† **853** METHYLMALONIC ACIDURIA ASSOCIATED WITH FAILURE OF LYSOSOMAL RELEASE OF VITAMIN B_{12}. David S. Rosenblatt, Angela Pottier, Nora V. Matiaszuk, Bernard A. Cooper and Rachel Laframboise. Centre for Human Genetics, MRC Genetics Group, and Depts. of Biology, Pediatrics, Physiology and Medicine, McGill University, Montreal; Réseau de Médecine Génétique du Québec, CHUL, Québec.

Inborn errors of vitamin B_{12} metabolism affect the synthesis of only Ado-B_{12} (Cbl A and Cbl B), total vitamin B_{12} accumulation and the synthesis of both Ado-B_{12} and CH_3-B_{12} (Cbl C and Cbl D) or the synthesis of only CH_3-B_{12} (Cbl E). It is known that after transcobalamin II (TCII)-B_{12} binds to specific receptors on the plasma membrane, the complex is internalized by means of adsorptive endocytosis, following which the endocytic vesicle fuses with a lysosome, and the TCII is degraded by lysosomal proteases releasing free B_{12} which exits the lysosome. Fibroblasts from a patient with minimal methylmalonic aciduria accumulated normal total vitamin B_{12} but only unbound CN-B_{12} when incubated in TCII-[^{57}Co]-CN-B_{12}. In contrast to control fibroblasts virtually all of the B_{12} was found in the lysosomal fraction of the cells. Treatment of the cells with chloroquine resulted in the accumulation of TCII-bound B_{12} in the lysosomal fraction in both control and mutant fibroblasts. These data suggest that fibroblasts from this patient are able to endocytose TCII-B_{12} and to release the B_{12} from TCII in the lysosome. Because the mutant cells do not allow the B_{12} to efflux across the lysosomal membrane, they accumulate neither Ado-B_{12} nor CH_3-B_{12}. The defect thus appears to involve vitamin B_{12} transport across the lysosomal membrane.

854 FOLIC ACID BLINDED TRIAL IN IDENTICAL TWINS WITH FRAGILE X SYNDROME. David S. Rosenblatt, Susan F. Zeesman, Michel J.J. Vekemans, Ellyn A. Duschenes, Fiona V. Hellstrom, Margie S. Golick, and Eva Andermann. Centre for Human Genetics, MRC Genetics Group, McGill-Montreal Children's Hospital Learning Centre, Departments of Pediatrics, Biology, Pathology and Neurology, McGill University, Montreal, Quebec, Canada.

The syndrome associated with the fragile X has become recognized as a common cause of mental retardation in males and some females. The fragile X chromosome is expressed only when cells from the patients are grown in medium deficient in folic acid or containing a folate antagonist. This syndrome has been the subject of numerous reports, and recent investigations have addressed the question of whether the mental retardation is amenable to treatment with folic acid.

Monozygous twin 14 year old mentally retarded boys with the fragile X syndrome were treated either with 10 mg folic acid p.o. daily or with placebo for three test periods of three month duration in a blind study. For each twin, tests of cognitive functioning, reading, spelling and mathematic skills, and linguistic and perceptual skills were compared. Although there was considerable variation in performance on these tests during the two baseline periods, there were no observable beneficial effects of therapy. The routine use of folic acid in patients with established mental retardation and the fragile X syndrome is not indicated.

855 COHEN SYNDROME IN ISRAEL: GENETIC AND ETHNIC BACKGROUND. Joseph Sack, Eitan Friedman, Efraim Gazit. (Spon. by Gerald W. Fischer). Sheba Medical Center, Tel Hashomer Israel.

Cohen syndrome, a congenital disorder first described in 1973, is characterized by universal occurrence of mental retardation of variable degree and facial anomalies (short filtrum, high nasal bridge, high arched palate, prominent central incisors, malformed ears) as well as narrow hands and feet. To determine the genetic and ethnic background of this disorder, we evaluated 32 affected children from 25 Israeli families. The sex ratio was equal. In the 7 families with more than one affected child, one set of identical twins with Cohen syndrome was noted. Of the remaining 6 families with multiple affected siblings, in only two were the affected children HLA-identical. By contrast, in one family two HLA-identical siblings were discordant for Cohen syndrome. No affected child had a parent with the disorder. The ethnic background of affected children, expressed as ratio of Ashkenazi background (European) to Sephardic background (Middle-Eastern) was 2.5:1, in contrast to the 0.7:1 ratio among Israeli births in general. We conclude that Cohen syndrome is probably an autosomal recessive disorder which is not linked to the HLA locus but which has a predisposition for certain ethnic backgrounds (Ashkenazi).

856 NORMAL INTELLIGENCE IN CHILD WITH 46,XY,r18/45,XY,-18 Jack P. Shonkoff and Philip L. Townes, Univ. of Mass. Med. Center, Dept. of Pediatrics, Worcester.

