† **811** PSEUDO-ZELLWEGER's - MULTIPLE PEROXISOMAL OXIDATIVE ENZYME DEFICIENCIES. Janna C. Collins, Isabelle Rapin, Francois Van Hoof and Sidney Goldfischer, Albert Einstein College of Medicine, Departments of Pediatrics, Neurology and Pathology, Bronx, N.Y. and International Institute of Cellular and Molecular Pathology, Brussels, Belgium. (spon by M.I. Cohen)

Zellweger's cerebro-hepato-renal syndrome (CHRS) is an autosomal recessive disorder of peroxisomal biogenesis with profound hypotonia and seizures from birth, fatal in the first year of life. Peroxisomes are undetectable in hepatocytes. Biochemical abnormalities secondary to the peroxisomal defect include abnormal C26:C22 fatty acid ratio, accumulation of bile acid intermediates, hyperpipecolatemia and reduced tissue plasmalogen content. Many of these abnormalities are also present in neonatal adrenoleukodystrophy (NALD) and infantile Refsum's disease, disorders with deficient or absent hepatic peroxisomes.

A female infant with clinical, chemical and pathological syndrome identical to CHRS survived to age 11 months. Her liver contained abundant peroxisomes, however D-amino acid oxidase activity and oxidase activity toward palmitoyl-CoA and decanyl-CoA were reduced by 80-85% while L-hydroxy acid oxidase was normal. The plasmalogen pathway enzyme dihydroxyacetone phosphate acyl transferase (DHAPAT) was present in normal amounts in fibroblasts and liver while it was virtually undetectible in CHRS fibroblasts.

This case of pseudo-Zellweger CHRS is a disease in which multiple peroxisomal oxidative activities are deficient rather than a disorder of peroxisomal biogenesis like CHRS, NALD and infantile Refsum's disease.

812 MITRAL VALVE PROLAPSE (MVP) AS A FEATURE OF FRONTO-METAPHYSEAL DYSPLASIA (FMD). Edwing A. Contreras, Joon M. Park and Rafael R. Garcia (sponsored by Surendra K. Varma). Texas Tech University Health Sciences Center, Department of Pediatrics, Lubbock, Texas.

FMD is a rare disorder of the bone and connective tissue consisting of a characteristic facies, prominent bony supraorbital ridges, progressive mixed hearing loss, and a series of musculoskeletal alterations including limited joint motion and poorly developed musculature, especially of the hypothenar and interosseous muscles of the hands. Other clinical findings include micrognathia and abnormal dentition with retained deciduous teeth. Roetgenographic examination demonstrates hyperostosis of calvarium with a "Nazi helmet" configuration of the cranial vault, thick frontal ridges with absence of frontal sinuses and splayed metaphysis of the long bones. A heart murmur has been reported in a third of the cases, however, no further delineation of the cardiovascular findings have been made.

We would like to report a 15 year old patient with typical features of this disorder who had MVP diagnosed by abnormal physical and echocardiographic findings. With mounting evidence that MVP may be a systemic connective tissue disorder, the findings of MVP in our patient is most likely related to the underlying connective tissue defect. Although MVP tends to be a benign disorder, it has been associated with infective endocarditis, cardiac arrhythmias and sudden death. Antibiotic prophylaxis against infective endocarditis is mandatory. In light of the potential morbidity, it is recommended that patients with FMD be investigated for the presence of MVP.

● **813** PRENATAL DIAGNOSIS AND GENETIC RISK IN ALPHA$_1$-ANTITRYPSIN DEFICIENCY PI TYPE ZZ, Diane W. Cox, Tammy Mansfield, Torben Bech-Hansen, Research Inst., Hospital for Sick Children, and U. of Toronto, Toronto, Canada.

A deficiency of the serum protease inhibitor, α_1-antitrypsin (AAT), is frequently associated with chronic obstructive lung disease in adult years. About 17% of individuals with the deficiency (PI type ZZ) develop evidence of liver abnormalities in the early months, and a portion of these proceed to cirrhosis. Prenatal diagnosis has previously been available by PI typing of a fetal blood sample, or by using synthetic oligonucleotide probes specific for M and Z AAT, on cultured amniocytes, although technical difficulties have been encountered with use of the latter. We have used a genomic probe (provided by Dr. S. Woo) on DNA digested with the restriction enzyme AvaII. We have found a pattern of DNA fragments unique to the PI Z allele found with 58/58 Z alleles and 0/47 non-Z, i.e. M or S, alleles. Reliable prenatal diagnosis can be carried out using only 2 µg. of DNA from non-cultured amniocytes or from chorion villus biopsies.

We have followed 25 children with AAT deficiency to 4 or more years of age (maximum 20 years) and have found that at least 65% appear to have a resolution of their liver abnormalities, while the remainder develop progressive liver disease and cirrhosis. We and others have found that the course of disease in PI ZZ sibs is frequently different within families. Sibs born after a child whose liver disease has resolved probably have about a 5-10% risk for developing severe liver disease. There are only a few reported families in which sibs have been born after a child with severe liver disease. The risk for severe liver disease in a subsequent child may be as high as 30% in these families.

