DIAGNOSIS OF FRAGILE X SYNDROME

Direct diagnosis by DNA analysis of the fragile X syndrome was studied in 511 persons from 63 families with the syndrome at the Institute National de la Sante et de la Recherce Medicale (INSERM), Unite 184, Faculte de Medecine, Strasbourg, France and other laboratories. Analysis of EcoRI and Eagl digests of DNA distinguished between the normal genotype, the permutation and the full mutation. The method was more reliable than cytogenetic testing. All 103 males and 31 of 59 females with full mutations had mental retardation. All mothers of affected children were carriers of either a permutation or a full mutation. Direct diagnosis by DNA analysis is an efficient primary test for the identification of fragile X syndrome after birth and prenatally (Rousseau F, Mandel JL et al. Direct diagnosis by DNA analysis of the fragile X syndrome of mental retardation. N Engl J Med Dec 12, 1991; 321:1673-81).

COMMENT. The authors propose that direct DNA diagnosis may be helpful in the differential diagnosis of mental retardation and in the genetic counseling of families with the fragile X syndrome. The use of a single EcoRI digestion to test for a fragile X mutation in boys or girls with unexplained mental retardation, late onset of speech, or autistic or hyperactive behavior is proposed even if there is no family history of mental retardation. The disease is caused by mutations that increase the size of a specific DNA fragment of the X chromosome. Affected persons have both a full mutation and abnormal DNA methylation. Persons with a smaller increase in the size of this DNA fragment (a permutation) have little or no risk of retardation but are at high risk of having affected children or grandchildren. Among persons with a full mutation, 100% of males and 50% of females will be mentally impaired, whereas the risk of retardation is about 3% in carriers of a permutation. The role of cytogenetic analysis in diagnosis must now be reevaluated.

The prenatal diagnosis of fragile X syndrome by direct detection of the unstable DNA sequence using Southern Blot Analysis is reported from The Department of Cytogenetics and Molecular Genetics, Adelaide Children's Hospital and Queen Victoria Hospital, Adelaide, Australia (Sutherland GR et al. N Engl J Med Dec 12, 1991; 325:1720-22). The carrier status of a cytogenetically normal woman in a family with the fragile X syndrome and the mutation in her male fetus were detected by analysis of a cordocentesis sample and led to the termination of the pregnancy.

Shapiro L from New York Medical College, Valhalla, NY, in an editorial, comments that cytogenetic analysis of fragile X syndrome may be relegated to a secondary role but should be used for index cases to verify that the typical fragile X mutation is present in the family

before DNA analyses are performed and genetic counseling undertaken. (N Engl J Med Dec 12, 1991; 325:1736-37).

NEUROCHEMICAL MARKERS IN RETT'S SYNDROME

The levels of endogenous biogenic amines and neurotransmitter receptors in the brains of 5 patients with Rett's syndrome and 6 normal controls were examined at The Johns Hopkins University, Kennedy Institute for Handicapped Children, The Department of Neurology and Pediatrics, The Johns Hopkins Hospital, Baltimore, MD and The National Institute of Mental Health, Washington, D.C. The patients with Rett's syndrome were all female and they had died at ages 4, 10, 12, 15, 21 years. The cause of death was unknown in 2, asphyxiation in 1, drowning in 1 and pneumonia, 1. The level of choline acetyltransferase activity was lower in many cortical and subcortical regions in the Rett syndrome brains as compared with the mean level in the controls. Endogenous dopamine levels in the superior frontal and superior temporal gyri, occipital cortex, and putamen were reduced. The authors note that these results suggest neurochemical features in Rett's syndrome similar to those found in Parkinson's and Alzheimer's diseases (Wenk GL, Moser H et al. Altered neurochemical markers in Rett's syndrome. Neurology Nov 1991; 41:1753-1756).

> **COMMENT.** The dopamine agonist, bromocriptine, used to treat girls with Rett's syndrome, has made them more relaxed, sociable, affectionate and attentive, the stereotyped hand-washing movements diminished and some patients spoke for the first time (Zappella M, Genazzani A. Wien Med Wochenschr 1986; 122:98). The hypothesis that a disturbance in the function of central dopaminergic systems in Rett's syndrome is related to a defect in maturation may also be extended to include the cholinergic neural system. The search for a biochemical marker for Rett's syndrome continues.

INFECTIOUS DISORDERS

MITOCHONDRIAL ENZYMES IN REYE'S SYNDROME

A nonuniform decrease in several mitochondrial residual enzyme activities in the liver and brain of a 42 year old woman who died with Reye's syndrome is reported from the Departments of Neurology and Pediatrics, Columbia Presbyterian Medical Center, New York, NY. Pyruvate carboxylase activity was negligible whereas subunits II and IV of cytochrome c oxidase were in normal quantities. There was no evidence for a specific insult to mitochondrial DNA or intramitochondrial protein synthesis. The trigger that precipitates the initial disturbance in the chemical micro environment of the mitochondrial matrix remains unknown. Restoration of mitochondrial ATP concentration repairs the disturbance of intramitrochondrial enzyme processing and is followed by recovery of organ function (Van Coster RN, De Vivo DC et al. Adult Reye's syndrome: a review with new evidence for a generalized