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D-Lysergic Acid in the Treatment of the Biological Features of Childhood Schizophrenia

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In the Children's Unit of Creedmoor State Hospital, with a resident population of 400 patients, ages 4 to 15, we have investigated responses of some of these children to d-lysergic acid and related drugs in the psychiatric, psychological and biochemical areas and the autonomic nervous system and have reported our impressions in various publications and meetings[1-4,7,10].

Our original interest in this drug was in part due to its psychedelic effects, hoping to break through the autistic defenses of severely schizophrenic children. We started in January 1961 and gave to five prepuberty autistic schizophrenic children, under careful personal observation, single doses of LSD-25 at weekly and semi-weekly intervals. It soon became evident, however, that these children did not show the psychotomimetic responses described in adults. They showed a heightening of mood, and what appeared to be a physiological stimulation in vasomotor areas, in muscle tone both visceral and locomotor, an increased awareness of the world about them and a lessening of stereotyped, rhythmic behavior, such as whirling. These are the areas of disturbance most significant in young schizophrenic children.

We were aware also of the theoretical interest in d-lysergic acid and its derivates as serotonin inhibitors, while it has been suggested that serotonin may play some part in the cause or course of schizophrenia[9].

Brodie[4] has described the effects of d-lysergic acid and its derivatives as "arousal and increased responsiveness to sensory stimuli, preponderance of sympathetic activity and increased skeletal muscle tone and activity." He indicated that this was due to interference with the action of serotonin. There are also the known effects of LSD of increasing the vividness of perception in all areas and emphasizing the reality of perceived objects. They are described for mescaline by Aldous Huxley in *The Doors of Perception*[8].

The tonic effects on the vascular bed, especially of the brain, of the d-lysergic acid derivatives, are of great interest. They have been shown specifically with UML-491, (Methysergide or Sansert, Sandoz) a methylated derivative of d-lysergic acid, in the preventive treatment of vascular or migraine headaches.[18] UML has less of a psychotomimetic effect and more serotonin inhibiting and autonomic nervous system activating effect than LSD-25. Dalessio[6] speaks of

"aberrations in central vasomotor functions. . . associated with excesses of cranial vascular reactivity which characterizes the migraine headache attack" and that "methysergide (Sansert) exerts its effect by modulating central vasomotor functions and potentiating vasoconstrictor responses of cranial blood vessels to serotonin."

We noted the marked similarity of symptoms in early childhood schizophrenia and migraine headache during an attack; in vasovegetative function, in autonomic nervous system patterns, in unpleasant perceptual distortions, in personality withdrawal response and the mood of instability and hostility.

Clinical Studies

We soon gave up the single dose at weekly and biweekly intervals, finding that the children could tolerate and benefit from daily doses up to 150 micrograms (orally in two divided doses).

The autistic children showed evidence of a gradual improvement in physical condition and maturation and in behavior. Their eyes were bright and they looked at us. Their facial expression was more alert and their color was more natural. Eating and sleeping habits improved. They were more responsive to the environment and improved in their ability to follow routine and made some small attempts at playing with an adult or another child. There seemed to be more comprehension of speech and attempts to communicate, though minimal. Disturbed behavior such as head banging and self-mutilation diminished markedly, although this behavior in these children had not responded to other forms of medication, which was entirely discontinued before and during the use of LSD. In general, these effects were

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most marked during the first weeks of treatment.

Encouraged by this preliminary study, we extended the use of LSD and also UML (8 to 12 mg. per day, orally in two divided doses) to about 50 children, including more young and some older autistic children, confirming the above observations and adding many others.

In a later study we gave these two drugs, LSD and UML, to a group of verbal but psychotic pre-adolescent boys. These schizophrenic patients showed similar disturbances in interpersonal relationships, reality contact, perception and autonomic patterning, but of course not to the same degree as the autistic children. They were anxious, preoccupied with fantasies and dreams, and hypochondriacal. They followed the routine of school and recreation in the hospital but had no individual psychotherapy.

The most notable effect in these children was an improvement in their overall behavior and attitudes, improved reality contact, and a trend toward more mature, almost adult type of thinking. For instance, bizarre fantasies and preoccupations disappeared or were denied, and more realistic though often somewhat paranoid and depressive ideas were expressed, often with considerable insight.