△ **814** EXPRESSION OF A BACTERIAL GENE IN TRANSGENIC MICE. Julie DeLoia, Lee Marban, and John Gearhart (Spon. by John W. Littlefield). Johns Hopkins University School of Medicine, Developmental Genetics Laboratory, Department of Pediatrics, Baltimore.

We studied the tissue specificity and the developmental stage of expression of a bacterial gene, Ecogpt, following its introduction into the pronuclei of fertilized mouse oocytes by microinjection. Ecogpt, a gene not present in mammalian cells, codes for XGPRT (xanthine guanine pyrophosphoribosyl transferase), a purine salvage enzyme. We looked for both the presence of the gene and activity of the enzyme in tissues of embryos, fetuses and adults. The vectors used to introduce Ecogpt included the 69% fragment of bovine papilloma virus, pSV2-gpt, RD-114, and polyomavirus.

Liveborn mice were assayed for the presence of the genes injected by Southern blot analysis of DNA extracted from tail tips. Where possible, we have assayed for enzyme activity by utilizing ^{14}C-xanthine as a substrate for XGPRT in cell homogenates, and at all stages of development we have used an immunocytochemical procedure to detect XGPRT in tissue sections. To date, our results indicate that the BPV vector is embryotoxic since in those few animals born with BPV sequences, they are highly rearranged and there is no XGPRT activity detectable.

815 GENETIC FACTORS AFFECTING METHYLMERCURY METABOLISM AND EXCRETION. Richard A. Doherty.

Thirty-five inbred mouse strains and feral mouse isolates have been screened for genetic variation in biotransformation (metabolism) and/or excretion of methylmercury. Our strategy was to examine mice from as many different origins as possible to cast a broad genetic (evolutionary) net to sample the largest possible array of genes which might influence metabolism of mercury compounds. Following a single, non-toxic dose of radiolabeled methylmercury chloride, extents of initial absorption and half-times of elimination were determined by least squares linear regression analyses of retained whole body radioactivity during an eight day period. Feces and urine were separately collected and analyzed for mercury content. Blood, brain, liver, kidney, testes and remaining carcass were weighed and counted at necropsy on day 8 to determine mercury distribution. Large interstrain differences in half-times of excretion of methylmercury (13.1 days to 3.2 days) were observed. Large differences in male vs. female rates of mercury excretion were seen in some mouse strains but not in others. We also found strain variation in the kidney mercury-binding sexual dimorphism previously discovered in our laboratory. Our studies should aid in elucidating specific cellular and molecular processes involved in the bioprocessing of mercury compounds and other metals. It is expected that formulation of genetic models will enable better delineation of possible hypersusceptible human subpopulations, which must be taken into account for rational hazard evaluation, including safe limits of exposure for all life cycle stages.(NIEHS ES01247&1248)

● **816** USE OF GENETIC LINKAGE COMBINED WITH SERUM CREATINE KINASE AND PYRUVATE KINASE FOR CARRIER DETECTION IN DUCHENNE DYSTROPHY. RA Doherty and RC Griggs, Rochester, NY; JR Mendell, Columbus, OH; MH Brooke, St. Louis, MO; GM Fenichel, Nashville, TN; JP Miller and M. Province, St. Louis, MO; RT Moxley, Rochester, NY; PM Conneally, Indianapolis, IN; and the CIDD Group.

Carrier detection in Duchenne dystrophy (DD) remains unsatisfactory since serum creatine kinase (CK) and pyruvate kinase (PK), the best available methods, can detect only 45% of obligate carriers (Muscle Nerve Jan 1985). Restriction fragment length polymorphisms (RFLPs) flanking the DD locus on the X-chromosome have been defined (Murray J et al, Nature 300:69,1982; Davies K et al, Nucleic Acids Res 11:2303, 1983). Thus the use of RFLPs for estimating probability of carrier status has become possible.

We have examined 71 families to determine the extent to which RFLP linkage studies could improve carrier detection above that possible with triplicate, age-corrected CK and PK analyses. The X chromosome genomic probes pL1.28 and λRC8 have been used in 21 families, including 38 obligate carriers. Probe L1.28 is informative in ~50% of families and probe λRC8 in ~20%. Although recombination occurs in ~15% of matings for pL1.28 and for λRC8, in selected informative families RFLP linkage data has clarified carrier status. Additional X-chromosome probes (p99-6,p58-1,p12; pB24-Kunkel; p754,p782-Pearson, and others) are being tested for informativeness for DD linkage analyses. These studies require the evaluation of multiple members of a family but provide more definitive carrier detection than CK-PK assays alone. (Supported in part by the Muscular Dystrophy Association).