We have developmentally followed a boy with ring 18 and monosomy 18 mosaicism (46,XY,r18/45,XY,-18) who is of average intelligence at 4 years of age and currently enrolled in a normal nursery school program. The proband was a 3289 gram product of an uncomplicated 42 week pregnancy. Initial examination revealed hypospadius and rockerbottom feet. The proband left the nursery at 24 hours of age in stable condition. Cytogenetic studies completed at 5 weeks of age revealed the ring 18 and monosomy 18 to be in a 90%:10% ratio. Medical history is significant for surgical correction of bilateral vertical tali, hypospadius, and bilateral inguinal hernias. Family history is unremarkable. Repeat cytogenetic studies at 2 years of age confirmed prior findings (90% 46,XY,r18; 10% 45,XY,-18). Parental karyotypes were normal. Early development was mildly delayed and intervention services initiated. Consistent progress was noted in all areas with strengths in visual-motor skills and relative deficits in expressive language and motor coordination. Assessment at 3 years 11 months revealed mental age of 3-10(Stanford-Binet), social age 3-7 (Vineland), visual-motor integration age equivalent of 3-10 (Beery), with delays in expressive language and articulation. Increased home-rearing of infants with chromosome abnormalities indicates a need to follow functional status over time before making definitive developmental prognoses.

857 TWO UNUSUAL CASES OF β-GLUCURONIDASE DEFICIENCY (MPS VII). Jacqueline Siegel, Michael W. Partington, and Joe T.R. Clarke. Hospital for Sick Children, Depts. of Pediatrics and Genetics, Toronto and Queen's University, Dept. of Pediatrics, Kingston, Ontario.

Two long-surviving brothers, 23 & 33 yrs old, with β-glucuronidase deficiency illustrate its unusual clinical heterogeneity. Both presented as neonates with club feet, inguinal hernias, hepatosplenomegaly, peripheral edema and hypertelorism. Their birth weights (4.7 and 4.2 kg) were greater than their normal sib (3.8 kg). Peripheral polymorphonuclear leukocytes contained Alder-Reilly bodies; x-rays of the younger sib at 1 mon of age showed minimal dysostosis; both had mucopolysaccharidurla (MPSuria). Psychomotor development, which was initially delayed, deteriorated slowly; they are currently severely to profoundly mentally retarded. Both are short (< 150 cm). The elder has severe degenerative osteoarthritis of the hips. Talipes equinovarus and inguinal hernias have recurred despite surgical correction. However, the facies are not typically coarse, and neither has corneal clouding or clinically apparent hepatosplenomegaly. Screening tests for MPSuria are now negative; however, both continue to exhibit Alder-Reilly granulations of the PMN leukocytes. β-glucuronidase activity in leukocytes and cultured fibroblasts was <1% of normal. Neonatal presentation of MPS VII associated with profound β-glucuronidase deficiency is evidently not incompatible with long survival. The presence of club feet and peripheral edema and the absence of significant dysostosis in these and other cases of MPS VII distinguish this from other MPS storage diseases.

858 ORAL TREATMENT OF INHERITED VITAMIN B12-RESPONSIVE METHYLMALONIC ACIDEMIA (MMA). Flemming Skovby*, John Harper, Maurice J. Mahoney, and Kay Tanaka. Univ. of Copenhagen, Rigshospitalet, Dept. of Pediat., Copenhagen, Denmark and Yale Univ. Sch. of Med., Dept. of Human Genet., New Haven, CT (Sponsored by U. Francke).

The natural history of the inherited MMAs depends partly on the location of the biochemical defect. Patients with defective synthesis of cobalamin cofactors who are responsive to vitamin B12 generally have a later onset of illness and a better long-term outcome than those with a defective methylmalonyl-CoA apomutase. Most vitamin B12-responsive patients have received the cofactor by IM injection. For the past 5 years, we have managed a child belonging to the cobalamin A class of MMA with oral therapy. The child presented in the neonatal period with ketoacidosis and was initially treated with IM vitamin B12. At age 9 months, she was switched to oral cyanocobalmin, 30 mg every 2-4 weeks. Her current regimen is 5 mg X 6 doses given over 72-84 hours every 2 weeks. Peak and trough B12 levels are 5000-10000 pg/ml and 900-2000 pg/ml. With oral B12, the level of urinary methylmalonate decreases from a pretreatment mean of 9.74 to a posttreatment mean of 3.57 mg/mg creatinine. Protein intake has been 2-2.5 g/kg/d throughout. In addition to satisfactory biochemical control, the child has shown good general health, no episodes of significant acidosis and a normal psychomotor development. Her height and weight are at the 3rd %ile. Our results demonstrate the feasibility of oral treatment with vitamin B12 in patients with this form of MMA.