750 UNIQUE CHROMOSOME ABNORMALITIES IN A CHILD WITH PRE-B CELL - B CELL LEUKEMIA. A.J. Cousineau, R. Gera, and R. Kulkarni. Michigan State University College of Human Medicine, Department of Pediatrics/Human Development, East Lansing, MI.

A seven-month-old white male presented with Acute Lymphoblastic leukemia (ALL) with 90% FAB L_2 phenotype, Tdt positive, intercytoplasmic and surface immunoglobulin positive blasts in the bone marrow, suggestive of Pre- B - B Cell malignancy. An occasional cell in the peripheral smear showed Auer rods. Cytochemical stains of the bone marrow were negative. Initial karyotype analysis showed 100% of the bone marrow cells with a male karyotype, trisomy 19 and pericentric inversion of 7: 47,XY,+19, inv(7). The patient achieved a short remission with ALL protocol. At relapse, blasts morphology and cytochemistry was suggestive of Acute Myeloid leukemia (AML) and in addition to the previously described chromosome abnormalities two new clones emerged, i.e., 47,XY,+19, inv(7), del(7q) and 47,XY,+19, inv del(7p). The patient was unresponsive to AML chemotherapy and subsequently expired. To our knowledge this is the first report of trisomy 19 in combination with inversion 7 in a leukemia with biphenotypic features. Although the morphological and cytochemical features of the leukemic cells changed to a myeloid type, the chromosome abnormalities typical of lymphoid malignancies persisted and could explain the poor clinical response of the patient to AML therapy.

751 DECREASED SWEAT VOLUME IN CYSTINOSIS. William A. Gahl, Van S. Hubbard, and Sheldon Orloff. Interinstitute Genetics Program, Clinical Center, NICHD, and NIADDK, National Institutes of Health, Bethesda, MD 20205

Sweat tests by pilocarpine iontophoresis were performed on 13 children age 2-9 years with nephropathic cystinosis; controls were 100 children age 1-18 years examined consecutively because of respiratory symptoms or failure to thrive, but not having cystic fibrosis. The mean amount of sweat for the cystinotic children was 97 mg $\pm$ 35 SEM (range 25-450) compared with 281 mg $\pm$ 12 SEM (range 86-587) for 100 controls ($p < 0.001$). Ten of 13 cystinotics, but only 3 of 100 controls, had sweat volumes less than 100 mg. One 12-year old benign cystinotic produced 420 mg of sweat. For 5 nephropathic cystinotics from whom an adequate amount of sweat for analysis was obtained, sweat chlorides were normal (range 15-23 mEq/l). Sweat volume was not related to the patient's age or history of cysteamine therapy. Symptoms did correlate with decreased sweat production. Eight cystinotic children, with sweat volumes of 25-87 mg each, experienced severe flushing and vomiting or practiced heat avoidance, while the remaining five (mean sweat volume 188 mg) had no clinically significant heat intolerance. Light microscopy of several skin biopsies revealed no sweat gland abnormalities. Cystinosis now joins fucosidosis as a lysosomal storage disorder with sweat abnormalities. Precautions against excessive heat exposure should be considered for children with nephropathic cystinosis.

● 752 LYSOSOMAL CYSTINE TRANSPORT:Mg^{++} EFFECTS AND I-CELL FIBROBLAST DEFECTS. W. Gahl, F. Tietze, J. Butler, and I. Bernardini (Spon. by J. Sidbury). Interinstitute Genetics Prog., CC, NICHD, NIADDK, NIH, Bethesda, MD 20205

In human leucocytes, egress and counter-transport studies have shown that cystine transport across lysosomal membranes is a saturable, stereospecific, and bidirectional process which is defective in cystinosis. $MgCl_2$/MgATP (each 2mM) shifted the pH optimum for cystine counter-transport from pH 6.5 to pH 5.5, where a 2-fold stimulation of cystine transport was observed. This was caused by Mg^{++}, not ATP, and was dose-dependent with a maximum at 4mM $MgCl_2$. Stimulation was prevented by EDTA or NaATP. $MgSO_4$ or $MnCl_2$ could replace $MgCl_2$. In other experiments, ^{35}S-cystine clearance from normal, cystinotic, and I-cell (Mucolipidosis II) fibroblasts was measured. Cells were loaded to roughly equivalent levels of ^{35}S-cystine, washed free of label, and harvested after 0, 30, 60, and 120 min at 37°C. ^{35}S-Cystine (nmol/mg protein) was measured and half-times for cystine clearance calculated. For 2 normal strains, mean $t_{\frac{1}{2}}$ was 38 min; cystinotic mean $t_{\frac{1}{2}}$ was 734 min; I-cell mean $t_{\frac{1}{2}}$ was over 800 min. I-Cells lack the enzyme responsible for formation of mannose-6-phosphate residues required for lysosomal enzyme recognition and uptake. From the cystine storage and impaired cystine clearance in I-cells, one may speculate that the cystine carrier requires a mannose-6-phosphate recognition marker, or that it may require processing by lysosomal hydrolases which are deficient in I-cell fibroblasts.

● 753 PANCREATIC ISLET CELL ANTIBODIES (ICSA) IN FAMILIES OF CHILDREN WITH TYPE I DIABETES MELLITUS (IDDM): DOMINANT INHERITANCE. Fredda Ginsberg-Fellner, Yayoi Toguchi, Mary E. Witt, Bonita H. Franklin and Pablo Rubinstein, Mt. Sinai School of Medicine, Department of Pediatrics and New York Blood Center, Laboratory of Immunogenetics, New York, N.Y.

