● 762 PHENYLALANINE PRODUCES CHANGES IN PLASMA L-DOPA, EEG MEAN POWER FREQUENCY AND PERFORMANCE IN TREATED PHENYLKETONURIC PATIENTS. Wilma L. Krause, Allen W. Averbook, Charles M. Epstein, June Kaufman, David Freides, Louis J. Elsas. Division of Medical Genetics, Departments of Pediatrics and Psychology, Emory University School of Medicine, Atlanta.

We previously reported in 10 patients with phenylketonuria (PKU) that performance and biogenic amine excretion fell when blood phenylalanine (phe) was elevated (Ped. Res. 17:213A, 1983). Here we extend this study to include four additional children with PKU age 7-10 years and evaluate electrical changes by EEG using mean power frequencies (MPF) determined by Fourier transformation. We altered the diet during three, nine-day periods using a triple-blind, double cross-over research protocol. All patients achieved a plasma phe concentration of greater than 1.2 μM during the loading phase. Plasma L-DOPA was measured and EEGs were performed on the 7,8, and 9th days of each study period. On the 9th day of each period, tests of neuropsychological performance, attention and vigilance were administered. During phe loading the plasma L-DOPA fell, tests of performance deteriorated and attention was not sustained. When blood phe was elevated the MPF of EEGs decreased reflecting a shift to slow wave forms. During periods of phe restricted diet these parameters reverted to baseline. We conclude that the EEG-MPF and certain tests of performance are impaired by high plasma phe concentration, that these effects are mediated through decreased L-DOPA, and that they are transient.

● 763 BIOCHEMICAL AND MORPHOLOGICAL PEROXISOMAL DEFECTS IN ZELLWEGER SYNDROME. Paul Lazaro, Virginia Black, Amiya K. Hajra, Nabanita S. Datta, Babu Bangaru and Joseph Dancis, The Rockefeller University, NYU School of Medicine, U. of Michigan, Departments of Cell Biology, Neurosciences and Pediatrics, New York City and Ann Arbor.

The report of absent peroxisomes and distorted mitochondria in liver and kidney of Zellweger syndrome suggested that the manifestations may be secondary to disturbed function of these organelles. The associated question of persistence of peroxisomal enzyme activity in the absence of peroxisomes was equally provocative.

Liver and intestinal biopsies from a patient with Zellweger syndrome were assayed for 3 peroxisomal enzymes. Catalase was present in both tissues in normal concentrations but was not sedimentable at 10,000 rpm for 30 min. Cyanide-insensitive β-oxidation of palmitoyl-CoA and dihydroxyacetone phosphate acyltransferase were not detectable in liver. Absence of the former could explain the reported accumulations of very long-chain fatty acids. The acyltransferase is essential in the synthesis of plasmalogens which are widely distributed in membranes but whose functions are poorly understood.

Peroxisomes could not be found in liver or intestine by EM. Mitochondria were normal. Rare, very small bodies were noted in intestine some of which were DAB-positive (catalase-containing).

These findings provide the first unequivocal evidence of a deficiency in peroxisomal enzymes in human disease. Zellweger syndrome may result from an interruption in peroxisomal formation.

● 764 ABERRANT COBALAMIN METABOLISM WITH HOMOCYSTINURIA AND METHYMALONIC ACIDURIA. Robert J. Mamlok, John N. Isenberg and David K. Rassin, Department of Pediatrics, the University of Texas Medical Branch at Galveston and Charles A. Hall, Veterans Administration Hospital, Albany Medical Center, New York.

Marked elevations in serum vitamin B_{12} (2523 pg/ml) and total serum folate (60 ng/ml) were noted in a malnourished, hypotonic eight month old hispanic male with macrocytic anemia. A positive urine nitroprusside screen was followed by measurements of homocystine(HCy)(36.5μmol/d), elevated cystathionine (40.8μmol/d) and methylmalonic acid(MMA)(457 mg/d) in 24h urine collections.

This excretion of HCy and MMA suggested an aberration in vitamin B_{12} handling since both pathways require cobalamin(Cbl) cofactors. Analysis of pretreatment serum by TLC and bioautography showed more than half the Cbl present migrated with the cyano-form(CN-Cbl), a marked reduction in the HCy cofactor(MeCbl) and a nearly normal percent of MMA cofactor(AdoCbl). Family screening studies did not reveal comparable levels of HCy or MMA. HCy loading indicated a delayed maternal methionine clearance.

A 90% reduction in 24h MMA excretion followed intramuscular hydroxocobalamin(OHCbl) but no consistent reduction in plasma or urine HCy was achieved on an unregulated diet. Anemia and macrocytosis resolved as muscle tone, auditory responsiveness and nutritive sucking improved with alternate day OHCbl therapy.

Our patient is most like "Cbl-C" variants previously described with severe multi-system involvement. Early macrocytic anemia, elevated serum vitamin B_{12}, and a unique cobalamin pattern suggest a potential new variant in this metabolic pathway.

● 765 NEOPTERIN DEFICIENCY: A CAUSE FOR HYPERPHENYLALANINEMIA. Reuben Matalon, Univ, of IL, Dept. of Peds., Chgo., and Bobbye Rouse, Univ. of TX, Dept. of Peds., Galveston, TX.

