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## Treatment of Autistic Schizophrenic Children with LSD-25 and UML-491

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Autistic schizophrenic children present challenging and baffling problems in treatment. Without attempting to deal again with the controversial issues concerning the definitions and etiological factors of either childhood schizophrenia [1] or the autistic reaction pattern [2], we will refer to the various treatment regimes attempted by Bender and co-workers in the past quarter of a century with these children. Many of the children have been followed subsequently into later childhood, adolescence, and adulthood [3]. Meanwhile, a new group of young autistic children are always available for new treatment endeavors as the new modes become available.

### THERAPEUTIC MEASURES AND RESULTS

Thus, the following have been tried [4]: Metrazol [5], electric convulsions [6], subshock insulin, many psychopharmaceutical agents [7-10], the milder antihistamines (Benadryl), amphetamines, anticonvulsants, muscle tone stimulants (Tolserol), meprobamates, phenothiazines, reserpines, antidepressants, tranquilizers, etc.

The goal in these therapeutic efforts has been to modify the secondary symptomatology associated with retarded, regressed, and disturbed behavior of the children. There has also been a conviction that the treatment goal was directed at some basic disorders associated with early schizophrenia. It was thought that the treatment not infrequently did succeed in nudging the lagging maturation in all behavior areas, thus enabling the child to carry on with a more normal development. It was also believed that plastic embryonic patterning, characteristically schizophrenic, in visceral-

vegetative functions should be overcome and that increased tone and motor patterns should be stimulated in the unstriated muscles of the vascular bed and of the respiratory and gastrointestinal systems as well as in the striated muscles of the motor systems. It was recognized that the perceptual sensitivity of the schizophrenic infant [11] and the perceptual distortion of the older child needed correction, but no direct approach seemed available. Of course, there are other problems: anxiety; stereotyped, rhythmic, and manneristic motility; mutism; inadequate or inappropriate language; psychosomatic or allergic illnesses; negativistic, ambivalent, and erratic attitudes and behavior; and regressive, fixated, and accelerated episodes in maturation. Autism appears to be a defensive reaction in the disorganization resulting from schizophrenic symptoms.

Many of the medical treatment measures, together with new social and educational experiences in a hospital and guidance and therapy for the parents, have been sufficiently successful in some cases and partially successful in an increasing number of cases to justify a search for more potent agents [12]. Furthermore, other significant observations have been made:

1. Prepuberty schizophrenic children react differently from adults to all physiological and pharmacological agents. This different response offers new data for understanding the schizophrenic phenomena, defense mechanisms, and the physiological and pharmacological agents. These areas of investigation justify much more exploration than has so far been done.

2. Children show much less side-effects to drugs so that larger doses can be used.

3. Children also appear to develop tolerance more slowly and do not suffer withdrawal symptoms when the drug is stopped.

4. Children's reactions to drugs are often paradoxical; for instance, tranquilizers prove to be maturational stimulants and behavior organizers and amphetamines do not interfere with sleep or appetite and improve interpersonal relations and learning ability.

With these experiences in mind and with awareness of the current interest in LSD-25 as a therapeutic agent [13] because of its psychotomimetic properties, it occurred to us that LSD might be effective in breaking through the autistic defense in chronically regressed, retarded, mute, and withdrawn children.

The theoretical interest in LSD as a serotonin inhibitor, with consideration of the possibility that serotonin is in some way re-

lated to schizophrenia, further justified this endeavor. Also, since LSD is an autonomic nervous system stimulant, it could be of particular value in treating schizophrenic children, in whom general tissue tone, especially the tone of the vascular system, and the pattern of the autonomic nervous system functions are impaired.

#### MATERIALS AND METHODS WITH LSD

A treatment program was planned for 14 schizophrenic children under the age of eleven, who had been under hospital care for a considerable period and previously tried on a variety of treatments with inadequate response. There were 11 boys and 3 girls with an age range of six to ten and a half years of age.

An acute experiment was planned first. In groups of five the children were given 25  $\mu$ g of LSD-25\* intramuscularly while under continuous observation. The two oldest boys, over ten years, near or in early puberty, reacted with disturbed anxious behavior. The oldest and most disturbed received Amytal sodium 150 mg intramuscularly and returned to his usual behavior. Neither of these boys was continued on this treatment program at that time.

