1963).

See also article by Cole, J. O. and Katz, M. M., The psychotomimetic drugs. J.A.M.A.' **187**:758 (1964), as well as an article in the April (1964) issue of the Scientific American.

Addendum

It seems clear from the cogent data presented at a recent symposium sponsored by the New York Academy of Science and the National Multiple Sclerosis Society, January 20–22, 1964, that experimental allergic encephalitis in animals has the immunologic qualities of a truly allergic process. The evidence presented includes (1) A specific low molecular weight protein is the allergen. (2) Passive transfer of sensitized adult lymphoid cells induce susceptibility to this allergen. (3) A delayed type of hypersensitivity is present. (4) The disease may be suppressed by passive transfer of encephalomyelitis serum. (5) Serum containing circulating antibody to whole brain induces demyelinization of neurons in tissue culture.

Since experimental allergic encephalitis is the closest model for multiple sclerosis, experimentation in man correlating the data for animals presented here should be organized. It is hoped that present regulations which deal with investigational drugs like LSD 25 will be changed so that the complicated clinical studies can be carried out by physicians taking care of multiple sclerosis patients and will not be prevented. At present only physicians with government (Federal and State) supported investigations may use LSD and its congeners with the exception of methysergide (Sansert).