ICSA and ICA are present in more than 90% of children at the onset of IDDM and also prior to its development. In addition 6-25% of unaffected sibs of IDDM probands also have such antibodies but most never develop IDDM. In the present study we have measured complement-dependent cytotoxic ICSA by a simple microcytotoxicity assay using as targets the cloned rat insulinoma line RIN-m. Cytotoxicity was positive if 50% of cells were killed after incubation with diluted, heat inactivated, rat liver powder-adsorbed sera followed by complement with ethidium bromide added after 90'; dead cells were identified under epiillumination with an inverted Leitz microscope. The sera of all unaffected first degree relatives of 112 IDDM probands were examined and the results were divided with reference to sharing of HLA haplotypes by the sibs with their respective diabetic probands. 23/186 (12.4%) sibs were ICSA-positive and this was most common in sibs whose diabetic sib was also ICSA-positive (32.1 vs. 3.8%, $p < .001$). Furthermore, ICSA were found predominantly in those sibs HLA-identical (7/44) or haploidentical (14/105) to their diabetic sib and were rare in HLA-nonidentical sibs (2/37, $p < .05$).

The results suggest that the tendency to produce ICSA may be inherited as a dominant trait, different from the inheritance of IDDM itself. Further studies are required to identify etiologic factors in the development of these ICSA.

● 754 TREATMENT OF HYPERPHENYLALANINEMIA V WITH TETRAHYDROBIOPTERIN (BH_4) AND NEUROTRANSMITTER (NT) PRECURSORS. Carol Greene, Howard Cann, Sheldon Milstein, Seymour Kaufman, Kym Faull, Jack Barchas. Stanford Univ Med Ctr, Depts of Peds and Psychiat & Behav Sci, Stanford, and NIH, NIMH, Bethesda.

In a 9 month infant with the spinal fluid (CSF) NT abnormalities of biopterin synthesis defect we compared treatment with: BH_4 high (20 mg/kg/d) dose only; BH_4 low (3 mg/kg/d), moderate (10 mg/kg/d) or high dose with the NT precursors dopa/carbidopa (10/1 mg/kg/d) and 5-hydroxytryptophan (5 mg/kg/d); and NT precusors with phenylalanine (phe) restricted diet. Over 4 months we evaluated clinical status, CSF biopterin, CSF NT major metabolites homovanilic acid (HVA), 5-hydroxyindolacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol, and CSF NT minor metabolites 3,4-dihydroxyphenylacetic acid, vanilmandelic acid, m-hydroxyphenylacetic acid (MHPAA), p-hydroxyphenylacetic acid (PHPAA) and indolacetic acid (IAA). Few control values for CSF biopterin and NT major metabolites and none for minor metabolites are known in children. Clinically the patient was well on NT precursors with or without BH_4 and deteriorated on BH_4 only. Liver enzymes, which were elevated at 4 months on BH_4 only, remained normal and blood phe was in good control. CSF biopterin increased to at or above normal with moderate or high dose BH_4 but virtually no response of HVA or 5-HIAA independent of NT precursors was seen. BH_4 at any but low dose altered the IAA/5-HIAA ratio and BH_4 at any dose increased PHPAA but not MHPAA. In this patient, the first in which NT minor metabolites have been measured on BH_4, the CSF major metabolites could be maintained at normal levels only with NT precursors but BH_4 modified the patterns of minor metabolites.

755 IDENTIFICATION OF SHORT CHAIN ACYL-CARNITINE ESTERS (SCAC) IN ORGANIC ACIDURIAS. George E. Hoganson, Dennis J. Paulson, Stanley Berlow, Austin L. Shug, University of Wisconsin Medical School, Center for Health Sciences, Departments of Genetics, Pediatrics and Neurology, Madison (spon. by Russell Chesney).

Increased acyl-carnitine ester and decreased free carnitine levels have been noted in patients with certain inborn errors of metabolism. In order to study carnitine metabolism in these patients a technique for the identification of SCAC was developed. SCAC were enzymatically converted to the corresponding coenzyme A (CoA) esters by reaction with carnitine acetyltransferase. Acetyl, propionyl, butryl and isovaleryl-carnitine esters have been tested todate and a linear relationship between initial acyl-carnitine and final acyl-CoA concentrations was present. Acyl-CoA's were identified using a HPLC technique. Urine samples from control patients in which SCAC were converted to acyl-CoA's showed a large peak of acetyl-CoA and small peak of propionyl-CoA. The acyl-CoA pattern in a patient with propionic acidemia (PA) showed a large peak of propionyl-CoA and smaller peak of acetyl-CoA. 50mg/kg oral L-carnitine in controls (n=4) resulted in an increase of urine carnitine levels from 0.10±0.03/0.8±0.07/µmole/mg/creat (mean±SD) (acyl/free carnitine levels) to 2.14±1.65/2.15±2.0 4 hours after L-carnitine. In a patient with PA, urine carnitine levels increased from 0.98/0.3 to 3.8/0.5 µmole/mg/creat and propionyl-carnitine was the major SCAC present. The ability of L-carnitine to increase acyl-group excretion may be of therapeutic benefit. This procedure for identification of SCAC offers an alternative to other methods used.