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Two years ago, a team of child development specialists and researchers at TRIMS joined a nationwide study to find out whether or not fenfluramine, an appetite-suppressant drug that also lowers brain serotonin, would improve the behavior and learning ability of autistic children and young adults.

Drs. Edward Geller, Edward Ritvo, and Betty Jo Freeman of the University of California at Los Angeles had shown that the drug helped three autistic boys control their severely disordered behavior and relate better to their families and environment. The children's plasma serotonin levels decreased and their IQ scores rose. After three months without medication, however, their serotonin levels were elevated again and their learning and behavioral improvements were gone.

Autism is included in *DSM-III* as one of the pervasive developmental disorders—disorders in which there is a *distortion* rather than only a delay in the multiple psychological skills necessary for socialization, learning, and language. Although the IQs of autistic persons range all the way from profound retardation to superior intelligence, most have severe learning and social deficits, and many injure themselves involuntarily.

About 40 percent of autistic persons have blood serotonin levels elevated to one degree or another, which suggests a link between autism and this biochemical abnormality—and the possibility that fenfluramine might be helpful.

The relationship of the neurotransmitter serotonin to autism is particularly interesting to researchers—and certainly to parents of autistic children—because understanding the biological mechanisms of this extremely disabling condition might contribute to treatment knowledge, keep more autistic people out of institutions, and, at its best, help to prevent the disorder. As Ritvo said, the study may at least reveal subcategories of autism by showing which kinds of patients respond to fenfluramine and which ones do not.

We joined this study with 17 other centers throughout the country. We chose 16 autistic persons for our group; the total nationally was 150. Our participants did not have seizures and were not taking psychotropic medications. Their IQs ranged from 9 on the Merrill-Palmer developmental scale to 124 on the

Fenfluramine and autism

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Wechsler Adult Intelligence Scale, their ages from nine to 24. Six participants were severely retarded, four were profoundly retarded; one-half of the 16 were nonverbal. All children were evaluated by our interdisciplinary team to confirm the diagnosis and identify factors that would exclude them from the study.

The final report of the multicenter collaborative study has not yet been published, but our study indicates so far that fenfluramine benefits some autistic persons and not others.

Our study was conducted in two phases. The first consisted of two weeks of baseline testing, followed by seven months during which parents and profes-

sional evaluators did not know whether the participants were taking fenfluramine or placebo. The intervals were one month of placebo, four months of fenfluramine, two months of placebo, in a sequence known only to the principal investigator (Lewis).

The second phase, from which data are not yet available, consisted of an eight-month double-blind study with a crossover at four months. All investigators, including Lewis, were blind during this phase.

The fenfluramine dosage was 1.5 mg/kg/day, divided into two doses administered every 12 hours. Fasting whole-blood serotonin was measured at each monthly visit with the fluorometric technique of Yuwiler. The participants' initial serotonin levels ranged from 128 to 560 ng/ml, mean 384 (normal children's levels are 250 to 350 ng/ml, those of normal adults 150 to 250).

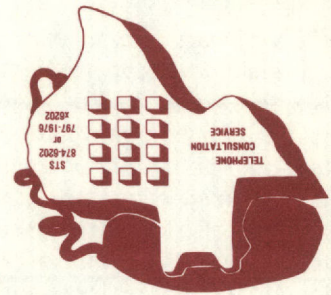
We measured the participants' intellectual levels at intervals and videotaped their behavior during play with standard toys in the presence of a nonresponding observer. We administered the Ritvo-Freeman Real Life Rating scale, adaptive behavior tests, measured the participants' height and weight, and videotaped child-parent interactions. The parents kept a log of the children's behavior at home.

After seven months of the first-phase study with 13 participants (several parents removed their children from the study because the children seemed not to be improving, or they lived too far from the clinic, or for another reason we will explain), we have come to these

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preliminary conclusions:

- Fenfluramine is effective in improving attention, relatedness, and language in some autistic persons.
- For most children the gains are not sufficient—our standard instruments are not sensitive enough to measure them—to result in significantly improved ratings of intelligence and adaptive behavior.
- The best result is the reduction of the autistic symptomatology itself. The drug seemed to improve the participants' relatedness and communication, reduce their bizarre behavior, and increase their attention to learning tasks. These were reflected by the parents' records and the behavioral scores of the Ritvo-Freeman scale.
- Fenfluramine, which is not yet approved for treatment of autism by the Federal Drug Administration and is one of the FDA's "orphan" drugs, is probably safe for this purpose. Gains outweigh possible side effects of slight weight loss and a few days' drowsiness at first. Contraindicators may be a history of depression and initial blood serotonin levels significantly below normal.

We also have some observations that will not surprise our colleagues.

- Gains on fenfluramine are much more significant in children who are also in highly structured programs. The medication heightens the effectiveness of a good program; it does not replace it.
- During the placebo periods, hyperactivity and inattentiveness returned in a few days, and the participants' serotonin levels reverted to near baseline levels when measured one month later. For the participants living in unstructured settings, relatedness and behavior also worsened during the placebo periods, but more gradually. In a structured setting, we believe, even without the drug, autistic persons may be able to retain the improvements they made during drug administration.

- With reduction of autistic symptoms, the children may exhibit mental age-appropriate behavior that may be misunderstood as misbehavior. Structure, counseling, training, and understanding are mandatory if the autistic person is to achieve maximal gains from his or her new awareness. For example, one participant's heightened consciousness of his disabilities depressed him and he dropped out of the study. We believe that antidepressant medication for him and counseling for the patient and family would have helped him understand his new feelings.

Although preliminary data from some of the other centers indicate that participants with the highest initial intellectual scores gained most from fenfluramine, a lower-functioning autistic child in our study experienced the greatest improvement. His IQ rose from 33 to 44 on the Merrill-Palmer scale.

We cannot make firm conclusions because our sample was small, and neither the results of our second-phase study nor those of the multicenter study are yet available. We hope to repeat the study with a larger sample, however, this time including a broader group of people with pervasive developmental disorders, particularly clients who suffer from self-injurious behavior and who may have to enter institutions if no other treatment is found.

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