The twelve other children reacted to the intramuscular injection of 25  $\mu$ g of LSD with similar behavior in varying degrees. They appeared to be in an elevated or "high" mood. They were gay and playful and accepted contact with an adult in their tentative, teasing, playful activities, which included ball playing, paper tearing, motor play, rhythmic hand clapping, and body swaying. They appeared flushed, bright eyed, and unusually interested in the environment. The height of the reaction occurred in 30 to 40 minutes and continued 2 to 3 hours. These acute experiments were repeated several times, and then the LSD was given orally and increased to 100  $\mu$ g once a week in the early morning. Then it was increased gradually to twice and three times a week as no untoward side-effects were noticed, and it was observed that the reaction to the drug persisted. Finally, it was given daily, and this was continued for six weeks until the time of this report.

As a brief description of these children it may be pointed out that before hospitalization all of these children had been examined by one or several professional workers in the community, and the diagnosis of autism and schizophrenia had been accepted. All these children and their parents, had experienced considerable psycho-

\* All of the LSD-25 was furnished by Sandoz Pharmaceuticals.

therapy, and all had had some form of physiological and pharmacological therapy in the hospital. The parents of this group of children were all adequate but could not keep the children at home because of the severity of the retarded, regressed, and disturbed behavior. The children were all without any useful language; some were completely mute, some had a few words they used occasionally, and the others had psychotic, noncommunicative language. None of these children were testable with any of the standard psychological tests nor would they perform any paper-pencil tests.

At the outset of the treatment, all were removed from the medication that they then were receiving. Blood, urine, and liver function tests were done. Blood was also drawn for Dr. Sankar's biochemical studies.

A Vineland Maturity Scale determination was made on each child (by Dr. Goldschmidt with ward personnel, teachers, and mothers). On this scale the estimated social maturity score ranged from 2-3 to 5-7 years, while their chronological ages ranged from 6-1 to 10-6 years. The range of the social maturity quotient was 32 to 60.

### RESULTS WITH LSD AND CONCLUSIONS

A summary of the re-evaluation of the children in the course of treatment is as follows:

1. All tolerated the drug without side-effects, toxic features, regressive behavior, or other untoward responses.
2. All were able to get along without any further medication, although they had been accustomed to receiving other medication before the LSD was given to them.
3. All have shown some mild degree of favorable response with slow and steady progression. The amount has varied from child to child. There have been no regressions although some children have had episodic recurrence of behavior familiar to them, such as feces smearing and aggressive contact with other children.
4. In general, they were happier; their mood was "high" in the hours following the ingestion of the drug, and this tended progressively to carry over through the whole day.
5. They have become more spontaneously playful with balls and balloons. They participate with increasing eagerness in motility play with adults and other children if directed by adults.
6. They no longer push other children away or show hostile aggression to them as much as they formerly did.
7. They seek positive contacts with adults, approaching them

with face uplifted and bright eyes, and respond to fondling, affection, etc.

8. Habit patterning is improved. They handle food better and eat better. Two became toilet trained.

9. Their physical condition has improved. Their color is rosy rather than blue or pale, and they have gained weight.

10. There is less stereotyped whirling and rhythmic behavior.

11. Ordinary environmental stimuli and situations are better understood and are reacted to appropriately. Thus, they respond to their own name and react appropriately to "yes" and "no." They fall into routine more spontaneously, and several carry out small commands. One anticipates routine and assists in holding a door open and directing other children to the dining room.

12. The Vineland Maturity Scale rating was qualitatively higher in all children. A quantitative gain of 1 point was shown by one child and 2 points by another child.

