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Neurobiological studies of Down's syndrome

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December 1984-
January 1985

In a series of tremendous intellectual and scientific tides, molecular biology has advanced the relief of so many human afflictions that the rest, stranded high and dry, seem like immovable hulks. But perhaps, to use a psychiatric metaphor, the immobility is not in the objects but in the observers. The broad field of mental retardation has lingered for decades on such a reef.

And little wonder. Compared to research of cancer, stroke, heart diseases, and environmental threats in our culture, or malnutrition, malaria, and population growth in the Third World, molecular biological research of mental retardation has been a grain of sand on a wide beach. Nobody has designed or built training programs or research empires to grind out the hard data, while the few who do sail those waters are regarded as scientific curiosities by their peers—well-meaning, maybe even intelligent and talented, but devoted to useless obscurity.

Dr. Jerome Lejeune, professor of fundamental genetics and chief of the department of cytogenetics at the Hospital for Sick Children in Paris, the founder of cytogenetics as a scientific field and the first to identify a human chromosomal disease—Down's syndrome—provided fresh inspiration for helpers of the mentally retarded in his recent visit to the Texas Medical Center.

Lejeune was the first to treat successfully a chromosomal disease with a drug—the "fragile-X" syndrome with folic acid derivatives. Fragile-X syndrome is the second commonest single cause of mental retardation after Down's syndrome. Lejeune was able to improve half of his patients, some remarkably. The improvement was sustained even after some children relapsed temporarily when they were given the drug trimethoprim for infections. Trimethoprim contains a folic acid antagonist.

Further, Lejeune's paradigm showed why children treated for cancer with methotrexate suffer intellectual losses when their brains are irradiated, but not otherwise. Irradiation allows methotrexate to cross the blood-brain barrier, and the drug interferes with folic acid metabolism in brain cells as well as cancer cells. The paradigm even explained why fragile-X syndrome disappeared as a laboratory diagnosis: the commercial supplier of culture medium had put too much folic acid in the medium and the X-chromosome was no longer fragile. Lejeune, recognizing the problem, reformulated the culture medium. The disease "reappeared"!

In lectures at Baylor and the University of Texas at Houston, and in a long, stimulating conversation at TRIMS, Lejeune talked about his current ideas on the molecular biology and therapy of Down's syndrome. First, he said, the laboratory must serve the clinic. The development of a large clinic and statistics on categorical mental development enabled the Lejeune group to study as few as 20 children for only six months to learn whether a drug was useful or not. When Lejeune demonstrated a direct association between glutathione peroxidase levels in the children's blood and their mental performance, the search for an effective drug was on.

Simultaneously, his and other laboratories began painstaking studies of the 21-q22 segment of chromosome 21, which he had shown to be crucial in Down's syndrome. Lejeune's model suggested that one or more of the enzymes coded by chromosome 21 hold the key to improvement in Down's syndrome, especially those associated with one-carbon metabolism, the apparent final common metabolic path for nearly all genetic causes of mental retardation (except the so-called storage diseases like Tay-Sachs).

Six enzymes of the 21-q22 segment are known so far, and two have critical roles in one-carbon transfer. Lejeune pointed out that acetylcholine, a key central neurotransmitter, is itself synthesized from three one-carbon fragments. He believes that the occurrence of Alzheimer's disease in 20 to 30 percent of his Down's patients is directly associated with acetylcholine imbalance.

Clinical experience suggests that both Down's syndrome and Alzheimer's disease include a defect in the brain's cholinergic system. In Down's syndrome, for example, the patients' eyes do not react normally to acetylcholine agonists that ordinarily contract the pupils quickly. Nor do Down's syndrome patients show the normal cholinergic pupillary narrowing reflex of intense thinking.

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We cannot study the biochemistry of living brain cells in these patients, but we may gain some information about brain metabolism from positron emission tomography (PET) and magnetic resonance scanning research in the Texas Medical Center. In Canada, researchers used live neurons (gained from surgical procedures for unrelated problems) to study the electrical activity of single neurons in Down's syndrome. The National Institute of Child Health and Human Development has asked for proposals to raise mice for studies of trisomy-16, a mouse analog of Down's syndrome. The model has many complications. Perhaps cultured connective tissue cells from Down's patients will have to do for most current studies.

The transformation of Down's syndrome from an unfathomable chromosomal curiosity to a knowable problem in molecular neurobiology has been long in coming, but its arrival seems certain. As in phenylketonuria, the key must involve enzymatic transactions. Early research on the fragile-X syndrome yielded a simple paradigm of one-carbon metabolism that seems promising for Down's syndrome. Lejeune's latest experiments with s-adenosylmethionine, a key one-carbon supplier, hold considerable promise. Among other activities, this compound has shown remarkable usefulness in relieving major depression in non-Down's syndrome adults and is known—unlike many previous experimental chemicals—to have central neural activity. Whether it will prove helpful in Down's syndrome remains to be seen.

Now, however, combined research in molecular biology and mental retardation looks good. And listening to Dr. Lejeune gave us new hope.

TRIMS THERAPY NOTES
Dec. 1984-Jan. 1985 Vol. 6, No. 1

Clinical newsletter of the Texas Research Institute of Mental Sciences, the research-training-patient care facility of the Texas Department of Mental Health and Mental Retardation, an equal opportunity employer.

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