None of these patients developed the acute psychotic reactions described in adults. Where suitable homes or placements in the community were feasible, these children left the hospital within nine months of the start of treatment and remained outside.

We have described schizophrenic children as unpatterned, with homeostatic instability, poor tone, pallor, and impaired physiological response to stress and illness. We noted the improved tone, flushing, decreased tendency to pallor and blueness of lips and fingers, improved gastro-intestinal regulation, weight gain, regularities of sleep and less irregularities in pulse and respiration with LSD and UML.

Specific studies on the autonomic nervous system were made by Dr. Gloria Faretra in 1963[7]. Thirty boys (17 schizophrenic), nine to twelve years of age, received injections of saline, adrenaline and pilocarpine, before receiving medication with LSD-25, UML-491 and psilocybin, and after two to four, or six to eight weeks of medication. Suitable clinical and psychological studies with records of blood pressure, pulse, and respiration were made with each injection (Funkenstein test).

Results showed an increasing potentiation of the normal blood pressure responses to epinephrine injection and a less marked action on the response to pilocarpine with all three medications. Pulse and respiration responses were less conclusive; temperature showed a slight decrease in each test series. There was no marked difference in findings when the cases were divided diagnostically and no differences among the three drugs.

These findings suggest that these drugs (LSD, UML and psilocybin) in children, potentiate the reactions of the sympathetic system, and either lower or have less marked effect on the para-sympathetic system. These effects continued in our test series for six to eight weeks. In addition, we observed during treatment with these drugs at this time and in previous studies, clinical changes in homeostatic functioning, such as improved color and tone, more patterned behavior, and better eating and sleeping habits, thereby relieving some of the disturbed and distressing symptoms of the schizophrenic child.

Psychological Studies:

Appropriate psychological studies were always made on the children before, during, and after treatment with these drugs. These were done by Leonard Cobrinik, Ph. D.

Autistic children cannot be tested on standardized psychometric tests that require their response or participation. For these children we used the Vineland Social Maturity Scale, which depends upon reports of an observing adult.

In the initial study on autistic boys whose chronological age was 6-1 to 10-0 years, the Vineland social maturity age (S.A.) before treatment was 2-3 to 5-7 years and the range of the social maturity quotient (S.Q.) was 32 to 60. After six weeks of treatment the Vineland Maturity Scale rating was qualitatively higher in all children. A quantitative gain of one point was made by one child and two points by another. Improvement was recorded in (1) happier "high" mood; (2) spontaneous playfulness; (3) less hostility to other children; (4) positive contact with adults; (5) habit patterning improved in eating (two became toilet trained); (6) less stereotyped whirling and rhythmic behavior; (7) better response to environment and routine. After 18 months, during which time three boys received medication with LSD or UML, their gain in social age on the Vineland Social Maturity Scale was

0.6 years to 1.2 years (average 1.1 years). The quality and extent of improvement seemed even greater than measured by the scale.

The 12 prepuberty psychotic schizophrenic boys, selected because they were verbal and could be interviewed psychiatrically and tested psychologically, were treated with LSD and UML. All were tested at the beginning of treatment with the WISC, the Rorschach, the Human Figure drawing, the Bender-Gestalt, and educational achievement tests. Half were retested once three months later, the other half had also a third test six months later, and three were tested a fourth time a year later.

Intellectual changes as seen in the psychometric tests, indicated improved maturity, better organization and motivation with a rise of IQ which was reflected in improved school work. The Rorschach and drawing tests also showed improved maturity and control with clearer thinking. Improvements were noted in children who were initially characterized as average or near average intelligence. They showed a decrease in strong feeling reactions (to color in Rorschach) and a decrease of individualized (or bizarre) thinking and fantasy, with a corresponding gain in accuracy of response. The most marked improvement was in the area of thinking disorders. Such changes as were noted occurred early in the treatment program, that is within the first three months period. Most of the gains were maintained over the longer period (about 1½ years) although there was some fluctuation or variability in the general level of response. Two children, less well endowed than the rest, did not show these evidences of psychological changes or intellectual gains but did show a marked difference in human figure drawings with more maturity and control.