A female born near term weighing 2.7kg had blood phenylalanine level of 4-6mg/dl at the age of 3 days. Subsequently, blood phenylalanine level was >20mg/dl and 58.4mg/dl with blood tyrosine 0.65mg/dl in the 3rd and 4th weeks of life. In the first week of life, the baby developed feeding problems, poor suck and poor muscle tone. Urinary neurotransmitters metabolites (VMA, HVA and 5HIAA) were found to be normal. The diagnosis of classical PKU was made and low phenylalanine diet was started. At the age of 6 months, in spite of good control of blood phenylalanine levels, the baby was found to be delayed, hypotonic, failed to gain weight and functioned at 2-3 months. She was also noted to be tremulous and had choreoform movement. An EEG and CT scan of the head were normal. Urinary pterins showed a profound deficiency of neopterin (N) and biopterin (B) (N=88.5ng/mg creatinine, B=36.6ng/mg creatinine; values which are 1% of the normal levels). However, the ratio of N/B was normal. The same deficiency was found in the plasma and CSF. The patient was placed on L-DOPA, Carbidopa and 5-hydroxytryptophan which caused clinical improvement. Since defects in the synthesis of biopterin cause very high levels of neopterin, the deficiency of neopterin in this child is the result of GTP-cyclohydrolase deficiency, a step required for the formation of dihydroneopterin triphosphate; similar to the case of Niederwieser et al (Eur J Peds 138:97, 1982). Normal N/B ratio is not sufficient to rule out defects in the synthesis of tetrahydrobiopterin.

● 766 MITOCHONDRIAL NADH - UBIQUINONE OXIDOREDUCTASE (Complex 1) DEFICIENCY IN AN INFANT WITH CONGENITAL LACTIC ACIDOSIS. R.Moreadith, M.Batshaw, T.Ohnishi, D.Kerr, B. Knox, D. Jackson, R. Hruban, J. Olson, B. Reynafarje, A. Lehninger. Johns Hopkins Med. Inst., Balto; U. of PA, Phila.

A white male, the product of a G1,P0 non-consanguineous 34 wk. pregnancy presented in the first month of life with hypoglycemia, progressive lactic acidosis (5→31 mM, normal<2.5) with increased lactic/pyruvate ratio (64:1) and hyperalaninemia (2.3 mM, nl <.44). Total plasma carnitine was 25 uM (normal >37). GLC of urine showed no accumulation of organic acids. There was progressive hypotonia, hepatomegaly, brain CT abnormalities and respiratory insufficiency leading to death at 16 wks. Enzymatic determination on fibroblasts and liver/skeletal muscle biopsy ruled out pyruvate carboxylase, pyruvate dehydrogenase, PEPCK, glucose-6-phosphatase and fructose 1-6 bisphosphatase deficiencies. There was increased glycogen and lipid and giant mitochondria with concentric whorls in muscle. Freshly isolated mitochondria from 4 tissues revealed a marked deficiency of NAD linked respiration but normal succinate linked respiration. Reduction of cyt c by NADH (rotanone sensitive) in permeabilized mitochondria revealed a deficiency of Complex 1, e.g., 5 nmol cytC reduced/min/mg skeleton muscle (control 206). However, Complex 1 activity reactive to ferricyanide was identical to control, suggesting the deficiency was in the Fe:S centers of Complex 1. Electron paramagnetic resonance spectroscopy of liver sub-mitochondrial particles revealed a selective absence of Fe:S centers. This represents the first case of a deficiency of the Fe:S centers of mitochondrial Complex 1.

767 WHEN ARE ANEUPLOID CELLS CLINICALLY SIGNIFICANT? Gregory P. Nowinski, Daniel L. Van Dyke, Golder N. Wilson, and Lester Weiss. Henry Ford Hospital and University of Michigan, Detroit and Ann Arbor, Michigan.

Some workers suggest a causal relationship between multiple miscarriages or offspring with trisomy 21 and low frequency hyperdiploidy in the parents. Others consider low frequency aneuploidy of no clinical significance. We compared the frequency of aneuploid cells in five groups of subjects, karyotyped from 1978-83: 79 parents of trisomy 21 patients, 164 other 1st and 2nd degree relatives of Downs patients, 702 subjects with multiple miscarriage, 341 phenotypically and karyotypically normal control parents (e.g., parent of a dysmorphic child or member of a translocation family), and 1,165 others (e.g., chromosomally normal dysmorphic and retarded individual, etc.). In all, 47,595 cells were analyzed from 2,451 subjects. A cell was called hyperdiploid only if the extra chromosome(s) was recognizable and structurally normal.

We found significant age and sex effects, but no other differences among the five groups of patients. Autosomal hypodiploidy (3.8% of cells) had no between group differences, but 45,X cells were age and sex associated: adult females .33%, adult males .17%, younger females .10%, and younger males .16%. Autosomal hyperdiploidy (.11% of cells) had no group, sex, or age differences. The frequency of X chromosome hyperdiploid cells was age and sex associated: adult females .26%, younger females .00%, adult males .04%, and younger males .00%. Females had a marked increase of X aneuploidy with age: age under 23 had .09% XO and .00% +X cells, age 23 to 34 had .31% XO and .21% +X cells, and age 34 to 50 had .64% XO and .60% +X cells.

In summary, the frequency of aneuploid cells was greater in females than males and was positively correlated with advancing age. Such cells were not more frequent in couples with multiple miscarriages or offspring with trisomy 21.