13. No children showed a recordable gain in the use of language.

Dr. Sankar's biochemical findings were as follows: the administration of LSD-25 to children seems to increase the inorganic phosphate of both plasma and erythrocytes. Thus, out of 26 laboratory analyses of 14 children, 18 samples showed an increase in the plasma inorganic phosphate within an hour after the drug was given parenterally. This increase amounted to approximately 26% on the average. Similar results (unpublished) have also been obtained in animals in our laboratories. However, as the therapeutic effects of LSD-25 given orally seem to become noticeable, this phosphate effect of LSD-25 either decreases or, on the other hand, there is a decrease in the plasma inorganic phosphate with an equal number of subjects showing an increase in the inorganic phosphate content of the erythrocytes. On repeated administration, out of 14 cases only 7 showed an increase in plasma inorganic phosphate while only 4 showed an increase in erythrocyte inorganic phosphate.

Our conclusions were that LSD-25 given daily in oral doses of 100  $\mu$ g to prepuberty autistic schizophrenic children appears to be an effective autonomic and central nervous system stimulant. It appears to have some effect on the tone of the vascular system, on the level of mood, and on the phosphorous level of the blood serum and erythrocytes as well as in the organizing of perceptual experiences. These changes appear to be chronic with continuous administration of the drug and to have a favorable influence on the clinical course.

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## EXPERIENCES WITH UML-491

Meanwhile, UML-491 (Sandoz) has become available. This is L-methyl-D-lysergic acid butanolamide, a methylated derivative of LSD. It is considered to be (like BOL) nonpsychotomimetic but a more powerful serotonin-inhibiting agent and more effective in relation to the autonomic nervous system. It has been promoted as a prophylactic against migraine headaches.\* It is in this connection that one of us (Dr. Bender) became acquainted with this pharmaceutical agent, in the search for relief from life-long classical migraine or vascular headaches.

During the years when schizophrenic children have been observed and migraine symptoms experienced, intriguing similarities of the two conditions have been noted. This includes the various autonomic nervous system disorders, distorted and hypersensitive reactions to perceptual experiences, the disorder in the tone of the vascular bed, the tendency to autistic withdrawal, and the familial histories. Serotonin has been under consideration as a factor in both conditions [14, 15]. It may be suggested also that the two conditions are self-exclusive.

The principle in the use of UML-491 for migraine headaches is based on its serotonin-inhibiting and autonomic nervous system effective properties. It is given prophylactically in sufficient dosage to maintain a chronic blood level (beginning with 8 mg daily in four divided doses and maintained with 4-mg Spacetabs twice daily).

After the first dose of UML, a reaction was observed similar to that of the children after their first dose of LSD. Subsequently, other similarities were noted between the response of schizophrenic children to LSD and that of the migraine symptoms to UML. The following were experienced: a lift in mood; motor restlessness; irritability; localized muscle tensions or spasms; mild "crawling" skin sensations; more clearly defined and satisfying visual (color) and auditory (music) experiences; a smoothing out of the autonomic nervous system functions; relief of episodic headaches; relief in perceptual hypersensitivity in visual, auditory, olfactory, and skin sensations and in allergic reactions; and a general sense of well-being with an improved sleep pattern.

Needless to say, this experience has encouraged us in the plan to pursue the study of LSD and its derivatives, especially UML, as therapeutic and investigative agents in childhood schizophrenia.

\*Sandoz Pharmaceuticals, especially Rudolph P. Bircher, M.D., has made available to us the information about this compound as well as the UML-491 itself for this study.

We immediately placed eight autistic schizophrenic children on UML-491, 8 mg in four divided doses orally. During the three initial weeks the children have tolerated the drug well. There have been some brief (20-minute) episodes of reactions to changing muscle tensions and kinesthetic sensations with clowning, staggering gait, and twisting of the neck, back, and arms. One child had a brief episode when his extremities were pale and cold and the superficial veins were conspicuous. He shivered and crawled into bed as though cold, but he soon recovered. In general, they reacted as the children receiving LSD, with a lift in mood and increased activity. They appear brighter, more outgoing, and less stereotyped in behavior.

### CONCLUSION

The use of these two drugs with the possible use of other derivatives, such as BOL, in autistic schizophrenic children with combined clinical and biochemical investigations will give us more knowledge about both the basic schizophrenic process and the defensive autism in children and also about the reaction of these dilysergic acid derivatives as central and autonomic nervous system stimulants and serotonin antagonists. Hopefully these drugs will also contribute to our efforts to find better therapeutic agents for early childhood schizophrenia.

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