Biochemical Studies

Biochemical studies were made by D.V. Siva Sankar, Ph.D. concurrently with most of these clinical studies[1,3,10]

The effect of a given single dose (100 micrograms) of LSD both at the beginning and in the course of therapy over a few weeks was studied. The children reacted with a rise in erythrocyte inorganic phosphates within one hour of the administration of LSD. However a single dose of LSD was less effective later in the period of study than in the beginning. Approximately 70% of the children showed an increase in the RBC inorganic phosphate in the beginning of the study, only 29% showed an increase later. This may indicate tolerance to, or a decreased effectiveness of, a given single dose of LSD in the later phase.

Sankar et al[11] have shown that the intake of labeled serotonin by blood platelets from autistic schizophrenic children was lower than that of non-schizophrenic children in the hospital at the same time. The blood content of serotonin was shown to be higher in autistic children also by Schain and Freedman[12]. It was thought that this may be due to a low metabolic rate of serotonin in these children.

Sankar[3] found that both LSD and UML increased the level of serotonin through a period of 23 days study, starting a week after the beginning of the administration of the drug, and persisted until the end of the study. With a crossover to reserpine the serotonin level was lowered.

The administration of LSD and UML increases the platelet uptake of serotonin in these children over the first few weeks, after which it decreases to a lower level. This raises questions about the metabolic rate of serotonin, the saturation point of platelets over a period of time.

Our studies by Sankar et al, 1964[10] seem to support the hypothesis that LSD-25 steps up metabolism and may act by binding serotonin and histamine and releasing norepinephrine. It is hypothesized that LSD-25 exerts its effects through the release of norepinephrine and activation of the sympathetic system. When there are high levels of serotonin, the homeostatic mechanisms may come into play and cause both inactivation of the serotonin by binding and further release of norepinephrine. This may be accompanied by reduction of the levels of free histamine and increase in the level of bound histamine.

Unpublished Current Studies

Doctors Dowling, Dooher and Winn are currently involved in a carefully structured study of six pairs of matched prepuberty schizophrenic boys. Six received LSD up to 150 micrograms daily, while the paired six received no drugs. The objective of the study is to observe for alterations or stabilization of several modalities during the first ten days of treatment with the LSD, during which time the children were examined for 1) soft neurological signs; 2) gross sensory functions; 3) gross memory function, and 4) perceptual motor and body image functions.

Neurological signs: The six control children showed the type of variability in functioning that is common in children of this age and always more marked in schizophrenic children. The children receiving the LSD showed alteration in hopping, tandem walking, drifting of outstretched arms, whirling, penmanship, and varying alterations in ocular convergence and pupillary responses.

Sensory perception: No alterations were observed by the gross methods used.

Memory function: No changes were noted in the tests used in any of the children other than learning effect evident in both controls and LSD-treated children, with the exception that three of the LSD-treated children were hesitant and distracted the first three days of the test, but returned to normal by the tenth.

Perceptual motor function: In the first days of LSD treatment, the Bender Visual Motor Gestalt test figures tended to become disorganized and expanded. By the tenth day reorganization appeared but was not complete.

Body image function: The human figure drawings changed most in individual children by expansion or constriction.

In general, alterations noted in neurological signs and memory function were most marked in the first three days and were returning to normal by the tenth. Alterations in visual motor and body image function were also most disorganized the first days and tended to reorganize, even with improvement, in the second week but remained dissimilar to pre-treatment observation or those on control children.

Summary

Schizophrenic children receiving d-lysergic acid or a derivative in daily adequate doses are without toxicity, side effects or gross emotional reactions. They show alterations in mood, appearance of physical well being, responsiveness, habit patterning, soft neurological signs, sympathetic nervous system stability, integrated perception, reality testing, thought processes, fantasy content and intellectual and personality maturity.

There are concurrent biochemical changes in the binding of serotonin and freeing of epinephrine. Some of these alterations occur in the first few days, others in the first few weeks and tend to level off, others continue for many months and are integrated into a more healthy and mature level in the development of the child.

Participating in these studies have been Gloria Faretra, M.D., Psychiatrist; D. V. Siva Sankar, Ph. D., Biochemist; Leonard Cobrinik, Ph. D., Psychologist; Lothar Goldschmidt, M. D., Psychiatrist; and many others. A current, still unpublished study, is being done by Lillian Dooher, M. D., Jean Dowling, M. D., and Don Winn, M. D.

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